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ABSTRACT

Objective: Immunosuppressed individuals are at a high risk of latent tuberculosis infection (LTBI) and clinical practice guidelines for the screening and management of LTBI in at risk patients have been developed. We assessed the scope, quality and consistency of clinical practice guidelines, on screening for LTBI, and the prevention of tuberculosis infection (TB) in high-risk patient populations.

Design: We conducted a systematic review of clinical practice guidelines. Methodological quality of these guidelines was assessed using the Appraisal of Guidelines for Research and Education (AGREE) II instrument. Textual synthesis was used to summarise and compare the recommendations.

Data sources: Electronic databases (MEDLINE, EMBASE, PsycINFO) and guideline registries were searched from inception to December 2017.

Results: Thirty-six guidelines were included. Nineteen focused on patients receiving medical immunosuppression, seven focused on transplantation, three on patients with human immunodeficiency virus and seven were generalised across all at risk populations. Most guidelines (n = 31, 86%) used a systematic approach to identify and appraise the evidence. The methodological quality of the guidelines varied with the overall mean AGREE II scores ranging from 32% to 91%. Guidelines performed poorly in terms of editorial independence (average score 35%, range 0-92%), however most were robust in defining their scope and purpose (average score 81%, range 64-100%). Guidelines recommended either or both, the tuberculin skin test and the interferon gamma release assay for screening. Treatment of LTBI with isoniazid was consistently recommended.

Conclusion: Clinical practice guidelines on LTBI vary in quality and scope. The recommendations for screening varied across guidelines, whilst recommendations for treatment were largely

consistent. Improving the consistency and quality of guidelines may help to optimise the screening and management of LTBI for improved patient outcomes.

Strengths and Limitations

- The current article systematically reviews clinical practice guidelines, which exist to facilitate the management of latent tuberculosis infection in immunosuppressed patients
- We appraise the similarities and differences in different immunosuppressed populations
- We use the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool to assess the quality of the guidelines
- 36 guidelines were found, however non-English guidelines were excluded, with only a few guidelines in low resource settings

INTRODUCTION

Immunosuppression increases the risk of reactivation of prior infection with *Mycobacterium tuberculosis* leading to tuberculosis (TB) disease. In high-income countries, the baseline risk of reactivation of latent TB infection (LTBI) varies between 6 and 20 per 100,000 persons per year.[1,2] The magnitude of the risk of TB reactivation among those who are immunosuppressed varies depending on the type of immunosuppression. The greatest risk is observed among solid organ transplant recipients, particularly in lung (15-fold higher compared to the general population)[3] and stem cell transplant recipients (6-10 fold higher)[4], followed by recipients of tumor necrosis factor (TNF) antagonists (5-7 fold higher).[5–8] The risk of TB reactivation in patients with human immunodeficiency virus (HIV) infection is 3–20 times higher than the general population[9,10] and causes up to 25% of deaths in these patients.[9]

Early detection of LTBI through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as prophylaxis to prevent the development of active TB. Screening often involves the use of the commercially available tuberculin skin test (TST) and an interferon gamma release assay (IGRA). IGRAs include the QuantiFERON-TB Gold (Cellestis Ltd, Australia) and the T-SPOT test (Oxford Immunotec, UK). However, there are potential drawbacks associated with screening. False negative results (2.8% in one setting[11]) with attendant false assurance and may lead, to late or missed, diagnoses, and delayed treatment. Conversely, false positive results may lead to unnecessary and inappropriate investigations which may be harmful.[12]

To advise health practitioners, clinical practice guidelines have provided evidence-based statements that include recommendations that inform practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.[13] As such, guidelines on screening for LTBI and prophylaxis in at-risk patient populations have been developed for a number of healthcare settings.

However, guidelines exist for specific patient subgroups and it is unclear if the recommendations may be generalisable to others, or if there is variability. Therefore, this review aims to assess and compare the rationale, scope, quality and consistency of clinical practice guidelines and consensus statements for the screening of LTBI, as well as for treatment against LTBI in immunosuppressed individuals.

METHODS

Selection criteria

Evidence-based clinical practice guidelines and consensus statements on screening for LTBI and prophylaxis against TB in immunosuppressed individuals published in English were eligible for inclusion. Patients who were medically immunocompromised (including chemotherapy, disease modifying agents and biological therapy), had received a solid organ or stem cell transplant, or HIV positive, were included. Draft or unpublished guidelines, conference or discussion papers, opinions, and guidelines and consensus statements replaced by updated and/or revised recommendations were excluded.

Literature search

We searched MEDLINE, Embase, and PsycINFO from database inception to December 2017. Medical Subject Heading (MeSH) terms and text words for "tuberculosis", "immunosuppressed", and "immunocompromised" were combined with terms relating to clinical practice guidelines and consensus statements (Appendix 1). Clinical guideline registries and reference lists were searched for additional clinical practice guidelines. Titles and abstracts were reviewed by two authors (TH and EA), and those which did not meet the inclusion criteria were excluded. Full text versions of potentially relevant guidelines or consensus statements were examined for eligibility.

Appraisal of guidelines and consensus statements

Methodological quality for clinical guidelines and consensus statements was assessed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[14] AGREE II is an internationally validated, rigorously developed 23-item tool used to evaluate independent domains of guideline development including: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Each item was rated on a seven-point scale ranging from strongly disagree (score 1) to strongly agree (score 7). The domain score was obtained by summing all scores of the individual items per domain and then standardising the total as a percentage of the maximum possible score for that domain:

$$\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$$

The minimum possible domain score would be the number of questions, multiplied by the number of appraisers, multiplied by 1 (strongly disagree). The maximum possible domain score is the number of questions, multiplied by the number of appraisers, multiplied by 7 (strongly agree). For each guideline, we calculated a quadratic weighted kappa (κ) score as a measure of inter-rater agreement. An overall weighted kappa was also calculated across all guidelines.

Textual synthesis

All text from each guideline were entered into the HyperRESEARCH software (ResearchWare Inc. 2011, version 3.0.3, Randolph MA) for storing, coding and searching textual data. Data was categorised by subheadings based on immunosuppression modality and by screening and treatment methods. Subsequently, we conducted a textual descriptive synthesis to analyse the content and consistency and the evidence base of the recommendations.

RESULTS

Characteristics of clinical practice guidelines

We included 36 guidelines (Figure 1) published from 2002 to 2017. The guidelines were focused on medical immunosuppression (19 guidelines),[1,15–32] solid organ and stem cell transplantation (seven guidelines),[3,33–38] and HIV (three guidelines).[9,39-40] Seven were general guidelines which were not specific to a particular patient group, and covered broadly, the detection of LTBI and its management.[10,41–46] The guidelines were published across 16 different countries from regions including North America, Western Europe, Australasia and South Africa. A summary of the guideline characteristics is provided in Table 1.

Of the guidelines based on medical immunosuppression, nine guidelines provided recommendations on prophylaxis across various medical specialties including dermatology, rheumatology, gastroenterology and respiratory medicine.[15,16,18,21,24,26,28,29,31] Four were specific to patients with rheumatoid arthritis,[20,23,25,27] of which, one focused only on patients receiving infliximab,[23] whilst two guidelines were specific to patients with psoriasis.[18,30] One guideline focused on patients with rheumatological or gastroenterological disease[15]. There were specific guidelines addressing inflammatory joint disease,[19] rheumatological disease[1], and autoimmune bullous diseases.[22] One guideline discussed patients at risk due to methotrexate therapy.[32] Of the transplantation guidelines, two guidelines were for kidney transplantation,[34,36] one for stem cell transplantation,[38] one for both solid and stem cell transplantation[33] and three for all forms of solid organ transplantation.[3,35,37]

Three guidelines addressed LTBI in patients with HIV.[9,39,40] There were seven other guidelines which discussed screening in all at risk populations.[10,41–46] Five of these also included discussion on

patients with HIV[41–45] and four focused on using IGRA alone.[41,43,44,46] Three guidelines were developed in countries with a high prevalence of TB (South Africa and Philippines).[20,24,40]

Across the guidelines, the methods for literature review were not always specified. Literature review was conducted in 31 of the guidelines (86%),[1,3,9,10,15–22,24,26–35,37–39,41–46] of which 12 based their recommendations on a combination of the literature review and expert consensus.[3,9,10,15–18,20,21,26,29,34,37,43–46] Two guidelines were based on expert consensus alone.[23,42] Nineteen guidelines graded the level of evidence.[3,9,10,17,18,24,27–29,30,32,34–39,42,46] Furthermore, 16 guidelines graded the strength of their recommendation.[3,9,10,24,26,28,29–34,38,39,41,45] Where evidence was graded, however, it was often of low quality and was weak. Only eight (22%) guidelines were peer reviewed,[9,10,17,19,20,24,29,30] with four (11%) made available for public consultation prior to publication.[9,19,20,24]

Methodological quality

Table 2 summarises the AGREE domain scores of each guideline. The mean score (and range) for all guidelines was 55% (0% – 100%). In terms of scope and purpose on average, 81% (64% – 100%) of criteria were met for all guidelines. The average scores for stakeholder involvement was 50% (19% – 94%), for rigor of development, 47% (10% – 91%), clarity and presentation, 73% (50% – 89%), applicability, 46% (0% – 92%), and editorial independence, 35% (0% – 92%). The overall mean score was 55% (32% – 91%).

Weighted Kappa scores (κ), to assess interrater agreement, ranged from a score between poor to very good, with the majority being moderate (0·41 – 0·60) to very good (0·81 – 1·00). The overall weighted score was 0·64 (95% CI 0·59 – 0·68), with good concordance between reviewers.

Textual synthesis

A summary of the guidelines and the recommendations are provided in table 3. Most guidelines recommended screening in all immunosuppressed patients, and prophylaxis if there was a clinical indication for LTBI.

Screening for latent TB infection

Populations of interest

Most clinical practice guidelines recommended screening for LTBI in patients commencing immunosuppression or were highly likely to commence immunosuppression, and patients immunosuppressed due to concurrent illness including patients with HIV and/or undergoing solid organ and bone-marrow transplantation.[3,15–20,22,24,26,33,35,37,39] Although, medical immunosuppression was mostly biological therapy, two guidelines, specified recommendations for patients who have received medical immunosuppression such as, methotrexate,[17,32] cyclosporine and T cell blocking agents for the management of autoimmune disease.[17]

Screening modalities and frequencies

A combination of TST and/or IGRA testing, chest X-ray (CXR), detailed background history (including previous exposure to other individuals with TB) and risk factor assessment (travel or migration from endemic areas) was the most frequent recommendation for LTBI screening in immunosuppressed individuals.[1,17,18,21,23,24,26,29–32] The recommended choices of screening modalities and of their frequency were reliant upon test availability and costs. The TST is widely available and economical.[10]

In guidelines pertaining to medical immunosuppression, the recommendations for screening varied considerably between the use of TST and IGRA. Concurrent testing with both TST and IGRA was

supported in six guidelines,[16,18,20,22,26,32] however, a further three guidelines recommended the use of IGRA alone.[15,28,30] Six guidelines supported TST alone for screening, but these recommendations were published prior to 2011.[17,19,21,23,24,27,29]. Two other guidelines recommended the use of either the TST or IGRA.[1,22]. Among BCG vaccinated individuals, one guideline recommended a two-step strategy for screening LTBI.[31] TST was often considered as the triage test. If positive, diagnostic IGRA was used to confirm the diagnoses. In addition to this, two further guidelines recommended IGRA alone, for BCG vaccinated individuals[16,17].

In patients who required long-term maintenance medical immunosuppression, repeat testing at yearly intervals using IGRA was recommended by three guidelines,[17,28,31] but two advocated against this, as the accuracy and utility of the IGRA, was deemed to be questionable.[16,27] IGRA was recommended by one guideline in the presence of (any) skin disease due to difficulties in inoculating the TST in many of these cases.[18]

For patients undergoing transplantation, patients with HIV and other patients not receiving medical immunosuppression, most clinical practice guidelines acknowledged the added value of including TST and IGRA in the screening algorithm,[9,10,28,33,35,37-39,41-46] because a single test has poor diagnostic accuracy, and a combination approach may increase detection of LTBI. However, one guideline specified the preference for IGRA over TST as the standard triage screening tool for LTBI in solid organ transplant recipients because of the concern of false positive findings with TST.[34]

Costs were also considered as a key factor in determining the frequencies and modalities of screening in immunosuppressed individuals. The World Health Organisation (WHO) have suggested IGRA and/or TST may be used in high and upper-middle income countries.[10] Given the anticipated costs of IGRA, the reasonable test accuracy of TST, and general acceptance of TST by

clinicians and patients, IGRA however, was recommended not to replace TST in low income countries.[10] In the high prevalence settings of South Africa and the Philippines, there was no reliable testing method, however a combined TST and IGRA approach was recommended in one guideline,[20] treating of all HIV patients without screening was recommended in another,[40] or a TST alone in one guideline.[24]

Defining screen positive and negative results

Criteria for TST positivity varied across guidelines. Some recommended a TST- induced reaction of at least 5 mm diameter in all populations, to allow for the treatment of patients in high risk settings.[17,19-21,26,35–37,40] Other recommended the threshold diameters ranged from 6mm to 20mm.[18–20,21,23,24,26,27,31,33] Where the TST result was initially negative, two guidelines recommended repeat testing.[23,45] In all guidelines, an individual was deemed to be at risk for LTBI if either the TST or IGRA was positive.

Are these recommendations valid?

Overall, the majority of guidelines recommended screening in at risk populations, mostly with a combined approach of TST and IGRA in immunosuppressed patients. There is a body of evidence available looking at the utility and validity of TST and IGRA test performance, however, when extrapolating to support recommendations in immunosuppressed populations, these recommendations were sourced largely from observational studies performed in middle to high income countries and did not include patients from low-resource settings, with low certainty of the evidence. The test sensitivity and specificity of TST and IGRA varies and most guidelines opted for tests to increase sensitivity to allow for increased detection of LTBI. Thus, the preference, was often for combining TST and IGRA, as this increases detection of LTBI,[1,18,33,35,44] especially in immunosuppressed individuals.[1,15] The IGRA is more specific for LTBI than TST, in particular for BCG vaccinated individuals[10,17,31,39,42,43,46] and is more sensitive in immunosuppressed

patients.[15,31,43] However, as the test properties of IGRA and TST differ between populations, most suggested care and caution should be considered for interpretation, particularly in immunosuppressed populations.

Treatment for latent TB infections

Population of interests

Either a positive TST or IGRA was considered sufficient evidence to warrant further evaluation. Prior to LTBI treatment, exclusion of active TB was recommended.[1,9,15,17,18,25,26,29,30,32,35,42–44] Once active TB was excluded, LTBI treatment was recommended. Treatment for LTBI was also indicted for those who were BCG vaccinated, because BCG status may indicate time spent in an area with a high prevalence of LTBI.[34] Furthermore, in South Africa, where there is a high prevalence of TB, treatment for LTBI was recommended in all patients after exclusion of active TB in the setting of HIV.[40] Also, most clinical practice guidelines recommended LTBI treatment, where clinical suspicion was high, regardless of the IGRA and TST test findings.[1,3,15,19,20,24,26,28,29,33,35–38]

Intervention and duration

Recommendations for the treatment of LTBI were largely similar across guidelines, regardless of the mode of immunosuppression. In most guidelines, isoniazid 300mg daily with pyridoxine was recommended for a duration of nine months.[3,9,16–21,24–27,29,31,33–39,42] Six months of both interventions were considered less efficacious.[18] Two guidelines suggested a flexible treatment regimen for 6-9 months of the combined therapies.[19,30] Four guidelines did not specify duration.[15,23,32,45]

Rifamcyin-based therapy (10mg/kg/day) either alone or for four[1,3,9,10,15–18,24,26,27,31,33,35-39,42] or three months[10] was the second most frequently reported treatment strategy among patients who were tested positive for LTBI. This was thought to be useful when isoniazid was contraindicated or not

tolerated,[27] with one guideline describing the option as cheaper, but with more drug-drug interactions.[18] Rifampicin plus isoniazid for three[1,10,15–19,25,26,29–31,39] or four months[10,24] was also an option. Other options included rifabutin for four months,[9,42] or three months of weekly rifapentine and isoniazid.[9,10] Finally, rifampicin and pyrazinamide for a shorter two-month regimen, was considered as an option in eight guidelines,[3,25,29,35–39] with most being in the transplantation setting. The shorter duration of treatment was considered as advantageous for those maintained on the transplant waiting list.[3,35–38] However, a biological therapy based guideline advised against this option due to the increased risk of hepatotoxicity.[24]

In the transplantation and HIV settings, some guidelines specified the need to avoid rifamycins, given the potential drug-drug interactions with calcineurin inhibitors and the protease inhibitors.[3,35,37] However, therapeutic drug monitoring may mitigate against the potential for such interactions.[34] Several other non-rifamycin based alternatives were recommended and included ethambutol with levofloxacin or moxifloxacin for six months,[3,37] 12 weeks of rifapentine and isoniazid, and six months of isoniazid with ethambutol.[24]

Close monitoring with monthly liver function tests and peripheral neuropathy was recommended whilst on treatment, for all patients.[3,9,10,17,18,26,31,35,37,40] Co-administration of Vitamin B6 (pyridoxine) was suggested universally, to reduce the risk of peripheral neuropathy associated with isoniazid. If there were treatment interruptions for more than two months, one guideline recommended clinical and radiological reassessment for TB.[42]

Timing of prophylaxis

In patients who are medically immunosuppressed, most guidelines recommended delaying medical therapy for one month after commencement of LTBI treatment, where possible, to reduce the risk of TB reactivation.[15–18,20,24–28] Alternative waiting periods varied between three weeks[25] to two

months.[30] One guideline preferred a prolonged delay, but did not provide a time frame.[21] However, if the underlying disease was severe, earlier institution of immunosuppressive agents was accepted[17,29] once exclusion of active TB was made.[28]

In the transplantation setting, guidelines recommended that patients with LTBI should commence treatment whilst on the waiting list where possible, with treatment ideally completed prior to transplantation.[3,33,35,37,38] However, treatment interruption peri-transplantation, with recommencement and completion of the treatment course once patients were clinically stable, may also be considered.[33,35,37] LTBI treatment should not delay transplantation.[38] In the setting of liver transplantation, the use of anti-TB medications has been associated with increased risk of hepatotoxicity. Thus, it was generally recommended that LTBI therapy be commenced after transplantation, to avoid drug-related fulminant hepatitis whilst waiting for a donor organ.[3,35,37]

In patients with HIV, the timing of commencement of anti-retroviral therapy in relation to LTBI treatment was not specified by clinical practice guidelines. Unlike treatment for active TB, immune reconstitution related to LTBI treatment has not been documented.[9] Generally, it was recommended to initiate or continue anti-retroviral treatment concurrently with treatment for LTBI.[39,40]

Are these recommendations valid?

Overall, clinical practice guidelines recommended the use of isoniazid or rifamycin based regimes for the treatment of LTBI. The evidence for the recommendations, however, were from observational studies and limited randomized control trials, conducted in high income countries, except in the HIV setting. In particular, there was very little evidence about the exact time frame of delay before initiating prophylaxis. In addition, the harms associated with treatment were only presented in 17 (52%) guidelines,[1,3,9,10,18,19,21,24,29,31,33,35–37,39,40,42] and the discussion was often very

brief, with an inadequate consideration of these harms, overall limiting the ability to generalise recommendations in poorly resourced settings, or complex patients.

DISCUSSION

Clinical practice guidelines for screening and treatment of LTBI vary in scope and their recommendations for screening modalities, frequency of screening and population groups for screening. The use of both TST and IGRA for screening was considered as the most frequently recommended LTBI screening practice, because of improved test performance characteristics in high risk, immunosuppressed populations. Guidelines did not specify how to interpret a mismatch in results between TST and IGRA, but recommended treatment where either test was positive. For treatment, most recommendations suggested the use of isoniazid based therapies for LTBI, but there were discrepancies in the duration and timing of commencing treatment. Nine months of isoniazid-based therapy appeared to be the suggested therapy for LTBI, and most agreed that LTBI should be initiated prior to commencement of immunosuppressive therapies.

Whilst most guidelines conducted a comprehensive literature review, the evidence base supporting the recommendations was limited to observational studies without trial-based evidence to support routine LTBI screening and treatment for LTBI in immunosuppressed patients. The rigor of guideline development lacks robustness. Less than half of the guidelines provided grading of the evidence and recommendations. Details regarding the methods used for formulating the recommendations were not adequately described, lacking transparency in the methodology and did not consistently link the recommendations to the corresponding level of evidence, both for screening and treatment of LTBI and the benefit-harm-cost relationship.

In this review, we found that public and stakeholder consultation was rarely reported in the development of the guidelines. Only 22% underwent a peer review process and 11% underwent public consultation. Engaging experts may improve guidelines by allowing criticism and suggestions.[19] Expert clinicians were consulted in guideline development, and included clinicians such as rheumatologists, gastroenterologists, dermatologists, thoracic physicians, infectious diseases physicians, and clinicians involved in treating patients with HIV. Public consultations and patient participation can also improve guideline applicability.[47] Although, four guidelines used public consultation, none elaborated on how they have contributed to guideline development. Guideline applicability may be improved by active consumer involvement and engagement in the development, design, and implementation process.

Inconsistencies exist in the recommendations for screening modalities and frequencies for LTBI. Most screening practices recommended combinations of TST and IGRA. The TST evokes delayed hypersensitivity after intradermal application of a purified protein derivative.[33] The TST is a relatively sensitive but not specific test, in particular among high risk and immunosuppressed individuals.[33] Furthermore, vaccination with Bacillus Calmette-Guerin (BCG) may give a false positive response.[15,34] Testing with IGRA identifies adaptive immune response to TB-specific antigens which are not present in BCG strains, enabling greater specificity.[42,43] While guidelines preferred a combination of both screening strategies, the validity of either test, the cost implications or applicability was not considered. Most guidelines recommended treatment for LTBI, including those who were screened negative but of high clinical risk. While this is of relevance and importance to at-risk, immunosuppressed patients, interventions such as isoniazid and alternatives including rifampicin are not without adverse complications. No guidelines specified contraindications to treatment, except in the case of liver transplantation, where treatment was recommended to be delayed until after transplantation due to the increased risk of hepatotoxicity.[3,35,37] Treatment of LTBI also has other potential drug toxicities, including

neuropathy and drug-drug interactions, particularly for rifampicin-based regimens. Although many guidelines acknowledged these toxicities, the impact of over-treatment and the potential risk of adverse drug reactions were not quantified. Only one guideline specified the growing concern of increasing rates multi-drug resistant tuberculosis secondary to excess chemoprophylaxis.[23] Furthermore, barriers to screening and treatment are only considered in one guideline, which stated that there were no barriers in a public hospital.[41] This therefore, would not apply, in under resourced settings, or where public healthcare is not available.

In our systematic review, we used a reliable and validated method using the Appraisal of Guidelines for Research and Evaluation (AGREE) II, to assess guidelines for the screening for and treatment of LTBI. There also was good agreement between the two reviewers. We have summarised the variability in the literature pertaining to LTBI, allowing for a consolidated approach to recommendations for screening and management of LTBI. However, limitations of our review are that we have only included guidelines written in the English language. Therefore, applicability of our findings to other settings, particularly those in low-income countries are uncertain. Future guidelines should consider the specific health issues that are applicable to the population of interests, such as in low-income settings, and consider cost implications and barriers to screening and treatment. Very few guidelines discussed non-TNF based immunosuppression. This included two well-established medications such as methotrexate and cyclophosphamide, for the management of autoimmune disease, as well as newer biological treatments.[17] Only one guideline specified newer monoclonal agents[30] and one for patients on regular methotrexate therapy.[32] One of the key challenges for guideline developers is the translation and dissemination of these recommendations in clinical practice that may transform care and improve health of the target population. Currently, there are limited training initiatives in the implementation of these guidelines in different cultural and resource settings. Future research, through direct engagement with local stakeholders, clinicians

and patients, should therefore assess the features and processes that underpin success in research translation, and adapt these strategies in practice.

Overall, the current clinical guidelines reaffirm the importance of LTBI screening and prophylaxis. Although, there are some discrepancies in terms of screening modalities, recommendation for the treatment of LTBI was consistent across all guidelines. Quality of evidence and rigor of guideline development varied. There is therefore a need for the development of a comprehensive and high-quality guideline, with international, multidisciplinary and stakeholder involvement to consolidate current evidence. This is critical to support evidence-based and patient-centred practice to improve patient outcomes.

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Table 1: Characteristics of the studies

Guidelines	Funding body	Country	Population	Target users	Writers	Evidence base	Evidence level	Grading	Guideline review	Update
ARA 2010[1]	Professional society	Australia	Biological therapy	Rheumatologists	Rheumatologists	Guidelines	NS	NS	NS	NS
Aguado et al 2009[3]	Industry, Professional society	Spain	Organ transplant	Transplant physicians	Transplant infectious disease specialists	Literature, consensus, Experts	I-III[a]	A-E[b]	NS	NS
CDC 2016[9]	Office of AIDS Research,	USA	HIV	Clinicians	Multi-disciplinary	Literature, experts	I-III[c]	A-C[d]	Expert review, public consultation	6 months
WHO 2015[10]	Ministry of health Italy, WHO,	WHO	All	Tuberculosis physicians	Multi-disciplinary	Literature, experts	GRADE[e]	Strong/conditional[f]	Expert review, peer review	2020
Beglinger et al 2007[15]	NS	Switzerland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, Experts	NS	NS	NS	NS
Cantini et al 2015[16]	NS	Italy	Biological therapy	Clinicians	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Doherty 2008[17]	Professional body	United States of America	Psoriasis patients	NS	Dermatologists	Literature, experts	I-IV (Shekelle et al)[g]	NS	Medical Board	NS

Duarte et al 2012[18]	NS	Portugal	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	A-D[h]	NS	NS	NS
Fonseca et al 2008[19]	NS	Portugal	Biological therapy	Rheumatologists	Multi-disciplinary	Literature, guidelines	NS	NS	Expert, public consultation	NS
Hodkinson et al 2013[20]	Professional body	South Africa	Patients with rheumatoid arthritis	Clinicians	Rheumatologists	Literature, guideline, expert, stakeholder	NS	NS	Public/stakeholder consultation	2 years
Kavanagh et al 2008[21]	Professional body	Ireland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, guidelines, experts	NS	NS	NS	NS
Keith et al 2014[22]	Nil	USA	Immunosuppression	Dermatologists	Multi-disciplinary	Literature, guidelines	NS	NS	NS	NS
Koike et al 2007[23]	Professional body, Government	Japan	Anti-TNF alpha therapy	Rheumatologists	NS	Experts	NS	NS	NS	NS
Lichauco et al 2006[24]	NS	Philippine	Biological therapy	Physicians	Multi-disciplinary	Literature, guidelines	Level 1-4[i]	PHEX guidelines[j]	Expert peer review, public consultation	NS
Salmon et al 2002[25]	Not specified	France	Rheumatoid arthritis	Rheumatologists	Multi-disciplinary	NS	NS	NS	NS	NS
Mir Viladrich et al 2016[26]	NS	Spain	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	NS	A-C, I-III[k]	NS	NS

Mok et al 2011[27]	NS	Hong Kong	Rheumatoid arthritis	Rheumatologists	Rheumatologists	Guidelines	A-D[l]	NS	NS	As required
Nordgaard-Lassen et al 2012[28]	NS	Denmark	Biological therapy	Clinicians	Gastroenterologists	Literature	I-IV[m]	A-C[n]	NS	NS
BTS 2005[29]	NS	United Kingdom	Anti TNF-alpha therapy	Physician	Multi-disciplinary	Literature, experts	SIGN[o]	SIGN[p]	Professional membership consultation, peer review	2008
Smith et al 2017[30]	British Association of Dermatologists	United Kingdom	Psoriasis	Dermatologists	Multi-disciplinary	Literature	GRADE[e]	GRADE: Strong/weak/no[q]	Professional membership consultation, peer review	As required
Solovic et al 2010[31]	NS	Europe	Biological therapy	Clinicians	Multi-disciplinary	Literature	NS	A-D[r]	NS	NS
Carrascosa et al 2016[32]	Gebro Pharma	Spain	Methotrexate therapy	Dermatologists	Dermatologists	Literature, guidelines	SIGN[o]	SIGN[p]	NS	NS
Bumbacea et al 2012[33]	Professional society	Europe	All transplant	Transplant physicians	Transplant infectious disease specialists	Literature, guidelines	NS	A-D[r]	NS	NS
KDIGO 2009[34]	KDIGO, multiple sponsors	International	Kidney transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	A-D[s]	Level 1-2, not graded[t]	NS	NS
Meiji et al 2014[35]	NS	Spain	Solid organ transplant	Transplant physicians	Multi-disciplinary	Literature	Level A-D, I-IV[h]	NS	NS	NS

EBPG 2002[36]	NS	Europe	Renal transplant	Transplant physicians	NS	NS	A-D[u]	NS	NS	NS
Subramanian 2013[37]	American Society of Transplantation	USA	Solid organ transplant recipients	Transplant physicians	Transplant infectious disease physicians	Literature, experts	I-III[h]	NS	NS	NS
Tomblyn et al 2009[38]	Member societies	International/ USA/Canada	Stem cell transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	I-III[v]	A-E[w]	NS	NS
Pozniak et al 2011[39]	Nil	United Kingdom	HIV	Physicians	HIV physicians	Literature, Guidelines	I-III[x]	A-E[y]	NS	NS
SA 2010[40]	NS	South Africa	HIV	HIV treatment providers	NS	NS	NS	NS	NS	NS
Santin et al 2016[41]	SEPAR, SEIMC	Spain	All	Any clinician	Multi-disciplinary	Literature	GRADE[e]	GRADE: weak/strong	NS	5 years
Al Jahdali et al 2010[42]	Professional society	Saudi Arabia	All susceptible patients	Clinicians	Multi-disciplinary	Experts	NS	NS	NS	NS
ECDC 2011[43]	ECDC	Europe	Immunocompromised	National bodies	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Mazurek et al 2010[44]	CDC	USA	All	Public health officials, physicians, others	Multi-disciplinary	Literature, experts	NS	NS	NS	NS

Taylor et al (CDC 2005)[45]	Professional bodies	United States of America	All	Health care workers	Multi-disciplinary	Literature, experts	I-III[z]	A-C[aa]	NS	NS
CTC 2008[46]	Public Health Agency	Canada	Immunocompromised patients	NS	Multi-disciplinary	Literature, experts	NS	NS	NS	Periodic

ARA Australian Rheumatological Association, NS not specified, CDC centre for disease control, AIDS acquired immunodeficiency syndrome, USA United States of America, HIV human immunodeficiency virus, WHO World Health Organisation, GRADE Grading of Recommendations Assessment, Development and Evaluation, TNF tumor necrosis factor, PHEX Philippine Guidelines on Periodic Health Examination, BTS British Thoracic Society, SIGN Scottish Intercollegiate Guidelines Network, IBD inflammatory bowel disease, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, SEPAR – Spanish society of Respiratory Disease and Thoracic Surgery, SEIMC Spanish Society of Infectious Disease and Clinical Microbiology, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee

a. I evidence from at least 1 well-designed and performed trial, II evidence from at least one well designed non randomised control study (RCT), cohort or case control or noncontrolled experimental study with non conclusive results, III expert opinion based on clinical experience, descriptive studies, report from expert panel
b. A Solid evidence of clinical benefit, B solid or moderately solid evidence for efficacy, but clinical benefit is limited C insufficient evidence for efficacy D moderately solid evidence for lack of efficacy E strong evidence for lack of efficacy.
c. I: One or more RCT with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomised trials or observational cohort studies with long-term clinical outcomes III: Expert opinion
d. A: Strong recommendation for the statement, B: Moderate recommendation for the statement, C: Optional recommendation for the statement
e. Grading of Recommendations Assessment, Development and Evaluation (GRADE) High Further research is very unlikely to change our confidence in the estimate of effect. Moderate Further research is likely to have an important impact on our confidence in the effect. Low Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate. Very low Any estimate of effect is very uncertain.
f. 1. A strong recommendation is one for which the Panel was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This could be either in favour of or against an intervention. 2. A conditional recommendation is one for which the Panel concluded that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the Panel was not confident about these trade-offs. Reasons for not being confident included: absence of high-quality evidence (data to support the recommendation are scant); presence of imprecise estimates of benefits or harms (new evidence may result in changing the balance of risk to benefit); uncertainty or variation regarding how different individuals value the outcomes (only applicable to a specific group, population or setting); small benefits and benefits that may not be worth the costs (including the costs of implementing the recommendation)
g. IA evidence includes evidence from meta-analysis of randomised controlled trials; IB evidence includes evidence from at least one randomised controlled trial; IIA evi-dence includes evidence from at least one controlled study without randomization; IIB evidence includes evidence from at least one other type of quasi-experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV evidence includes evidence from expert committee reports or opinions or clin-ical experience of respected authorities, or both
h. Evidence level definitions not specified
i. Level 1 An RCT that demonstrates a statistically significant difference in at lest one major outcome or if the difference is not statistically significant, an RCT of adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results Level 2 An RCT that does not meet the Level 1 criteria Level 3 A non-randomised trial with concurrent controls selected by some systematic method Level 4 Before-after study or case series (at least 10 patients) with historical controls or controls drawn from other studies Level 5 Case series (at least 10 patients) without controls. Experts' opinion and clinical experience are included.
j. Level 1: Evaluation of evidence satisifies all of the following criteria: 1. effective treatment is documented in randomised controlled trials that observe effects on clinical outcomes 2. the condition being screened has local prevalence data 3. the screening test is validated and 4. the cost-effectiveness of the screening test, as well as treatment for the disease have been evaluated Level 2: Evaluation of evidence satisfies #1 but not all of #2, #3, and #4 Level 3: Evaluation of evidence satisfies #2, #3, or #4 but not #1 Level 4: Evaluation of evidence satisfies none of the criteria
k. Recommendations according to categories of strength: A Good evidence to support the recommendation B Moderate evidence to support the recommendation C poor evidence that does not enable the recommendation to be either supported or rejected. Recommendations according to the scientific quality. Grade I recommendation based on at least one well-designed, controlled, RCT Grade II recommendation based on at least one well-designed, but not RCT, cohort studies, multiple time-series studies or very evident results in uncontrolled trials Grade III recommendation based on the opinion of experts, descriptive studies or clinical experience

l. Category A At least one RCT or meta-analyses of RCTs, or reviews if these contain category A references Category B At least one controlled trial without randomization or at least one other type of experimental study, or extrapolated recommendations from RCTs or meta-analyses Category C Non-experimental descriptive studies, such as comparative studies, correlational studies, and case-control studies, which are extrapolated from RCTs, non-randomised controlled studies, or other experimental studies Category D Expert committee reports or opinions or clinical experience of respected authorities. Also includes all abstracts

m. I Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, II Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, III Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, IV Descriptive studies, expert opinions and narrative reviews

n. A Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, B Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, OR Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, C Descriptive studies, expert opinions and narrative reviews

o. 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. 12 Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias. 2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal. 2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal. 22 Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal. 3 Non-analytical studies (e.g. case reports, case series). 4 Expert opinion

p. A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results. B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+. C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+. D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

q. Strong recommendation for use of an intervention: Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator, Weak recommendation for the use of an intervention: Risks and benefits of the intervention are finely balanced; many patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected, No recommendation: Insufficient evidence to support any recommendation, Strong recommendation against the use of an intervention: Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the interventions

r. A Evidence is from end-points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made Category A requires substantial numbers of studies involving substantial numbers of participants, B Evidence is from end-points of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent, C Evidence is from outcomes of uncontrolled or non-randomised trials or from observational studies, D This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories The Panel consensus is based on clinical experience or knowledge that does not meet the criteria listed above

s. A high, B moderate, C low, D very low

t. Level 1: we recommend, level 2: we suggest, no grade: used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence

u. A: guidelines are supported by at least one large published RCT or more, B: guidelines are supported by large open trials or smaller trials with consensus results; C: guidelines are derived from small or controversial studies, or represent the opinion of the group of experts

v. I Evidence from at least one well-executed randomised, controlled trial; II Evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments; III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

w. A Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered; B Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. Should generally be offered. C Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences, (e.g., drug toxicity, drug interactions), or cost of the chemoprophylaxis or alternative approaches. Optional. D Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered

x. I. At least one properly randomised trial with clinical endpoints II. Clinical trials either not randomised or conducted in other populations III. Expert opinion

y. A Preferred; should generally be offered B Alternative; acceptable to offer C Offer when preferred or alternative regimens cannot be given D Should generally not be offered E Should never be offered

z. I evidence from at least one RCT, II evidence from 1) at least one well-designed clinical trial, without randomization, 2) cohort or case-controlled analytic studies 3) multiple times series 4) dramatic results from uncontrolled experiments III evidence from opinions of respected authoritis on the basis of cumulative public health experience, descriptive studies, or reports of expert committees

aa. A highly recommended in all circumstances, II recommended; implementation might be dependent on resource availability, C might be considered under exceptional circumstances

Table 2: Grade of recommendation

Guideline name	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)	Weighted Kappa Scores (Quadratic)	95% CI
ARA 2010[1]	75	31	10	67	25	0	0.74	0.56-0.92
Aguado et al 2009[3]	72	28	24	72	29	58	0.76	0.62-0.90
CDC 2016[9]	89	89	81	75	77	83	0.29	-0.14-0.71
WHO 2015[10]	97	94	88	89	92	88	0.67	0.27-1.00
Beglinger et al 2007[15]	75	42	23	67	25	0	0.72	0.54-0.91
Cantini et al 2015[16]	89	53	55	89	56	38	0.80	0.63-0.97
Doherty 2008[17]	92	44	75	86	71	58	0.55	0.19-0.91
Duarte et al 2012[18]	86	44	31	83	52	0	0.67	0.46-0.89
Fonseca et al 2008[19]	92	72	73	86	60	4	0.74	0.53-0.95
Hodkinson et al 2013[20]	83	83	56	75	71	25	0.00	-0.27-0.27
Kavanagh et al 2008[21]	64	33	29	67	15	0	0.61	0.39-0.82
Keith et al 2014[22]	83	42	45	50	19	42	0.61	0.27-0.92
Koike et al 2007[23]	78	33	28	56	10	29	0.41	0.08-0.75
Lichauco et al 2006[24]	89	69	67	78	65	0	0.64	0.27-1.00
Mir Viladrich et al 2016[26]	81	42	29	75	40	42	0.66	0.44-0.88
Mok et al 2011[27]	69	36	28	53	27	33	0.53	0.24-0.82

Nordgaard-Lassen et al 2012[28]	78	39	48	64	35	0	0.75	0.60-0.90
Salmon et al 2002[25]	72	42	13	64	0	0	0.76	0.55-0.97
BTS 2005[29]	92	69	91	89	71	63	0.32	-0.05-0.70
Smith et al 2017[30]	94	61	80	83	65	75	0.77	0.51-1.00
Solovic et al 2010[31]	69	33	35	81	44	38	0.66	0.41-0.92
Carrascosa et al 2016[32]	67	42	46	61	21	83	0.71	0.56-0.87
Bumbacea et al 2012[33]	69	44	43	81	40	67	0.48	0.13-0.84
KDIGO 2009[34]	100	78	67	75	65	92	0.21	-0.07-0.48
Meiji et al 2014[35]	64	25	28	72	25	38	0.67	0.43-0.89
EBPG 2002[36]	86	67	68	89	77	75	0.18	-0.05-0.41
Subramanian 2013[37]	75	42	42	78	54	42	0.31	-0.10-0.71
Tomblyn et al 2009[38]	81	58	43	69	35	17	0.44	0.15-0.74
Pozniak et al 2011[39]	81	42	38	64	56	0	0.73	0.51-0.95
SA 2010[40]	78	19	10	78	69	0	0.91	0.85-0.98
Santin et al 2016[42]	92	58	74	83	67	88	0.73	0.49-0.97
Al Jahdali et al 2010[42]	83	58	32	75	46	0	0.58	0.35-0.81
ECDC 2011[43]	72	31	33	69	29	17	0.41	0.14-0.67

Mazurek et al 2010[44]	78	72	71	72	60	8	0.57	0.33-0.81
Taylor et al (CDC 2005)[45]	75	44	28	58	38	0	0.26	0.09-0.47
CTC 2008[46]	83	50	52	69	40	46	0.29	0.01-0.58

Table 3: Summary of recommendations

Guidelines	Population	Screening process				Treatment method	Treatment duration	Timing before immunosuppression
		History	TST	IGRA	CXR			
ARA 2010[1]	Biological therapy		X	X	X	Isoniazid[a]	6-9 months	1-2 months
Aguado et al 2009[3]	Transplant recipients	X	X		X	Isoniazid	9 months	Before transplant
CDC 2016[9]	HIV patients		X	X		Isoniazid	9 months	NS
WHO 2015[10]	low-middle income countries		X	X		Isoniazid	6 months	NS
Beglinger et al 2007[15]	Biological therapy	X		X	X	Isoniazid OR rifampicin	NS	1 month
Cantini et al 2015[16]	Biological therapy	X	X	X		Isoniazid	9 months	1 month
Doherty 2008[17]	Psoriasis patients	X	X	X	X	Isoniazid	9 months	1-2 months or longer
Duarte et al 2012[18]	Biological therapy	X	X	X		Isoniazid	9 months	1-2 months
Fonseca et al 2008[19]	Biological therapy	X	X		X	Isoniazid	6-9 months	1 month
Hodkinson et al 2013[20]	Patients with rheumatoid arthritis	X	X	X	X	Isoniazid	9 months	1 month
Kavanagh et al 2008[21]	Biological therapy	X	X		X	Isoniazid	9 months	Pre-immunosuppression
Keith et al 2014[22]	Bullous dermatosis		X	X		NS	NS	NS

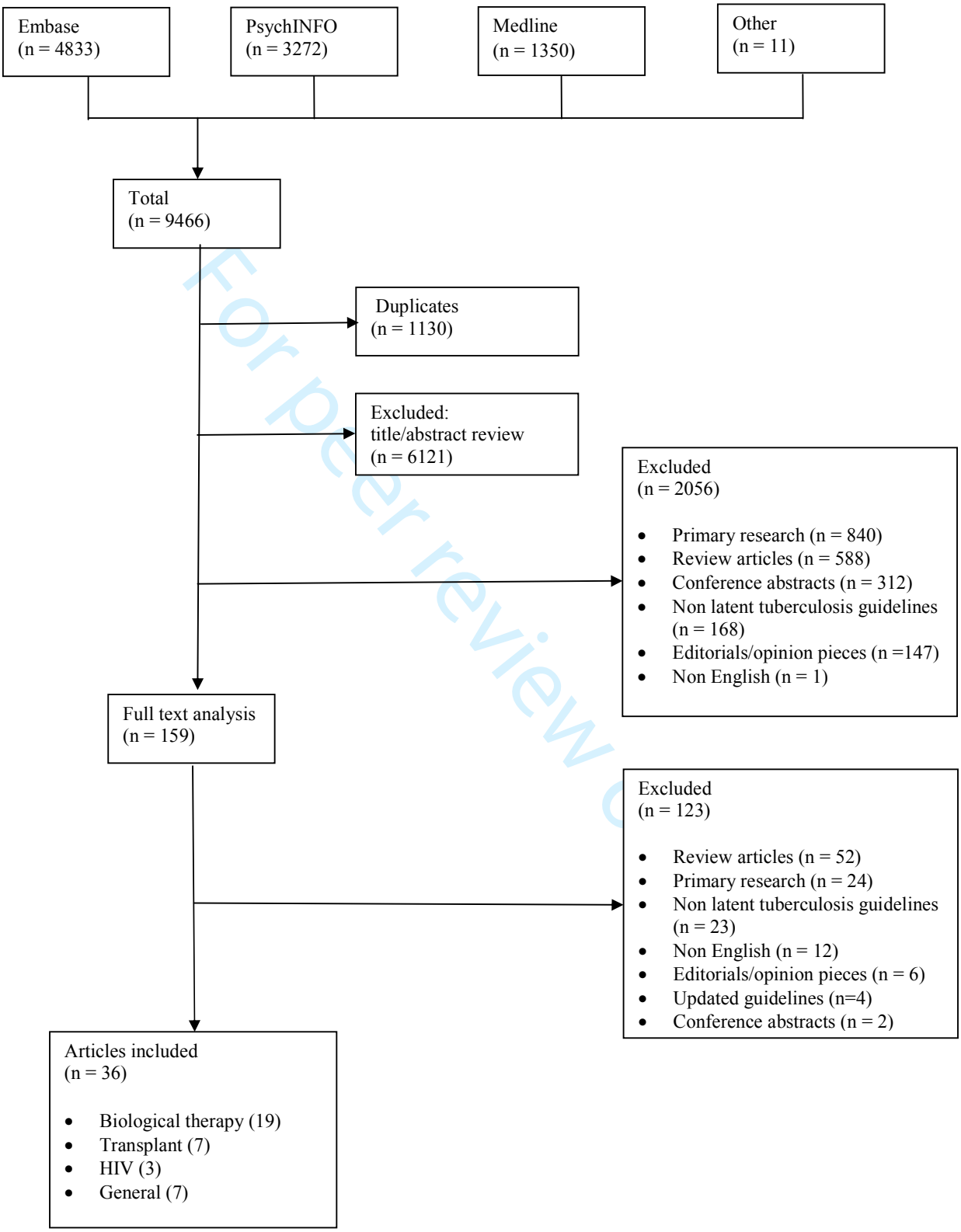
Koike et al 2007[23]	Biological therapy	X	X		X	Isoniazid	NS	NS
Lichauco et al 2006[24]	Biological therapy		X		X	Isoniazid	9 months	1 month
Salmon et al 2002[25]	Biological therapy		X		X	Rifampicin and pyrazinamide	2 months	3 weeks
Mir Viladrich et al 2016[26]	Biological therapy	X	X	X		Isoniazid	9 months	4 weeks
Mok et al 2011[27]	Biological therapy		X			Isoniazid	9 months	4 weeks
Nordgaard-Lassen et al 2012[28]	Biological therapy		X	X		Isoniazid	9 months	4 weeks
BTS 2005[29]	Biological therapy	X	X		X	Isoniazid	6 months	Concurrent
Smith et al 2009[30]	Biological therapy			X	X	Isoniazid OR Isoniazid and rifampicin	6 months OR 3 months	2 months
Solovic et al 2010[31]	Biological therapy	X	X	X	X	Isoniazid	9 months	4 weeks
Carrasoca et al 2016[32]	Methotrexate therapy		X	X	X	Isoniazid	NS	NS
Bumbacea et al 2012[33]	Transplant recipients		X	X		NS	NS	Before transplant
KDIGO 2009[34]	Renal transplant	X	X			Isoniazid	9 months	NS
Meiji et al 2014[35]	Transplant recipients		X	X		Isoniazid	9 months	NS
EBPG 2002[36]	Renal transplant recipients	X	X		X	Isoniazid	9 months	NS

Subramanian 2013[37]	Transplant recipients	X	X	X	X	Isoniazid	9 months	Before or after transplant
Tomblyn et al 2009[38]	HCT recipients	X	X	X		Isoniazid	9 months	NS
Pozniak et al 2011[39]	HIV patients		X	X		Isoniazid	6 months	NS
SA 2010[40]	HIV patients		X			Isoniazid	6 months	NS
Santin et al 2016[41]	HIV patients	X	X	X		NS	NS	NS
	Biological therapy	X	X	X		NS	NS	NS
	Transplant recipients	X	X	X		NS	NS	NS
Al Jahdali et al 2010[42]	Susceptible populations		X	X		Isoniazid	9 months	NS
ECDC 2011[43]	Immunocompromised		X	X		NS	NS	NS
Mazurek et al 2010[44]	Susceptible populations	X	X	X	X	NS	NS	NS
Taylor et al (CDC 2005)[45]	Susceptible populations	X	X			Isoniazid	NS	NS
CTC 2008[46]	Immunocompromised		X	X		NS	NS	NS

TST tuberculin skin test, IGRA interferon gamma release assay, CXR Chest X ray, ARA Australian Rheumatological Association, CDC centre for disease control, HIV human immunodeficiency virus, NS not specified, WHO World Health Organisation, BTS British Thoracic Society, IBD inflammatory bowel disease, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee

a. Where isoniazid is used, it is always provided concurrently with pyridoxine prophylaxis

Figure 1: Search Results



* Articles from references, other online databases

Appendix 1: Search strategy

1. TB
2. Tuberculosis
3. Mycobacteria
4. 1 OR 2 OR 3
5. Immunosuppression
6. Immunocompromised
7. Immunodeficient
8. Immunosuppressed
9. Immunosuppress
10. Steroids
11. Chemotherapy
12. TNF
13. Tumor necrosis factor
14. Transplant
15. HIV
16. Human immunodeficiency virus
17. Biologic
18. Monoclonal
19. Lupus
20. Autoimmune
21. Rheumatoid
22. Vasculitits
23. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. Guideline
25. Position
26. Consensus
27. Recommendations
28. Recommendation
29. Clinical practice
30. 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 4 AND 23 AND 30

Disclosures

There are no competing interests to report for this study

Ethics was not required for this work

There are no external sources of funding for this work

This manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted and all discrepancies have been explained

Author contributions:

Tasnim Hasan
- Database search, selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

Eric Au
- Selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

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- Preparation of manuscript and editing

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- Preparation of manuscript and editing

Germaine Wong
- Preparation of manuscript and editing

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Thematic analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	36
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12,15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	nil

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines

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Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines

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ABSTRACT

Objective: Immunosuppressed individuals are at a high risk of latent tuberculosis infection (LTBI) and clinical practice guidelines for the screening and management of LTBI in at risk patients have been developed. We assessed the scope, quality and consistency of clinical practice guidelines on screening for LTBI and the prevention of tuberculosis infection (TB) in high-risk patient populations.

Design: We conducted a systematic review of clinical practice guidelines. Methodological quality of these guidelines was assessed using the Appraisal of Guidelines for Research and Education (AGREE) II instrument. Textual synthesis was used to summarise and compare the recommendations.

Data sources: Electronic databases (MEDLINE, EMBASE, PsycINFO) and guideline registries were searched from inception to December 2017.

Results: Thirty-eight guidelines were included. Nineteen focused on patients receiving medical immunosuppression, seven on transplantation, three on patients with human immunodeficiency virus and nine were generalised across all at risk populations. Most guidelines (n = 32, 84%) used a systematic approach to identify and appraise the evidence. The methodological quality of the guidelines varied with the overall mean AGREE II scores ranging from 35% to 80%. Guidelines performed poorly in terms of editorial independence (average score 35%, range 0-92%), however most were robust in defining their scope and purpose (average score 80%, range 56-100%). Guidelines recommended either or both the tuberculin skin test and the interferon gamma release assay for screening. Treatment of LTBI with isoniazid was consistently recommended.

Conclusion: Clinical practice guidelines on LTBI vary in quality and scope. The recommendations for screening varied across guidelines, whilst recommendations for treatment were largely consistent. Improving the consistency and quality of guidelines may help to optimise the screening and management of LTBI for improved patient outcomes.

Strengths and Limitations

- This study systematically reviewed published clinical practice guidelines for screening and management of latent tuberculosis infection in immunosuppressed patients.
- We used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool, to assess the quality of the guidelines.
- We included 38 guidelines and 11 non-English guidelines were excluded, with only few guidelines published in low resource settings.

INTRODUCTION

Immunosuppression increases the risk of reactivation of prior infection with *Mycobacterium tuberculosis* leading to tuberculosis (TB) disease. In high-income countries, the baseline risk of reactivation of latent TB infection (LTBI) varies between 6 and 20 per 100,000 persons per year.[1,2] The magnitude of the risk of TB reactivation among those who are immunosuppressed varies depending on the types of immunosuppression. The excess risk is highest among solid organ transplant recipients, particularly in lung (15-fold higher compared to the general population)[3] and stem cell transplant recipients (6-10 fold higher),[4] followed by recipients of tumour necrosis factor (TNF) antagonists (5-7 fold higher).[5–8] The risk of TB reactivation in patients with human immunodeficiency virus (HIV) infection is 3–20 times higher than the general population[9,10] and causes up to 25% of deaths in these patients.[9]

Early detection of LTBI through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as treatment to prevent the development of active TB. Screening often involves the use of the commercially available tuberculin skin test (TST) and an interferon gamma release assay (IGRA). IGRAs include the QuantiFERON-TB Gold Plus (Cellestis Ltd, Australia) and the T-SPOT test (Oxford Immunotec, UK). However, there are potential drawbacks associated with screening. False negative results (2.8% in one setting[11]) with attendant false assurance may lead to late or missed diagnoses and delayed treatment. Conversely false positive results may lead to unnecessary and inappropriate investigations which may be harmful.[12] There is also a lack of a valid and accurate reference standard for diagnosing LTBI in immunosuppressed populations, rendering the true test performance characteristics of IGRA difficult to ascertain.

To advise health practitioners, clinical practice guidelines have provided evidence-based

recommendations that inform practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.[13] As such, guidelines on screening for LTBI and treatment in at-risk populations have been developed in various healthcare settings. However, it is unclear if these recommendations may be generalisable to others, or if there is variability. Therefore, this review aims to assess and compare the rationale, scope, quality and consistency of clinical practice guidelines and consensus statements for the screening of LTBI, as well as for treatment against LTBI in immunosuppressed individuals.

METHODS

Selection criteria

Evidence-based clinical practice guidelines and consensus statements on screening for LTBI and treatment for LTBI in immunosuppressed individuals published in English were eligible for inclusion. Patients who were medically immunocompromised (including chemotherapy, disease modifying agents and biological therapy), had received a solid organ or stem cell transplant, or HIV positive were included. Draft or unpublished guidelines, conference or discussion papers, opinions, and guidelines and consensus statements replaced by updated and/or revised recommendations were excluded.

Literature search

We searched MEDLINE, Embase, and PsycINFO from database inception to December 2017. Medical Subject Heading (MeSH) terms and text words for "tuberculosis", "immunosuppressed", and "immunocompromised" were combined with terms relating to clinical practice guidelines and consensus statements (Appendix 1). Clinical guideline registries and reference lists were searched for additional clinical practice guidelines. Titles and abstracts were reviewed by two authors (TH and EA), and those which did not meet the inclusion criteria were excluded. Full text versions of potentially relevant guidelines or consensus statements were examined for eligibility.

Appraisal of guidelines and consensus statements

The methodological quality was assessed independently by TH and EA, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[14] AGREE II is an internationally validated, rigorously developed 23-item tool used to evaluate independent domains of guideline development including: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Each item was rated on a seven-point scale ranging from strongly disagree (score 1) to strongly agree (score 7). The domain score was obtained by summing all scores of the individual items per domain and then standardising the total as a percentage of the maximum possible score for that domain:

$$\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$$

The minimum possible domain score would be the number of questions multiplied by the number of appraisers, multiplied by 1 (strongly disagree). The maximum possible domain score is the number of questions multiplied by the number of appraisers, multiplied by 7 (strongly agree). The 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. An overall weighted kappa was also calculated across all guidelines.

Textual synthesis

All text from each guideline were entered into the HyperRESEARCH software (ResearchWare Inc. 2011, version 3.0.3, Randolph MA) for storing, coding and searching textual data. Data was

categorised by subheadings based on immunosuppression modality and by screening and treatment methods. Subsequently, we conducted a textual descriptive synthesis to analyse the content, consistency and evidence base of the recommendations.

Patient and public involvement:

There was no patient or public involvement in this study

RESULTS

Characteristics of clinical practice guidelines

We included 38 guidelines (Figure 1) published from 2002 to 2017. These guidelines focused on medical immunosuppression (19 guidelines),[1,15–32] solid organ and stem cell transplantation (seven guidelines),[3,33–38] and in HIV settings (three guidelines).[9,39-40] Nine were general guidelines which were not specific to a particular patient group and covered the detection of LTBI and its management.[10,41–46] These guidelines were published across 16 different countries from regions including North America, Western Europe, Asia, Australia and South Africa. A summary of the guideline characteristics is provided in Table 1.

Of the guidelines that discussed medical immunosuppression, nine provided recommendations for treatment across various medical specialties including dermatology, rheumatology, gastroenterology and respiratory medicine.[15,16,18,21,24,26,28,29,31] Four were specific to patients with rheumatoid arthritis,[20,23,25,27] of which one focused only on patients receiving infliximab,[23] whilst two guidelines were specific to patients with psoriasis.[18,30] One guideline focused on patients with rheumatological or gastroenterological disease.[15] There were specific guidelines addressing inflammatory joint disease,[19] rheumatological disease,[1] and autoimmune bullous diseases.[22] One guideline discussed patients at risk due to methotrexate therapy.[32] Of the transplantation guidelines, two guidelines were

for kidney transplantation,[34,36] one for stem cell transplantation,[38] one for both solid organ and stem cell transplantation[33] and three for all forms of solid organ transplantation.[3,35,37]

Three guidelines addressed LTBI in patients with HIV.[9,39,40] There were nine other guidelines which discussed screening in all at risk populations.[10,41–48] Six of these also included discussion on patients with HIV[41–45,47] and four were IGRA specific guidelines, although, these guidelines also used TST as part of their screening strategies.[41,43,44,46] Three guidelines were developed in countries with a high prevalence of TB (South Africa and Philippines).[20,24,40]

Across the guidelines, the methods for literature review were not always specified. Literature review was conducted in 32 guidelines (84%),[1,3,9,10,15–22,24,26–35,37–39,41–46,48] of which 12 based their recommendations on a combination of the literature review and expert consensus.[3,9,10,15–18,20,21,26,29,34,37,43–46] Two guidelines were based on expert consensus alone.[23,42] Twenty guidelines graded the level of evidence.[3,9,10,17,18,24,27–29,30,32,34–39,42,46,48] Furthermore, 17 guidelines graded the strength of their recommendations.[3,9,10,24,26,28,29–34,38,39,41,45,48] Where evidence was graded, it was often of low quality. Only nine (24%) guidelines were peer reviewed,[9,10,17,19,20,24,29,30,48] with five (13%) made available for public consultation prior to publication.[9,19,20,24,48] Only one guideline included a formal cost-effectiveness analysis[48] 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.

Methodological quality

Table 2 summarises the AGREE domain scores of each guideline. The mean AGREE score (and range) for all guidelines was 55% (0% – 100%). In terms of scope and purpose, on average 80% (56% – 100%) of criteria were met for all guidelines. The average scores for stakeholder

involvement was 51% (11% – 97%), for rigor of development 47% (10% – 93%), clarity and presentation 74% (50% – 92%), applicability 47% (0% – 92%), and editorial independence 35% (0% – 92%). The overall domain mean score was 55% (35% – 80%).

Weighted Kappa scores (κ) to assess interrater agreement ranged from a score between poor to very good, with the majority being moderate (0·41 – 0·60) to very good (0·81 – 1·00). The overall weighted score was 0·65 (95% CI 0·60 – 0·69), with good concordance between reviewers. The AGREE scores did not improve with later guidelines and over time.

Textual synthesis

A summary of the guidelines and the recommendations are provided in table 3. Most guidelines recommended screening in all immunosuppressed patients, and treatment if there was clinical evidence of LTBI.

Screening for latent TB infection

Populations of interest

Most clinical practice guidelines recommended screening for LTBI in patients commencing immunosuppression or were highly likely to commence immunosuppression, and patients immunosuppressed due to concurrent illness, including patients with HIV and/or undergoing solid organ and bone-marrow transplantation.[3,15–20,22,24,26,33,35,37,39,47,48] Although, medical immunosuppression was mostly biological therapy, two guidelines specified recommendations for patients who have received medical immunosuppression such as methotrexate,[17,32] cyclosporine and T cell blocking agents for the management of autoimmune disease.[17] A third guideline which considered all immunosuppressed patients also specified the use of non-biological therapies.[47]

Screening modalities and frequencies

A combination of TST and/or IGRA testing, chest X-ray (CXR), detailed background history (including previous exposure to other individuals with TB) and risk factor assessment (travel or migration from endemic areas) was the most frequent recommendation for LTBI screening in immunosuppressed individuals.[1,17,18,21,23,24,26,29–32,47] The recommended choice of screening modalities and their frequency were reliant upon test availability and costs. The TST is widely available and economical.[10]

In guidelines pertaining to medical immunosuppression, the recommendations for screening varied considerably between the use of TST and IGRA. Concurrent testing with both TST and IGRA was supported in six guidelines,[16,18,20,22,26,32] however, three recommended the use of IGRA alone.[15,28,30] Seven guidelines supported TST screening alone, but these recommendations were published prior to 2011.[17,19,21,23,24,27,29] Two other guidelines recommended the use of either the TST or IGRA.[1,22] In addition, two other guidelines recommended IGRA for BCG vaccinated individuals.[16,17]

In patients who require long-term maintenance medical immunosuppression, repeat testing at yearly intervals using IGRA was recommended by three guidelines,[17,28,31] but two advocated against this, as the benefits of frequent IGRA screening was questionable.[16,27] IGRA was recommended by one guideline in the presence of (any) skin disease due to difficulties in inoculating the TST in many of these cases.[18]

For transplant recipients, those with HIV and other immunosuppressed individuals, most guidelines acknowledged the added value of including TST and IGRA in the screening algorithm.[9,10,33,35,37-39,41-46,48]. Two guidelines specified the preference for IGRA over TST as the standard triage screening tool for LTBI, because of the high false positive rates associated with TST,[34] particularly among those who had been vaccinated with Bacillus Calmette-Guerin (BCG).[47] However, across all

guidelines, among BCG vaccinated individuals, two guideline recommended a two-step strategy for screening LTBI.[31,42] TST was often considered as the triage test. If negative, IGRA was recommended as the second test to confirm the diagnosis. This has also been recommended to increase case detection in five other guidelines.[17,20,30,35,46]

Costs were also considered as a key factor in determining the frequency and modality of screening in immunosuppressed individuals. The World Health Organisation (WHO) have suggested IGRA and/or TST may be used in high and upper-middle income countries.[10] Given the anticipated costs of IGRA, and the general acceptance of TST by clinicians and patients, TST was preferred in low income countries, despite the lower test accuracies of TST.[10] In the high prevalence settings of South Africa and the Philippines, there was no reliable testing method: a combined TST and IGRA approach was recommended in one guideline,[20] treatment of all HIV patients without screening was recommended in another,[40] and TST alone in one guideline.[24]

Defining screen positive and negative results

Criteria for TST positivity varied across guidelines. Some recommended a TST-induced reaction of at least 5 mm diameter in all populations, to allow for the treatment of patients in high risk settings.[17,19-21,26,35–37,40,48] Other recommendations for the threshold diameter ranged from 6mm to 20mm.[18–20,21,23,24,26,27,31,33] Where the TST result was initially negative, two guidelines recommended repeat testing.[23,45] In all guidelines, an individual was deemed to be at risk for LTBI if either the TST or IGRA was positive.

Are these recommendations valid?

There is a body of evidence assessing the test performance characteristics of TST and IGRA in the general population. However, these recommendations were sourced largely from observational studies performed in middle to high income countries and did not include immunosuppressed

patients from low-resource settings, and with low certainty of the evidence. Given the low test sensitivity of TST in immunosuppressed patients, some guidelines suggested a two-stage screening; first using TST and then IGRA to increase the detection rates of LTBI. [17,20,30,35,46] Among those who are immunosuppressed and had previously been vaccinated with BCG, IGRA generally performs better than TST. IGRA test sensitivity and specificity varies between 67-75% and 93-99% respectively.[33,43] However, given the concerns of spectrum bias, most guidelines suggested caution in the interpretation of test results among immunosuppressed hosts.

Treatment for latent TB infection

Population of interests

Either a positive TST or IGRA was considered sufficient evidence to warrant further evaluation. Prior to LTBI treatment, exclusion of active TB was recommended.[1,9,15,17,18,25,26,29,30,32,35,42–44,47,48] Once active TB was excluded, LTBI treatment was recommended. Treatment for LTBI was also indicated for those who were BCG vaccinated, because BCG status may indicate time spent in an area with a high prevalence of LTBI.[34] Furthermore, in South Africa, where there is a high prevalence of TB, treatment for LTBI was recommended in all patients after exclusion of active TB in the setting of HIV.[40] Also, most clinical practice guidelines recommended LTBI treatment where clinical suspicion was high, regardless of the IGRA and TST test findings.[1,3,15,19,20,24,26,28,29,33,35–38]

Intervention and duration

Recommendations for the treatment of LTBI were largely similar across guidelines, regardless of the mode of immunosuppression. In most guidelines, isoniazid 300 mg daily with pyridoxine was recommended for a duration of nine months.[3,9,16–21,24–27,29,31,33–39,42] Six months of isoniazid therapy was considered less efficacious,[18] but was recommended in one guideline.[48] Three guidelines

suggested a flexible treatment regimen of 6-9 months of the combined therapies.[19,30,47] Four guidelines did not specify duration.[15,23,32,45]

Rifamycin-based therapy (10 mg/kg/day) either alone or for three[10] or four[1,3,9,10,15–18,24,26,27,31,33,35-39,42] months was the second most frequently reported treatment strategy among patients who tested positive for LTBI. This was thought to be useful when isoniazid was contraindicated or not tolerated,[27] with one guideline describing the option as cheaper, but with more drug-drug interactions.[18] Rifampicin plus isoniazid for three[1,10,15–19,25,26,29–31,39] or four months[10,24] was also an option. Rifampicin plus isoniazid for three months was stipulated as a primary alternative therapy to isoniazid in two guidelines.[30,48] Other options included rifabutin for four months,[9,42] or three months of weekly rifapentine and isoniazid.[9,10] Finally, rifampicin and pyrazinamide for a shorter two-month regimen was considered as an option in eight guidelines,[3,25,29,35–39] with most being in the transplantation setting. The shorter duration of treatment was considered advantageous for those maintained on the transplant waiting list.[3,35–38] However, a biological therapy based guideline advised against this option due to the increased risk of hepatotoxicity.[24]

In the transplantation and HIV settings, some guidelines specified avoidance of rifamycins, given the potential drug-drug interactions with calcineurin inhibitors and protease inhibitors.[3,35,37] However, therapeutic drug monitoring may mitigate against the potential for such interactions.[34] Several other non-rifamycin based alternatives were recommended and included ethambutol with levofloxacin or moxifloxacin for six months,[3,37] 12 weeks of rifapentine and isoniazid, and six months of isoniazid with ethambutol.[24]

Close monitoring with monthly liver function tests and for peripheral neuropathy was recommended whilst on treatment for all patients.[3,9,10,17,18,26,31,35,37,40,47] Co-administration of Vitamin B6 (pyridoxine) was suggested universally, to reduce the risk of peripheral neuropathy associated with

isoniazid. If there were treatment interruptions for more than two months, one guideline recommended clinical and radiological reassessment for TB.[42]

Timing of preventive therapy

In patients who are medically immunosuppressed, most guidelines recommended delaying medical therapy for one month after commencement of LTBI treatment where possible, to reduce the risk of TB reactivation.[15–18,20,24–28] Alternative waiting periods varied between three weeks[25,47] to two months.[30] One guideline preferred a prolonged delay, but did not provide a time frame.[21] However, if the underlying disease was severe, earlier institution of immunosuppressive agents was accepted[17,29] once active TB was excluded.[28]

In transplant setting, patients with LTBI are recommended to commence treatment on the waiting list where possible, with treatment ideally completed prior to transplantation.[3,33,35,37,38] However, treatment interruption peri-transplantation, with recommencement and completion of the treatment course once patients were clinically stable, may also be considered.[33,35,37] LTBI treatment should not delay transplantation.[38] In the setting of liver transplantation, the use of anti-TB medications has been associated with increased risk of hepatotoxicity. Thus, it was generally recommended that LTBI therapy be commenced after transplantation, to avoid drug-related fulminant hepatitis whilst waiting for a donor organ.[3,35,37]

In patients with HIV, the timing of commencement of anti-retroviral therapy in relation to LTBI treatment was not specified by clinical practice guidelines. Unlike treatment for active TB, immune reconstitution related to LTBI treatment has not been documented.[9] Generally, it was recommended to initiate or continue anti-retroviral treatment concurrently with treatment for LTBI.[39,40]

Are these recommendations valid?

Overall, clinical practice guidelines recommended the use of isoniazid or rifamycin based regimes for the treatment of LTBI. The evidence for recommendations was largely sourced from observational studies in high income countries. There was very little evidence about the exact time frame of delay before initiating treatment. In addition, the harms associated with treatment were only presented in 18 (47%) guidelines,[1,3,9,10,18,19,21,24,29,31,33,35–37,39,40,42,47] thus limiting the ability to generalise recommendations to low-income countries and in complex patients.

DISCUSSION

Clinical practice guidelines for screening and treatment of LTBI vary in scope and their recommendations for screening modalities, frequency of screening and the target populations of interest. The two-stage screening approach of TST and IGRA was most frequently recommended because of improved test performance characteristics in high risk, immunosuppressed populations. Guidelines did not specify how to interpret a mismatch in results between TST and IGRA, but recommended treatment where either test was positive. For treatment, most recommendations suggested the use of isoniazid-based therapies for LTBI, but there were discrepancies in the duration and timing of commencing treatment. Nine months of isoniazid-based therapy appeared to be the preferred therapy for LTBI, and most agreed that treatment of LTBI should be initiated prior to commencement of immunosuppressive therapies.

Whilst most guidelines conducted a comprehensive literature review, the evidence base supporting the recommendations was limited to observational studies without trial-based evidence to support routine screening and treatment for LTBI in immunosuppressed patients. The rigor of guideline development lacks robustness. Less than half of the guidelines provided grading of the evidence and recommendations. Details regarding the methods used for formulating the recommendations were not adequately described, lacking transparency in the methodology and did not consistently link the

recommendations to the corresponding level of evidence, both for screening and treatment of LTBI and the benefit-harm-cost relationship.

In this review, we found that public and stakeholder consultation was rarely reported in the development of the guidelines. Only 22% underwent a peer review process and 11% underwent public consultation. Engaging experts may improve guidelines by allowing criticism and suggestions.[19] Expert clinicians were consulted in guideline development, and included clinicians such as rheumatologists, gastroenterologists, dermatologists, thoracic physicians, infectious diseases physicians and clinicians involved in treating patients with HIV. Public consultations and patient participation can also improve guideline applicability.[49] Although four guidelines used public consultation, none elaborated on how they have contributed to guideline development. Guideline applicability may be improved by active consumer involvement and engagement in the development, design, and implementation process.

Inconsistencies exist in the recommendations for screening modalities and frequencies for LTBI. The TST evokes delayed hypersensitivity after intradermal application of a purified protein derivative.[33] TST generally performs poorly in immunosuppressed patients, with reported estimates of 89% and 71% for test sensitivity and specificity, respectively.[43] The lower test specificity may be due to the cross-reactivity with prior BCG vaccination[15,34] and infections with non-TB mycobacteria. Testing with IGRA identifies adaptive immune response to TB-specific antigens which are not present in BCG strains, enabling greater specificity.[42,43] Test sensitivity of TST and IGRA is uncertain or may be reduced among immunosuppressed hosts because of anergy.[33] 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.[50] Statistical methods such as latent class and Bayesian mixture analyses may overcome this limitation.[51,52]

Most guidelines recommended treatment for LTBI, including those who were screened negative but of high clinical risk. While this is of relevance and importance to at-risk immunosuppressed patients, interventions such as isoniazid and alternatives including rifampicin are not without adverse complications. No guidelines specified contraindications to treatment, except in the case of liver transplantation, where treatment was recommended to be delayed until after transplantation due to the increased risk of hepatotoxicity.[3,35,37] Treatment of LTBI also has other potential drug toxicities, including neuropathy and drug-drug interactions, particularly for rifampicin-based regimens. Although many guidelines acknowledged these toxicities, the impact of over-treatment and the potential risk of adverse drug reactions were not quantified. Only two guidelines specified the growing concern of increasing rates of multi-drug resistant tuberculosis secondary to excess exposure to drug therapy.[23,47] Furthermore, barriers to screening and treatment are only considered in one guideline, which stated that there were no barriers in a public hospital.[41] This therefore, would not apply in under-resourced settings, or where public healthcare is not available.

In our systematic review, we used a reliable and validated method using the Appraisal of Guidelines for Research and Evaluation (AGREE) II to assess guidelines for the screening for and treatment of

LTBI. There was good agreement between the two reviewers. We have summarised the variability in the literature pertaining to LTBI, allowing for a consolidated approach to recommendations for screening and management of LTBI. However, limitations of our review are that we have only included guidelines written in the English language. Therefore, applicability of our findings to other settings, particularly those in low-income countries are uncertain. Future guidelines should consider the specific health issues that are applicable to the population of interest, such as in low-income settings, and consider cost implications and barriers to screening and treatment. Very few guidelines discussed non-TNF based immunosuppression. This included two well-established medications – methotrexate and cyclophosphamide – for the management of autoimmune disease, as well as newer biological treatments.[17] Only one guideline included newer monoclonal agents[30] and one for patients on regular methotrexate therapy.[32] One of the key challenges for guideline developers is the translation and dissemination of these recommendations in clinical practice, which may transform care and improve health of the target population. Currently, there are limited training initiatives in the implementation of these guidelines in different cultural and resource settings. Future research, through direct engagement with local stakeholders, clinicians and patients should therefore assess the features and processes that underpin success in research translation, and adapt these strategies in practice.

Overall, the current clinical guidelines reaffirm the importance of LTBI screening and treatment. Although, there are some discrepancies in terms of screening modalities, recommendation for the treatment of LTBI was consistent across all guidelines. 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 guidelines development and patient-centred practice to improve patient outcomes.

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Table 1: Characteristics of the studies

Guidelines	Funding body	Country	Population	Target users	Writers	Evidence base	Evidence level	Grading	Guideline review	Update
ARA 2010[1]	Professional society	Australia	Biological therapy	Rheumatologists	Rheumatologists	Guidelines	NS	NS	NS	NS
Aguado et al 2009[3]	Industry, Professional society	Spain	Organ transplant	Transplant physicians	Transplant infectious disease specialists	Literature, consensus, Experts	I-III[a]	A-E[b]	NS	NS
CDC 2016[9]	Office of AIDS Research,	USA	HIV	Clinicians	Multi-disciplinary	Literature, experts	I-III[c]	A-C[d]	Expert review, public consultation	6 months
WHO 2015[10]	Ministry of health Italy, WHO,	WHO	All	Tuberculosis physicians	Multi-disciplinary	Literature, experts	GRADE[e]	Strong/conditional[f]	Expert review, peer review	2020
Beglinger et al 2007[15]	NS	Switzerland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, Experts	NS	NS	NS	NS
Cantini et al 2015[16]	NS	Italy	Biological therapy	Clinicians	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Doherty 2008[17]	Professional body	United States of America	Psoriasis patients	NS	Dermatologists	Literature, experts	I-IV (Shekelle et al)[g]	NS	Medical Board	NS

Duarte et al 2012[18]	NS	Portugal	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	A-D[h]	NS	NS	NS
Fonseca et al 2008[19]	NS	Portugal	Biological therapy	Rheumatologists	Multi-disciplinary	Literature, guidelines	NS	NS	Expert, public consultation	NS
Hodkinson et al 2013[20]	Professional body	South Africa	Patients with rheumatoid arthritis	Clinicians	Rheumatologists	Literature, guideline, expert, stakeholder	NS	NS	Public/stakeholder consultation	2 years
Kavanagh et al 2008[21]	Professional body	Ireland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, guidelines, experts	NS	NS	NS	NS
Keith et al 2014[22]	Nil	USA	Immunosuppression	Dermatologists	Multi-disciplinary	Literature, guidelines	NS	NS	NS	NS
Koike et al 2007[23]	Professional body, Government	Japan	Anti-TNF alpha therapy	Rheumatologists	NS	Experts	NS	NS	NS	NS
Lichauco et al 2006[24]	NS	Philippine	Biological therapy	Physicians	Multi-disciplinary	Literature, guidelines	Level 1-4[i]	PHEX guidelines[j]	Expert peer review, public consultation	NS
Salmon et al 2002[25]	Not specified	France	Rheumatoid arthritis	Rheumatologists	Multi-disciplinary	NS	NS	NS	NS	NS
Mir Viladrich et al 2016[26]	NS	Spain	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	NS	A-C, I-III[k]	NS	NS

Mok et al 2011[27]	NS	Hong Kong	Rheumatoid arthritis	Rheumatologists	Rheumatologists	Guidelines	A-D[l]	NS	NS	As required
Nordgaard-Lassen et al 2012[28]	NS	Denmark	Biological therapy	Clinicians	Gastroenterologists	Literature	I-IV[m]	A-C[n]	NS	NS
BTS 2005[29]	NS	United Kingdom	Anti TNF-alpha therapy	Physician	Multi-disciplinary	Literature, experts	SIGN[o]	SIGN[p]	Professional membership consultation, peer review	2008
Smith et al 2017[30]	British Association of Dermatologists	United Kingdom	Psoriasis	Dermatologists	Multi-disciplinary	Literature	GRADE[e]	GRADE: Strong/weak/no[q]	Professional membership consultation, peer review	As required
Solovic et al 2010[31]	NS	Europe	Biological therapy	Clinicians	Multi-disciplinary	Literature	NS	A-D[r]	NS	NS
Carrascosa et al 2016[32]	Gebro Pharma	Spain	Methotrexate therapy	Dermatologists	Dermatologists	Literature, guidelines	SIGN[o]	SIGN[p]	NS	NS
Bumbacea et al 2012[33]	Professional society	Europe	All transplant	Transplant physicians	Transplant infectious disease specialists	Literature, guidelines	NS	A-D[r]	NS	NS
KDIGO 2009[34]	KDIGO, multiple sponsors	International	Kidney transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	A-D[s]	Level 1-2, not graded[t]	NS	NS
Meiji et al 2014[35]	NS	Spain	Solid organ transplant	Transplant physicians	Multi-disciplinary	Literature	Level A-D, I-IV[h]	NS	NS	NS

EBPG 2002[36]	NS	Europe	Renal transplant	Transplant physicians	NS	NS	A-D[u]	NS	NS	NS
Subramanian 2013[37]	American Society of Transplantation	USA	Solid organ transplant recipients	Transplant physicians	Transplant infectious disease physicians	Literature, experts	I-III[h]	NS	NS	NS
Tomblyn et al 2009[38]	Member societies	International/ USA/Canada	Stem cell transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	I-III[v]	A-E[w]	NS	NS
Pozniak et al 2011[39]	Nil	United Kingdom	HIV	Physicians	HIV physicians	Literature, Guidelines	I-III[x]	A-E[y]	NS	NS
SA 2010[40]	NS	South Africa	HIV	HIV treatment providers	NS	NS	NS	NS	NS	NS
Santin et al 2016[41]	SEPAR, SEIMC	Spain	All	Clinicians	Multi-disciplinary	Literature	GRADE[e]	GRADE: weak/strong	NS	5 years
Al Jahdali et al 2010[42]	Professional society	Saudi Arabia	All susceptible patients	Clinicians	Multi-disciplinary	Experts	NS	NS	NS	NS
ECDC 2011[43]	ECDC	Europe	Immunocompromised	National bodies	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Mazurek et al 2010[44]	CDC	USA	All	Public health officials, physicians, others	Multi-disciplinary	Literature, experts	NS	NS	NS	NS

Taylor et al (CDC 2005)[45]	Professional bodies	United States of America	All	Health care workers	Multi-disciplinary	Literature, experts	I-III[z]	A-C[aa]	NS	NS
CTC 2008[46]	Public Health Agency	Canada	Immunocom promised patients	NS	Multi-disciplinary	Literature, experts	NS	NS	NS	Periodic
Japanese Society for Tuberculosis 2014[47]	NS	Japan	All susceptible populations	Clinicians	NS	NS	NS	NS	NS	NS
NICE 2016[48]	NCCCC	United Kingdom	All susceptible populations	All health care workers and public	Multi-disciplinary	Literature review	GRADE[e]	Offer/ do not offer/ consider[bb]	Stakeholders, peer review	As required

ARA Australian Rheumatological Association, NS not specified, CDC centre for disease control, AIDS acquired immunodeficiency syndrome, USA United States of America, HIV human immunodeficiency virus, WHO World Health Organisation, GRADE Grading of Recommendations Assessment, Development and Evaluation, TNF tumor necrosis factor, PHEX Philippine Guidelines on Periodic Health Examination, BTS British Thoracic Society, SIGN Scottish Intercollegiate Guidelines Network, IBD inflammatory bowel disease, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, SEPAR – Spanish society of Respiratory Disease and Thoracic Surgery, SEIMC Spanish Society of Infectious Disease and Clinical Microbiology, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence, NCCCC The National Collaborating Centre for Chronic Conditions

a. I evidence from at least 1 well-designed and performed trial, II evidence from at least one well designed non randomised control study (RCT), cohort or case control or noncontrolled experimental study with non conclusive results, III expert opinion based on clinical experience, descriptive studies, report from expert panel
b. A Solid evidence of clinical benefit, B solid or moderately solid evidence for efficacy, but clinical benefit is limited C insufficient evidence for efficacy D moderately solid evidence for lack of efficacy E strong evidence for lack of efficacy.
c. I: One or more RCT with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomised trials or observational cohort studies with long-term clinical outcomes III: Expert opinion
d. A: Strong recommendation for the statement, B: Moderate recommendation for the statement, C: Optional recommendation for the statement
e. Grading of Recommendations Assessment, Development and Evaluation (GRADE) High Further research is very unlikely to change our confidence in the estimate of effect. Moderate Further research is likely to have an important impact on our confidence in the effect. Low Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate. Very low Any estimate of effect is very uncertain.
f. 1. A strong recommendation is one for which the Panel was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This could be either in favour of or against an intervention. 2. A conditional recommendation is one for which the Panel concluded that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the Panel was not confident about these trade-offs. Reasons for not being confident included: absence of high-quality evidence (data to support the recommendation are scant); presence of imprecise estimates of benefits or harms (new evidence may result in changing the balance of risk to benefit); uncertainty or variation regarding how different individuals value the outcomes (only applicable to a specific group, population or setting); small benefits and benefits that may not be worth the costs (including the costs of implementing the recommendation)
g. IA evidence includes evidence from meta-analysis of randomised controlled trials; IB evidence includes evidence from at least one randomised controlled trial; IIA evidence includes evidence from at least one controlled study without randomization; IIB evidence includes evidence from at least one other type of quasi-experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
h. Evidence level definitions not specified
i. Level 1 An RCT that demonstrates a statistically significant difference in at lest one major outcome or if the difference is not statistically significant, an RCT of adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results Level 2 An RCT that does not meet the Level 1 criteria Level 3 A non-randomised trial with concurrent controls selected by some systematic method

Level 4 Before-after study or case series (at least 10 patients) with historical controls or controls drawn from other studies Level 5 Case series (at least 10 patients) without controls. Experts' opinion and clinical experience are included.

j. Level 1: Evaluation of evidence satisfies all of the following criteria: 1. effective treatment is documented in randomised controlled trials that observe effects on clinical outcomes 2. the condition being screened has local prevalence data 3. the screening test is validated and 4. the cost-effectiveness of the screening test, as well as treatment for the disease have been evaluated Level 2: Evaluation of evidence satisfies #1 but not all of #2, #3, and #4 Level 3: Evaluation of evidence satisfies #2, #3, or #4 but not #1 Level 4: Evaluation of evidence satisfies none of the criteria

k. Recommendations according to categories of strength: A Good evidence to support the recommendation B Moderate evidence to support the recommendation C poor evidence that does not enable the recommendation to be either supported or rejected. Recommendations according to the scientific quality. Grade I recommendation based on at least one well-designed, controlled, RCT Grade II recommendation based on at least one well-designed, but not RCT, cohort studies, multiple time-series studies or very evident results in uncontrolled trials Grade III recommendation based on the opinion of experts, descriptive studies or clinical experience

l. Category A At least one RCT or meta-analyses of RCTs, or reviews if these contain category A references Category B At least one controlled trial without randomization or at least one other type of experimental study, or extrapolated recommendations from RCTs or meta-analyses Category C Non-experimental descriptive studies, such as comparative studies, correlational studies, and case-control studies, which are extrapolated from RCTs, non-randomised controlled studies, or other experimental studies Category D Expert committee reports or opinions or clinical experience of respected authorities. Also includes all abstracts

m. I Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, II Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, III Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, IV Descriptive studies, expert opinions and narrative reviews

n. A Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, B Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, OR Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, C Descriptive studies, expert opinions and narrative reviews

o. 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. 12 Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias. 2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal. 2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal. 22 Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal. 3 Non-analytical studies (e.g. case reports, case series). 4 Expert opinion

p. A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results. B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+. C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+. D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

q. Strong recommendation for use of an intervention: Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator, Weak recommendation for the use of an intervention: Risks and benefits of the intervention are finely balanced; many patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected, No recommendation: Insufficient evidence to support any recommendation, Strong recommendation against the use of an intervention: Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the interventions

r. A Evidence is from end-points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made Category A requires substantial numbers of studies involving substantial numbers of participants, B Evidence is from end-points of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent, C Evidence is from outcomes of uncontrolled or non-randomised trials or from observational studies, D This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories The Panel consensus is based on clinical experience or knowledge that does not meet the criteria listed above

s. A high, B moderate, C low, D very low

t. Level 1: we recommend, level 2: we suggest, no grade: used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence

u. A: guidelines are supported by at least one large published RCT or more, B: guidelines are supported by large open trials or smaller trials with consensus results; C: guidelines are derived from small or controversial studies, or represent the opinion of the group of experts

v. I Evidence from at least one well-executed randomised, controlled trial; II Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments; III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

w. A Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered; B Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. Should generally be offered. C Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences, (e.g., drug toxicity, drug interactions), or cost of the chemoprophylaxis or alternative approaches. Optional. D Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered

x. I. At least one properly randomised trial with clinical endpoints II. Clinical trials either not randomised or conducted in other populations III. Expert opinion

y. A Preferred; should generally be offered B Alternative; acceptable to offer C Offer when preferred or alternative regimens cannot be given D Should generally not be offered E Should never be offered

z. I evidence from at least one RCT, II evidence from 1) at least one well-designed clinical trial, without randomization, 2) cohort or case-controlled analytic studies 3) multiple times series 4) dramatic results from uncontrolled experiments III evidence from opinions of respected authorities on the basis of cumulative public health experience, descriptive studies, or reports of expert committees

aa. A highly recommended in all circumstances, II recommended; implementation might be dependent on resource availability, C might be considered under exceptional circumstances

bb. A Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal. B Level 2++, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 1++ or 1+. C Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 2++. D Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus *or* extrapolated from level 2 clinical evidence supplemented with health economic modelling. D (GPP) A good practice point (GPP) is a recommendation based on the experience of the GDG.

Table 2: Grade of recommendation

Guideline name	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)	Weighted Kappa Scores (Quadratic)	95% CI
ARA 2010[1]	75	31	10	67	25	0	0.74	0.56-0.92
Aguado et al 2009[3]	72	28	24	72	29	58	0.76	0.62-0.90
CDC 2016[9]	89	89	81	75	77	83	0.29	-0.14-0.71
WHO 2015[10]	97	94	88	89	92	88	0.67	0.27-1.00
Beglinger et al 2007[15]	75	42	23	67	25	0	0.72	0.54-0.91
Cantini et al 2015[16]	89	53	55	89	56	38	0.80	0.63-0.97
Doherty 2008[17]	92	44	75	86	71	58	0.55	0.19-0.91
Duarte et al 2012[18]	86	44	31	83	52	0	0.67	0.46-0.89
Fonseca et al 2008[19]	92	72	73	86	60	4	0.74	0.53-0.95
Hodkinson et al 2013[20]	83	83	56	75	71	25	0.00	-0.27-0.27
Kavanagh et al 2008[21]	64	33	29	67	15	0	0.61	0.39-0.82
Keith et al 2014[22]	83	42	45	50	19	42	0.61	0.27-0.92
Koike et al 2007[23]	78	33	28	56	10	29	0.41	0.08-0.75
Lichauco et al 2006[24]	89	69	67	78	65	0	0.64	0.27-1.00
Mir Viladrich et al 2016[26]	81	42	29	75	40	42	0.66	0.44-0.88
Mok et al 2011[27]	69	36	28	53	27	33	0.53	0.24-0.82

Nordgaard-Lassen et al 2012[28]	78	39	48	64	35	0	0.75	0.60-0.90
Salmon et al 2002[25]	72	42	13	64	0	0	0.76	0.55-0.97
BTS 2005[29]	92	69	91	89	71	63	0.32	-0.05-0.70
Smith et al 2017[30]	94	61	80	83	65	75	0.77	0.51-1.00
Solovic et al 2010[31]	69	33	35	81	44	38	0.66	0.41-0.92
Carrascosa et al 2016[32]	67	42	46	61	21	83	0.71	0.56-0.87
Bumbacea et al 2012[33]	69	44	43	81	40	67	0.48	0.13-0.84
KDIGO 2009[34]	100	78	67	75	65	92	0.21	-0.07-0.48
Meiji et al 2014[35]	64	25	28	72	25	38	0.67	0.43-0.89
EBPG 2002[36]	86	67	68	89	77	75	0.18	-0.05-0.41
Subramanian 2013[37]	75	42	42	78	54	42	0.31	-0.10-0.71
Tomblyn et al 2009[38]	81	58	43	69	35	17	0.44	0.15-0.74
Pozniak et al 2011[39]	81	42	38	64	56	0	0.73	0.51-0.95
SA 2010[40]	78	19	10	78	69	0	0.91	0.85-0.98
Santin et al 2016[42]	92	58	74	83	67	88	0.73	0.49-0.97
Al Jahdali et al 2010[42]	83	58	32	75	46	0	0.58	0.35-0.81
ECDC 2011[43]	72	31	33	69	29	17	0.41	0.14-0.67

Mazurek et al 2010[44]	78	72	71	72	60	8	0.57	0.33-0.81
Taylor et al (CDC 2005)[45]	75	44	28	58	38	0	0.26	0.09-0.47
CTC 2008[46]	83	50	52	69	40	46	0.29	0.01-0.58
Japanese Society for Tuberculosis 2014[47]	56	11	26	67	60	0	0.67	0.52-0.82
NICE 2016[48]	100	97	93	92	69	83	0.52	0.09-0.96

ARA Australian Rheumatological Association, CDC centre for disease control, WHO World Health Organisation, BTS British Thoracic Society, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence

Table 3: Summary of recommendations

Guidelines	Population	Screening process				Treatment method	Treatment duration	Timing before immunosuppression
		History	TST	IGRA	CXR			
ARA 2010[1]	Biological therapy		X	X	X	Isoniazid[a]	6-9 months	1-2 months
Aguado et al 2009[3]	Transplant recipients	X	X		X	Isoniazid	9 months	Before transplant
CDC 2016[9]	HIV patients		X	X		Isoniazid	9 months	NS
WHO 2015[10]	low-middle income countries		X	X		Isoniazid	6 months	NS
Beglinger et al 2007[15]	Biological therapy	X		X	X	Isoniazid OR rifampicin	NS	1 month
Cantini et al 2015[16]	Biological therapy	X	X	X		Isoniazid	9 months	1 month
Doherty 2008[17]	Psoriasis patients	X	X		X	Isoniazid	9 months	1-2 months or longer
Duarte et al 2012[18]	Biological therapy	X	X	X		Isoniazid	9 months	1-2 months
Fonseca et al 2008[19]	Biological therapy	X	X		X	Isoniazid	6-9 months	1 month
Hodkinson et al 2013[20]	Patients with rheumatoid arthritis	X	X	X	X	Isoniazid	9 months	1 month
Kavanagh et al 2008[21]	Biological therapy	X	X		X	Isoniazid	9 months	Pre-immunosuppression
Keith et al 2014[22]	Bullous dermatosis		X	X		NS	NS	NS

Koike et al 2007[23]	Biological therapy	X	X		X	Isoniazid	NS	NS
Lichauco et al 2006[24]	Biological therapy		X		X	Isoniazid	9 months	1 month
Salmon et al 2002[25]	Biological therapy		X		X	Rifampicin and pyrazinamide	2 months	3 weeks
Mir Viladrich et al 2016[26]	Biological therapy	X	X	X		Isoniazid	9 months	4 weeks
Mok et al 2011[27]	Biological therapy		X			Isoniazid	9 months	4 weeks
Nordgaard-Lassen et al 2012[28]	Biological therapy			X		Isoniazid	9 months	4 weeks
BTS 2005[29]	Biological therapy	X	X		X	Isoniazid	6 months	Concurrent
Smith et al 2009[30]	Biological therapy			X	X	Isoniazid OR Isoniazid and rifampicin	6 months OR 3 months	2 months
Solovic et al 2010[31]	Biological therapy	X	X	X	X	Isoniazid	9 months	4 weeks
Carrasoca et al 2016[32]	Methotrexate therapy		X	X	X	Isoniazid	NS	NS
Bumbacea et al 2012[33]	Transplant recipients		X	X		NS	NS	Before transplant
KDIGO 2009[34]	Renal transplant	X	X			Isoniazid	9 months	NS
Meiji et al 2014[35]	Transplant recipients		X	X		Isoniazid	9 months	NS
EBPG 2002[36]	Renal transplant recipients	X	X		X	Isoniazid	9 months	NS

Subramanian 2013[37]	Transplant recipients	X	X	X	X	Isoniazid	9 months	Before or after transplant
Tomblyn et al 2009[38]	HCT recipients	X	X	X		Isoniazid	9 months	NS
Pozniak et al 2011[39]	HIV patients		X	X		Isoniazid	6 months	NS
SA 2010[40]	HIV patients		X			Isoniazid	6 months	NS
Santin et al 2016[41]	HIV patients	X	X	X		NS	NS	NS
	Biological therapy	X	X	X		NS	NS	NS
	Transplant recipients	X	X	X		NS	NS	NS
Al Jahdali et al 2010[42]	Susceptible populations		X	X		Isoniazid	9 months	NS
ECDC 2011[43]	Immunocompromised		X	X		NS	NS	NS
Mazurek et al 2010[44]	Susceptible populations	X	X	X	X	NS	NS	NS
Taylor et al (CDC 2005)[45]	Susceptible populations	X	X	X		Isoniazid	NS	NS
CTC 2008[46]	Immunocompromised		X	X		NS	NS	NS
Japanese Society for Tuberculosis 2014[47]	Susceptible populations	X		X	X	Isoniazid	6-9 months	3 weeks before immunosuppression NS for transplant
NICE 2016[48]	Susceptible populations	X	X	X		Isoniazid OR Isoniazid and	6 months OR 3 months	NS

	rifampicin

TST tuberculin skin test, IGRA interferon gamma release assay, CXR Chest X ray, ARA Australian Rheumatological Association, CDC centre for disease control, HIV human immunodeficiency virus, NS not specified, WHO World Health Organisation, BTS British Thoracic Society, IBD inflammatory bowel disease, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence

a. Where isoniazid is used, it is always provided concurrently with pyridoxine prophylaxis

Figure 1: Database search strategy
The medical databases EMBASE, PsychINFO and Medline were searched for articles relevant to tuberculosis in an immunosuppressed setting, using the search strategy described in Appendix 1. A total of 9467 articles were found and compiled into the EndNote software (Clarivate Analytics 2017, version X7), of which 1130 articles were duplicate articles. From the remaining articles, 6121 articles were excluded by abstract review, primarily because they were irrelevant. A further 2056 articles were removed during a second review of titles and abstracts. 160 articles were reviewed in full of which 122 were excluded as they did not fulfil guideline or relevance criteria. 38 articles were included in our final review

Disclosures

Ethics was not required for this work

There are no external sources of funding for this work

This manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted and all discrepancies have been explained

Data sharing – data are available on request

Conflicts of interest
SC reports grants from MSD Australia, outside the submitted work

Author contributions:
Tasnim Hasan
- Database search, selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

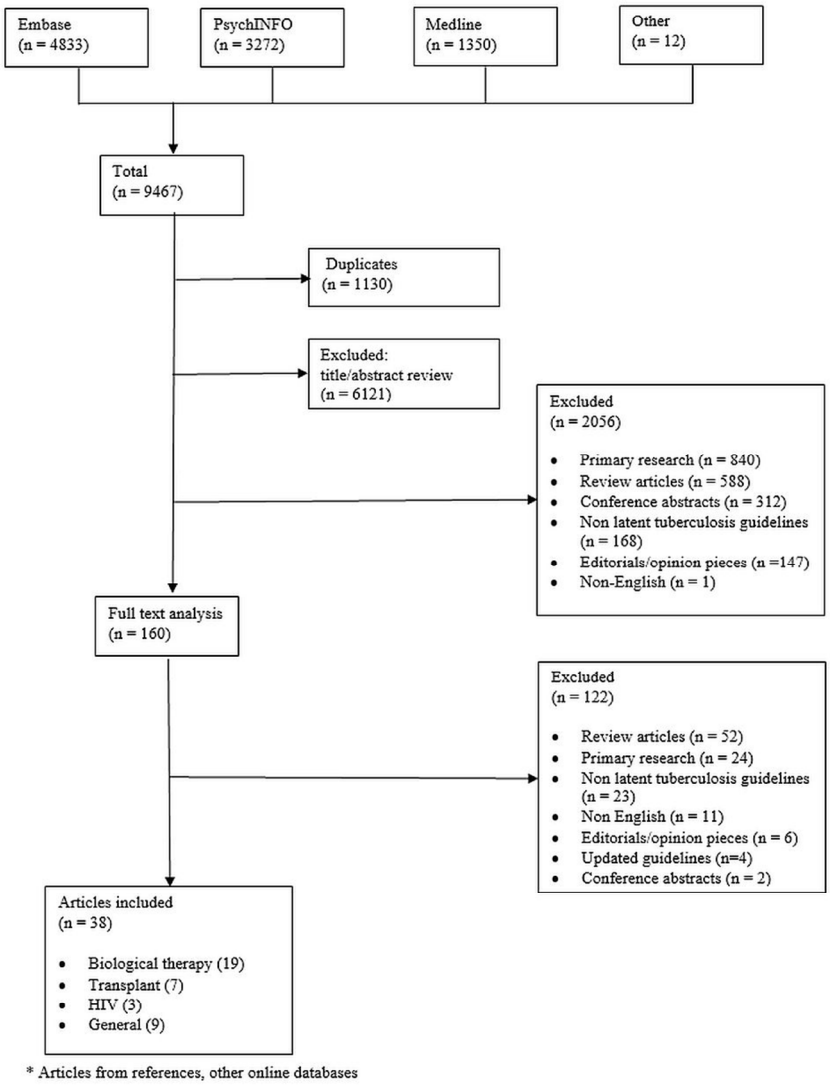
Eric Au
- Selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

Sharon Chen
- Preparation of manuscript and editing

Allison Tong
- Preparation of manuscript and editing

Germaine Wong
- Preparation of manuscript and editing

Figure 1: Database search strategy



Database search strategy

90x115mm (300 x 300 DPI)

Appendix 1: Search strategy

1. TB
2. Tuberculosis
3. Mycobacteria
4. 1 OR 2 OR 3
5. Immunosuppression
6. Immunocompromised
7. Immunodeficient
8. Immunosuppressed
9. Immunosuppress
10. Steroids
11. Chemotherapy
12. TNF
13. Tumor necrosis factor
14. Transplant
15. HIV
16. Human immunodeficiency virus
17. Biologic
18. Monoclonal
19. Lupus
20. Autoimmune
21. Rheumatoid
22. Vasculitits
23. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. Guideline
25. Position
26. Consensus
27. Recommendations
28. Recommendation
29. Clinical practice
30. 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 4 AND 23 AND 30

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Thematic analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	36
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12,15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	nil

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines

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Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines

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Keywords: latent tuberculosis, immunosuppression, screening

Word count: 3995

ABSTRACT

Objective: Immunosuppressed individuals are at a high risk of latent tuberculosis infection (LTBI) and clinical practice guidelines for the screening and management of LTBI in at risk patients have been developed. We assessed the scope, quality and consistency of clinical practice guidelines on screening for LTBI and the prevention of tuberculosis infection (TB) in high-risk patient populations.

Design: We conducted a systematic review of clinical practice guidelines. Methodological quality of these guidelines was assessed using the Appraisal of Guidelines for Research and Education (AGREE) II instrument. Textual synthesis was used to summarise and compare the recommendations.

Data sources: Electronic databases (MEDLINE, EMBASE, PsycINFO) and guideline registries were searched from inception to December 2017.

Results: Thirty-eight guidelines were included. Nineteen focused on patients receiving medical immunosuppression, seven on transplantation, three on patients with human immunodeficiency virus and nine were generalised across all at risk populations. Most guidelines (n = 32, 84%) used a systematic approach to identify and appraise the evidence. The methodological quality of the guidelines varied with the overall mean AGREE II scores ranging from 35% to 80%. Guidelines performed poorly in terms of editorial independence (average score 35%, range 0-92%), however most were robust in defining their scope and purpose (average score 80%, range 56-100%). Guidelines recommended either or both the tuberculin skin test and the interferon gamma release assay for screening. Treatment of LTBI with isoniazid was consistently recommended.

Conclusion: Clinical practice guidelines on LTBI vary in quality and scope. The recommendations for screening varied across guidelines, whilst recommendations for treatment were largely consistent. Improving the consistency and quality of guidelines may help to optimise the screening and management of LTBI for improved patient outcomes.

Strengths and Limitations

- This study systematically reviewed published clinical practice guidelines for screening and management of latent tuberculosis infection in immunosuppressed patients.
- We used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, an internationally validated tool, to assess the quality of the guidelines.
- We included 38 guidelines and 11 non-English guidelines were excluded, with only few guidelines published in low resource settings.

INTRODUCTION

Immunosuppression increases the risk of reactivation of prior infection with *Mycobacterium tuberculosis* leading to tuberculosis (TB) disease. In high-income countries, the baseline risk of reactivation of latent TB infection (LTBI) varies between 6 and 20 per 100,000 persons per year.[1,2] The magnitude of the risk of TB reactivation among those who are immunosuppressed varies depending on the types of immunosuppression. The excess risk is highest among solid organ transplant recipients, particularly in lung (15-fold higher compared to the general population)[3] and stem cell transplant recipients (6-10 fold higher),[4] followed by recipients of tumour necrosis factor (TNF) antagonists (5-7 fold higher).[5–8] The risk of TB reactivation in patients with human immunodeficiency virus (HIV) infection is 3–20 times higher than the general population[9,10] and causes up to 25% of deaths in these patients.[9]

Early detection of LTBI through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as treatment to prevent the development of active TB. Screening often involves the use of the commercially available tuberculin skin test (TST) and an interferon gamma release assay (IGRA). IGRAs include the QuantiFERON-TB Gold Plus (Cellestis Ltd, Australia) and the T-SPOT test (Oxford Immunotec, UK). However, there are potential drawbacks associated with screening. False negative results (2.8% in one setting[11]) with attendant false assurance may lead to late or missed diagnoses and delayed treatment. Conversely false positive results may lead to unnecessary and inappropriate investigations which may be harmful.[12] There is also a lack of a valid and accurate reference standard for diagnosing LTBI in immunosuppressed populations, rendering the true test performance characteristics of IGRA difficult to ascertain.

To advise health practitioners, clinical practice guidelines have provided evidence-based

recommendations that inform practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.[13] As such, guidelines on screening for LTBI and treatment in at-risk populations have been developed in various healthcare settings. However, it is unclear if these recommendations may be generalisable to others, or if there is variability. Therefore, this review aims to assess and compare the rationale, scope, quality and consistency of clinical practice guidelines and consensus statements for the screening of LTBI, as well as for treatment against LTBI in immunosuppressed individuals.

METHODS

Selection criteria

Evidence-based clinical practice guidelines and consensus statements on screening for LTBI and treatment for LTBI in immunosuppressed individuals published in English were eligible for inclusion. Patients who were medically immunocompromised (including chemotherapy, disease modifying agents and biological therapy), had received a solid organ or stem cell transplant, or HIV positive were included. Draft or unpublished guidelines, conference or discussion papers, opinions, and guidelines and consensus statements replaced by updated and/or revised recommendations were excluded.

Literature search

We searched MEDLINE, Embase, and PsycINFO from database inception to December 2017. Medical Subject Heading (MeSH) terms and text words for "tuberculosis", "immunosuppressed", and "immunocompromised" were combined with terms relating to clinical practice guidelines and consensus statements (Appendix 1). Clinical guideline registries and reference lists were searched for additional clinical practice guidelines. Titles and abstracts were reviewed by two authors (TH and EA), and those which did not meet the inclusion criteria were excluded. Full text versions of potentially relevant guidelines or consensus statements were examined for eligibility.

Appraisal of guidelines and consensus statements

The methodological quality was assessed independently by TH and EA, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[14] AGREE II is an internationally validated, rigorously developed 23-item tool used to evaluate independent domains of guideline development including: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Each item was rated on a seven-point scale ranging from strongly disagree (score 1) to strongly agree (score 7). The domain score was obtained by summing all scores of the individual items per domain and then standardising the total as a percentage of the maximum possible score for that domain:

$$\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$$

The minimum possible domain score would be the number of questions multiplied by the number of appraisers, multiplied by 1 (strongly disagree). The maximum possible domain score is the number of questions multiplied by the number of appraisers, multiplied by 7 (strongly agree). The 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. An overall weighted kappa was also calculated across all guidelines.

Textual synthesis

All text from each guideline were entered into the HyperRESEARCH software (ResearchWare Inc. 2011, version 3.0.3, Randolph MA) for storing, coding and searching textual data. Data was

categorised by subheadings based on immunosuppression modality and by screening and treatment methods. Subsequently, we conducted a textual descriptive synthesis to analyse the content, consistency and evidence base of the recommendations.

Patient and public involvement:

There was no patient or public involvement in this study

RESULTS

Characteristics of clinical practice guidelines

We included 38 guidelines (Figure 1) published from 2002 to 2017. These guidelines focused on medical immunosuppression (19 guidelines),[1,15–32] solid organ and stem cell transplantation (seven guidelines),[3,33–38] and in HIV settings (three guidelines).[9,39-40] Nine were general guidelines which were not specific to a particular patient group and covered the detection of LTBI and its management.[10,41–46] These guidelines were published across 16 different countries from regions including North America, Western Europe, Asia, Australia and South Africa. A summary of the guideline characteristics is provided in Table 1.

Of the guidelines that discussed medical immunosuppression, nine provided recommendations for treatment across various medical specialties including dermatology, rheumatology, gastroenterology and respiratory medicine.[15,16,18,21,24,26,28,29,31] Four were specific to patients with rheumatoid arthritis,[20,23,25,27] of which one focused only on patients receiving infliximab,[23] whilst two guidelines were specific to patients with psoriasis.[18,30] One guideline focused on patients with rheumatological or gastroenterological disease.[15] There were specific guidelines addressing inflammatory joint disease,[19] rheumatological disease,[1] and autoimmune bullous diseases.[22] One guideline discussed patients at risk due to methotrexate therapy.[32] Of the transplantation guidelines, two guidelines were

for kidney transplantation,[34,36] one for stem cell transplantation,[38] one for both solid organ and stem cell transplantation[33] and three for all forms of solid organ transplantation.[3,35,37]

Three guidelines addressed LTBI in patients with HIV.[9,39,40] There were nine other guidelines which discussed screening in all at risk populations.[10,41–48] Six of these also included discussion on patients with HIV[41–45,47] and four were IGRA specific guidelines, although, these guidelines also used TST as part of their screening strategies.[41,43,44,46] Three guidelines were developed in countries with a high prevalence of TB (South Africa and Philippines).[20,24,40]

Across the guidelines, the methods for literature review were not always specified. Literature review was conducted in 32 guidelines (84%),[1,3,9,10,15–22,24,26–35,37–39,41–46,48] of which 12 based their recommendations on a combination of the literature review and expert consensus.[3,9,10,15–18,20,21,26,29,34,37,43–46] Two guidelines were based on expert consensus alone.[23,42] Twenty guidelines graded the level of evidence.[3,9,10,17,18,24,27–29,30,32,34–39,42,46,48] Furthermore, 17 guidelines graded the strength of their recommendations.[3,9,10,24,26,28,29–34,38,39,41,45,48] Where evidence was graded, it was often of low quality. Only nine (24%) guidelines were peer reviewed,[9,10,17,19,20,24,29,30,48] with five (13%) made available for public consultation prior to publication.[9,19,20,24,48] Only one guideline included a formal cost-effectiveness analysis[48] 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.

Methodological quality

Table 2 summarises the AGREE domain scores of each guideline. The mean AGREE score (and range) for all guidelines was 55% (0% – 100%). In terms of scope and purpose, on average 80% (56% – 100%) of criteria were met for all guidelines. The average scores for stakeholder

involvement was 51% (11% – 97%), for rigor of development 47% (10% – 93%), clarity and presentation 74% (50% – 92%), applicability 47% (0% – 92%), and editorial independence 35% (0% – 92%). The overall domain mean score was 55% (35% – 80%).

Weighted Kappa scores (κ) to assess interrater agreement ranged from a score between poor to very good, with the majority being moderate (0·41 – 0·60) to very good (0·81 – 1·00). The overall weighted score was 0·65 (95% CI 0·60 – 0·69), with good concordance between reviewers. The AGREE scores did not improve with later guidelines and over time.

Textual synthesis

A summary of the guidelines and the recommendations are provided in table 3. Most guidelines recommended screening in all immunosuppressed patients, and treatment if there was clinical evidence of LTBI.

Screening for latent TB infection

Populations of interest

Most clinical practice guidelines recommended screening for LTBI in patients commencing immunosuppression or were highly likely to commence immunosuppression, and patients immunosuppressed due to concurrent illness, including patients with HIV and/or undergoing solid organ and bone-marrow transplantation.[3,15–20,22,24,26,33,35,37,39,47,48] Although, medical immunosuppression was mostly biological therapy, two guidelines specified recommendations for patients who have received medical immunosuppression such as methotrexate,[17,32] cyclosporine and T cell blocking agents for the management of autoimmune disease.[17] A third guideline which considered all immunosuppressed patients also specified the use of non-biological therapies.[47]

Screening modalities and frequencies

A combination of TST and/or IGRA testing, chest X-ray (CXR), detailed background history (including previous exposure to other individuals with TB) and risk factor assessment (travel or migration from endemic areas) was the most frequent recommendation for LTBI screening in immunosuppressed individuals.[1,17,18,21,23,24,26,29–32,47] The recommended choice of screening modalities and their frequency were reliant upon test availability and costs. The TST is widely available and economical.[10]

In guidelines pertaining to medical immunosuppression, the recommendations for screening varied considerably between the use of TST and IGRA. Concurrent testing with both TST and IGRA was supported in six guidelines,[16,18,20,22,26,32] however, three recommended the use of IGRA alone.[15,28,30] Seven guidelines supported TST screening alone, but these recommendations were published prior to 2011.[17,19,21,23,24,27,29] Two other guidelines recommended the use of either the TST or IGRA.[1,22] In addition, two other guidelines recommended IGRA for BCG vaccinated individuals.[16,17]

In patients who require long-term maintenance medical immunosuppression, repeat testing at yearly intervals using IGRA was recommended by three guidelines,[17,28,31] but two advocated against this, as the benefits of frequent IGRA screening was questionable.[16,27] IGRA was recommended by one guideline in the presence of (any) skin disease due to difficulties in inoculating the TST in many of these cases.[18]

For transplant recipients, those with HIV and other immunosuppressed individuals, most guidelines acknowledged the added value of including TST and IGRA in the screening algorithm.[9,10,33,35,37-39,41-46,48]. Two guidelines specified the preference for IGRA over TST as the standard triage screening tool for LTBI, because of the high false positive rates associated with TST,[34] particularly among those who had been vaccinated with Bacillus Calmette-Guerin (BCG).[47] However, across all

guidelines, among BCG vaccinated individuals, two guideline recommended a two-step strategy for screening LTBI.[31,42] TST was often considered as the triage test. If negative, IGRA was recommended as the second test to confirm the diagnosis. This has also been recommended to increase case detection in five other guidelines.[17,20,30,35,46]

Costs were also considered as a key factor in determining the frequency and modality of screening in immunosuppressed individuals. The World Health Organisation (WHO) have suggested IGRA and/or TST may be used in high and upper-middle income countries.[10] Given the anticipated costs of IGRA, and the general acceptance of TST by clinicians and patients, TST was preferred in low income countries, despite the lower test accuracies of TST.[10] In the high prevalence settings of South Africa and the Philippines, there was no reliable testing method: a combined TST and IGRA approach was recommended in one guideline,[20] treatment of all HIV patients without screening was recommended in another,[40] and TST alone in one guideline.[24]

Defining screen positive and negative results

Criteria for TST positivity varied across guidelines. Some recommended a TST-induced reaction of at least 5 mm diameter in all populations, to allow for the treatment of patients in high risk settings.[17,19-21,26,35–37,40,48] Other recommendations for the threshold diameter ranged from 6mm to 20mm.[18–20,21,23,24,26,27,31,33] Where the TST result was initially negative, two guidelines recommended repeat testing.[23,45] In all guidelines, an individual was deemed to be at risk for LTBI if either the TST or IGRA was positive.

Are these recommendations valid?

There is a body of evidence assessing the test performance characteristics of TST and IGRA in the general population. However, these recommendations were sourced largely from observational studies performed in middle to high income countries and did not include immunosuppressed

patients from low-resource settings, and with low certainty of the evidence. Given the low test sensitivity of TST in immunosuppressed patients, some guidelines suggested a two-stage screening; first using TST and then IGRA to increase the detection rates of LTBI. [17,20,30,35,46] Among those who are immunosuppressed and had previously been vaccinated with BCG, IGRA generally performs better than TST. IGRA test sensitivity and specificity varies between 67-75% and 93-99% respectively.[33,43] However, given the concerns of spectrum bias, most guidelines suggested caution in the interpretation of test results among immunosuppressed hosts.

Treatment for latent TB infection

Population of interests

Either a positive TST or IGRA was considered sufficient evidence to warrant further evaluation. Prior to LTBI treatment, exclusion of active TB was recommended.[1,9,15,17,18,25,26,29,30,32,35,42–44,47,48] Once active TB was excluded, LTBI treatment was recommended. Treatment for LTBI was also indicated for those who were BCG vaccinated, because BCG status may indicate time spent in an area with a high prevalence of LTBI.[34] Furthermore, in South Africa, where there is a high prevalence of TB, treatment for LTBI was recommended in all patients after exclusion of active TB in the setting of HIV.[40] Also, most clinical practice guidelines recommended LTBI treatment where clinical suspicion was high, regardless of the IGRA and TST test findings.[1,3,15,19,20,24,26,28,29,33,35–38]

Intervention and duration

Recommendations for the treatment of LTBI were largely similar across guidelines, regardless of the mode of immunosuppression. In most guidelines, isoniazid 300 mg daily with pyridoxine was recommended for a duration of nine months.[3,9,16–21,24–27,29,31,33–39,42] Six months of isoniazid therapy was considered less efficacious,[18] but was recommended in one guideline.[48] Three guidelines

suggested a flexible treatment regimen of 6-9 months of the combined therapies.[19,30,47] Four guidelines did not specify duration.[15,23,32,45]

Rifamycin-based therapy (10 mg/kg/day) either alone or for three[10] or four[1,3,9,10,15–18,24,26,27,31,33,35-39,42] months was the second most frequently reported treatment strategy among patients who tested positive for LTBI. This was thought to be useful when isoniazid was contraindicated or not tolerated,[27] with one guideline describing the option as cheaper, but with more drug-drug interactions.[18] Rifampicin plus isoniazid for three[1,10,15–19,25,26,29–31,39] or four months[10,24] was also an option. Rifampicin plus isoniazid for three months was stipulated as a primary alternative therapy to isoniazid in two guidelines.[30,48] Other options included rifabutin for four months,[9,42] or three months of weekly rifapentine and isoniazid.[9,10] Finally, rifampicin and pyrazinamide for a shorter two-month regimen was considered as an option in eight guidelines,[3,25,29,35–39] with most being in the transplantation setting. The shorter duration of treatment was considered advantageous for those maintained on the transplant waiting list.[3,35–38] However, a biological therapy based guideline advised against this option due to the increased risk of hepatotoxicity.[24]

In the transplantation and HIV settings, some guidelines specified avoidance of rifamycins, given the potential drug-drug interactions with calcineurin inhibitors and protease inhibitors.[3,35,37] However, therapeutic drug monitoring may mitigate against the potential for such interactions.[34] Several other non-rifamycin based alternatives were recommended and included ethambutol with levofloxacin or moxifloxacin for six months,[3,37] 12 weeks of rifapentine and isoniazid, and six months of isoniazid with ethambutol.[24]

Close monitoring with monthly liver function tests and for peripheral neuropathy was recommended whilst on treatment for all patients.[3,9,10,17,18,26,31,35,37,40,47] Co-administration of Vitamin B6 (pyridoxine) was suggested universally, to reduce the risk of peripheral neuropathy associated with

isoniazid. If there were treatment interruptions for more than two months, one guideline recommended clinical and radiological reassessment for TB.[42]

Timing of preventive therapy

In patients who are medically immunosuppressed, most guidelines recommended delaying medical therapy for one month after commencement of LTBI treatment where possible, to reduce the risk of TB reactivation.[15–18,20,24–28] Alternative waiting periods varied between three weeks[25,47] to two months.[30] One guideline preferred a prolonged delay, but did not provide a time frame.[21] However, if the underlying disease was severe, earlier institution of immunosuppressive agents was accepted[17,29] once active TB was excluded.[28]

In transplant setting, patients with LTBI are recommended to commence treatment on the waiting list where possible, with treatment ideally completed prior to transplantation.[3,33,35,37,38] However, treatment interruption peri-transplantation, with recommencement and completion of the treatment course once patients were clinically stable, may also be considered.[33,35,37] LTBI treatment should not delay transplantation.[38] In the setting of liver transplantation, the use of anti-TB medications has been associated with increased risk of hepatotoxicity. Thus, it was generally recommended that LTBI therapy be commenced after transplantation, to avoid drug-related fulminant hepatitis whilst waiting for a donor organ.[3,35,37]

In patients with HIV, the timing of commencement of anti-retroviral therapy in relation to LTBI treatment was not specified by clinical practice guidelines. Unlike treatment for active TB, immune reconstitution related to LTBI treatment has not been documented.[9] Generally, it was recommended to initiate or continue anti-retroviral treatment concurrently with treatment for LTBI.[39,40]

Are these recommendations valid?

Overall, clinical practice guidelines recommended the use of isoniazid or rifamycin based regimes for the treatment of LTBI. The evidence for recommendations was largely sourced from observational studies in high income countries, thus limiting the ability to generalise recommendations to low-income countries. There was very little evidence about the exact time frame of delay before initiating treatment. 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.[1,3,9,10,18,19,21,24,29,31,33,35–37,39,40,42,47,48]

DISCUSSION

Clinical practice guidelines for screening and treatment of LTBI vary in scope and their recommendations for screening modalities, frequency of screening and the target populations of interest. The two-stage screening approach of TST and IGRA was most frequently recommended because of improved test performance characteristics in high risk, immunosuppressed populations. Guidelines did not specify how to interpret a mismatch in results between TST and IGRA, but recommended treatment where either test was positive. For treatment, most recommendations suggested the use of isoniazid-based therapies for LTBI, but there were discrepancies in the duration and timing of commencing treatment. Nine months of isoniazid-based therapy appeared to be the preferred therapy for LTBI, and most agreed that treatment of LTBI should be initiated prior to commencement of immunosuppressive therapies.

Whilst most guidelines conducted a comprehensive literature review, the evidence base supporting the recommendations was limited to observational studies without trial-based evidence to support routine screening and treatment for LTBI in immunosuppressed patients. The rigor of guideline development lacks robustness. Less than half of the guidelines provided grading of the evidence and recommendations. Details regarding the methods used for formulating the recommendations were

not adequately described, lacking transparency in the methodology and did not consistently link the recommendations to the corresponding level of evidence, both for screening and treatment of LTBI and the benefit-harm-cost relationship.

In this review, we found that public and stakeholder consultation was rarely reported in the development of the guidelines. Only 22% underwent a peer review process and 11% underwent public consultation. Engaging experts may improve guidelines by allowing criticism and suggestions.[19] Expert clinicians were consulted in guideline development, and included clinicians such as rheumatologists, gastroenterologists, dermatologists, thoracic physicians, infectious diseases physicians and clinicians involved in treating patients with HIV. Public consultations and patient participation can also improve guideline applicability.[49] Although four guidelines used public consultation, none elaborated on how they have contributed to guideline development. Guideline applicability may be improved by active consumer involvement and engagement in the development, design, and implementation process.

Inconsistencies exist in the recommendations for screening modalities and frequencies for LTBI. The TST evokes delayed hypersensitivity after intradermal application of a purified protein derivative.[33] TST generally performs poorly in immunosuppressed patients, with reported estimates of 89% and 71% for test sensitivity and specificity, respectively.[43] The lower test specificity may be due to the cross-reactivity with prior BCG vaccination[15,34] and infections with non-TB mycobacteria. Testing with IGRA identifies adaptive immune response to TB-specific antigens which are not present in BCG strains, enabling greater specificity.[42,43] Test sensitivity of TST and IGRA is uncertain or may be reduced among immunosuppressed hosts because of anergy.[33] 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.[50] Statistical methods such as latent class and Bayesian mixture analyses may overcome this limitation.[51,52]

Most guidelines recommended treatment for LTBI, including those who were screened negative but of high clinical risk. While this is of relevance and importance to at-risk immunosuppressed patients, interventions such as isoniazid and alternatives including rifampicin are not without adverse complications. No guidelines specified contraindications to treatment, except in the case of liver transplantation, where treatment was recommended to be delayed until after transplantation due to the increased risk of hepatotoxicity.[3,35,37] Treatment of LTBI also has other potential drug toxicities, including neuropathy and drug-drug interactions, particularly for rifampicin-based regimens. Although many guidelines acknowledged these toxicities, the impact of over-treatment and the potential risk of adverse drug reactions were not quantified. Only two guidelines specified the growing concern of increasing rates of multi-drug resistant tuberculosis secondary to excess exposure to drug therapy.[23,47] Furthermore, barriers to screening and treatment are only considered in one guideline, which stated that there were no barriers in a public hospital.[41] This therefore, would not apply in under-resourced settings, or where public healthcare is not available.

In our systematic review, we used a reliable and validated method using the Appraisal of Guidelines for Research and Evaluation (AGREE) II to assess guidelines for the screening for and treatment of

LTBI. There was good agreement between the two reviewers. We have summarised the variability in the literature pertaining to LTBI, allowing for a consolidated approach to recommendations for screening and management of LTBI. However, limitations of our review are that we have only included guidelines written in the English language. Therefore, applicability of our findings to other settings, particularly those in low-income countries are uncertain. Future guidelines should consider the specific health issues that are applicable to the population of interest, such as in low-income settings, and consider cost implications and barriers to screening and treatment. Very few guidelines discussed non-TNF based immunosuppression. This included two well-established medications – methotrexate and cyclophosphamide – for the management of autoimmune disease, as well as newer biological treatments.[17] Only one guideline included newer monoclonal agents[30] and one for patients on regular methotrexate therapy.[32] One of the key challenges for guideline developers is the translation and dissemination of these recommendations in clinical practice, which may transform care and improve health of the target population. Currently, there are limited training initiatives in the implementation of these guidelines in different cultural and resource settings. Future research, through direct engagement with local stakeholders, clinicians and patients should therefore assess the features and processes that underpin success in research translation, and adapt these strategies in practice.

Overall, the current clinical guidelines reaffirm the importance of LTBI screening and treatment. Although, there are some discrepancies in terms of screening modalities, recommendation for the treatment of LTBI was consistent across all guidelines. 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 guidelines development and patient-centred practice to improve patient outcomes.

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Table 1: Characteristics of the studies

Guidelines	Funding body	Country	Population	Target users	Writers	Evidence base	Evidence level	Grading	Guideline review	Update
ARA 2010[1]	Professional society	Australia	Biological therapy	Rheumatologists	Rheumatologists	Guidelines	NS	NS	NS	NS
Aguado et al 2009[3]	Industry, Professional society	Spain	Organ transplant	Transplant physicians	Transplant infectious disease specialists	Literature, consensus, Experts	I-III[a]	A-E[b]	NS	NS
CDC 2016[9]	Office of AIDS Research,	USA	HIV	Clinicians	Multi-disciplinary	Literature, experts	I-III[c]	A-C[d]	Expert review, public consultation	6 months
WHO 2015[10]	Ministry of health Italy, WHO,	WHO	All	Tuberculosis physicians	Multi-disciplinary	Literature, experts	GRADE[e]	Strong/conditional[f]	Expert review, peer review	2020
Beglinger et al 2007[15]	NS	Switzerland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, Experts	NS	NS	NS	NS
Cantini et al 2015[16]	NS	Italy	Biological therapy	Clinicians	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Doherty 2008[17]	Professional body	United States of America	Psoriasis patients	NS	Dermatologists	Literature, experts	I-IV (Shekelle et al)[g]	NS	Medical Board	NS

Duarte et al 2012[18]	NS	Portugal	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	A-D[h]	NS	NS	NS
Fonseca et al 2008[19]	NS	Portugal	Biological therapy	Rheumatologists	Multi-disciplinary	Literature, guidelines	NS	NS	Expert, public consultation	NS
Hodkinson et al 2013[20]	Professional body	South Africa	Patients with rheumatoid arthritis	Clinicians	Rheumatologists	Literature, guideline, expert, stakeholder	NS	NS	Public/stakeholder consultation	2 years
Kavanagh et al 2008[21]	Professional body	Ireland	Anti TNF-alpha therapy	Clinicians	Multi-disciplinary	Literature, guidelines, experts	NS	NS	NS	NS
Keith et al 2014[22]	Nil	USA	Immunosuppression	Dermatologists	Multi-disciplinary	Literature, guidelines	NS	NS	NS	NS
Koike et al 2007[23]	Professional body, Government	Japan	Anti-TNF alpha therapy	Rheumatologists	NS	Experts	NS	NS	NS	NS
Lichauco et al 2006[24]	NS	Philippine	Biological therapy	Physicians	Multi-disciplinary	Literature, guidelines	Level 1-4[i]	PHEX guidelines[j]	Expert peer review, public consultation	NS
Salmon et al 2002[25]	Not specified	France	Rheumatoid arthritis	Rheumatologists	Multi-disciplinary	NS	NS	NS	NS	NS
Mir Viladrich et al 2016[26]	NS	Spain	Biological therapy	Clinicians	Multi-disciplinary	Guidelines, experts	NS	A-C, I-III[k]	NS	NS

Mok et al 2011[27]	NS	Hong Kong	Rheumatoid arthritis	Rheumatologists	Rheumatologists	Guidelines	A-D[l]	NS	NS	As required
Nordgaard-Lassen et al 2012[28]	NS	Denmark	Biological therapy	Clinicians	Gastroenterologists	Literature	I-IV[m]	A-C[n]	NS	NS
BTS 2005[29]	NS	United Kingdom	Anti TNF-alpha therapy	Physician	Multi-disciplinary	Literature, experts	SIGN[o]	SIGN[p]	Professional membership consultation, peer review	2008
Smith et al 2017[30]	British Association of Dermatologists	United Kingdom	Psoriasis	Dermatologists	Multi-disciplinary	Literature	GRADE[e]	GRADE: Strong/weak/no[q]	Professional membership consultation, peer review	As required
Solovic et al 2010[31]	NS	Europe	Biological therapy	Clinicians	Multi-disciplinary	Literature	NS	A-D[r]	NS	NS
Carrascosa et al 2016[32]	Gebro Pharma	Spain	Methotrexate therapy	Dermatologists	Dermatologists	Literature, guidelines	SIGN[o]	SIGN[p]	NS	NS
Bumbacea et al 2012[33]	Professional society	Europe	All transplant	Transplant physicians	Transplant infectious disease specialists	Literature, guidelines	NS	A-D[r]	NS	NS
KDIGO 2009[34]	KDIGO, multiple sponsors	International	Kidney transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	A-D[s]	Level 1-2, not graded[t]	NS	NS
Meiji et al 2014[35]	NS	Spain	Solid organ transplant	Transplant physicians	Multi-disciplinary	Literature	Level A-D, I-IV[h]	NS	NS	NS

EBPG 2002[36]	NS	Europe	Renal transplant	Transplant physicians	NS	NS	A-D[u]	NS	NS	NS
Subramanian 2013[37]	American Society of Transplantation	USA	Solid organ transplant recipients	Transplant physicians	Transplant infectious disease physicians	Literature, experts	I-III[h]	NS	NS	NS
Tomblyn et al 2009[38]	Member societies	International/ USA/Canada	Stem cell transplant recipients	Clinicians	Multi-disciplinary	Literature, experts	I-III[v]	A-E[w]	NS	NS
Pozniak et al 2011[39]	Nil	United Kingdom	HIV	Physicians	HIV physicians	Literature, Guidelines	I-III[x]	A-E[y]	NS	NS
SA 2010[40]	NS	South Africa	HIV	HIV treatment providers	NS	NS	NS	NS	NS	NS
Santin et al 2016[41]	SEPAR, SEIMC	Spain	All	Clinicians	Multi-disciplinary	Literature	GRADE[e]	GRADE: weak/strong	NS	5 years
Al Jahdali et al 2010[42]	Professional society	Saudi Arabia	All susceptible patients	Clinicians	Multi-disciplinary	Experts	NS	NS	NS	NS
ECDC 2011[43]	ECDC	Europe	Immunocompromised	National bodies	Multi-disciplinary	Literature, experts	NS	NS	NS	NS
Mazurek et al 2010[44]	CDC	USA	All	Public health officials, physicians, others	Multi-disciplinary	Literature, experts	NS	NS	NS	NS

Taylor et al (CDC 2005)[45]	Professional bodies	United States of America	All	Health care workers	Multi-disciplinary	Literature, experts	I-III[z]	A-C[aa]	NS	NS
CTC 2008[46]	Public Health Agency	Canada	Immunocompromised patients	NS	Multi-disciplinary	Literature, experts	NS	NS	NS	Periodic
Japanese Society for Tuberculosis 2014[47]	NS	Japan	All susceptible populations	Clinicians	NS	NS	NS	NS	NS	NS
NICE 2016[48]	NCCCC	United Kingdom	All susceptible populations	All health care workers and public	Multi-disciplinary	Literature review	GRADE[e]	Offer/ do not offer/ consider[bb]	Stakeholders, peer review	As required

ARA Australian Rheumatological Association, NS not specified, CDC centre for disease control, AIDS acquired immunodeficiency syndrome, USA United States of America, HIV human immunodeficiency virus, WHO World Health Organisation, GRADE Grading of Recommendations Assessment, Development and Evaluation, TNF tumor necrosis factor, PHEX Philippine Guidelines on Periodic Health Examination, BTS British Thoracic Society, SIGN Scottish Intercollegiate Guidelines Network, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, SEPAR – Spanish society of Respiratory Disease and Thoracic Surgery, SEIMC Spanish Society of Infectious Disease and Clinical Microbiology, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence, NCCCC The National Collaborating Centre for Chronic Conditions

a. I evidence from at least 1 well-designed and performed trial, II evidence from at least one well designed non randomised control study (RCT), cohort or case control or noncontrolled experimental study with non conclusive results, III expert opinion based on clinical experience, descriptive studies, report from expert panel
b. A Solid evidence of clinical benefit, B solid or moderately solid evidence for efficacy, but clinical benefit is limited C insufficient evidence for efficacy D moderately solid evidence for lack of efficacy E strong evidence for lack of efficacy.
c. I: One or more RCT with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomised trials or observational cohort studies with long-term clinical outcomes III: Expert opinion
d. A: Strong recommendation for the statement, B: Moderate recommendation for the statement, C: Optional recommendation for the statement
e. Grading of Recommendations Assessment, Development and Evaluation (GRADE) High Further research is very unlikely to change our confidence in the estimate of effect. Moderate Further research is likely to have an important impact on our confidence in the effect. Low Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate. Very low Any estimate of effect is very uncertain.
f. 1. A strong recommendation is one for which the Panel was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This could be either in favour of or against an intervention. 2. A conditional recommendation is one for which the Panel concluded that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the Panel was not confident about these trade-offs. Reasons for not being confident included: absence of high-quality evidence (data to support the recommendation are scant); presence of imprecise estimates of benefits or harms (new evidence may result in changing the balance of risk to benefit); uncertainty or variation regarding how different individuals value the outcomes (only applicable to a specific group, population or setting); small benefits and benefits that may not be worth the costs (including the costs of implementing the recommendation)
g. IA evidence includes evidence from meta-analysis of randomised controlled trials; IB evidence includes evidence from at least one randomised controlled trial; IIA evidence includes evidence from at least one controlled study without randomization; IIB evidence includes evidence from at least one other type of quasi-experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
h. Evidence level definitions not specified
i. Level 1 An RCT that demonstrates a statistically significant difference in at lest one major outcome or if the difference is not statistically significant, an RCT of adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results Level 2 An RCT that does not meet the Level 1 criteria Level 3 A non-randomised trial with concurrent controls selected by some systematic method

Level 4 Before-after study or case series (at least 10 patients) with historical controls or controls drawn from other studies Level 5 Case series (at least 10 patients) without controls. Experts' opinion and clinical experience are included.

j. Level 1: Evaluation of evidence satisfies all of the following criteria: 1. effective treatment is documented in randomised controlled trials that observe effects on clinical outcomes 2. the condition being screened has local prevalence data 3. the screening test is validated and 4. the cost-effectiveness of the screening test, as well as treatment for the disease have been evaluated Level 2: Evaluation of evidence satisfies #1 but not all of #2, #3, and #4 Level 3: Evaluation of evidence satisfies #2, #3, or #4 but not #1 Level 4: Evaluation of evidence satisfies none of the criteria

k. Recommendations according to categories of strength: A Good evidence to support the recommendation B Moderate evidence to support the recommendation C poor evidence that does not enable the recommendation to be either supported or rejected. Recommendations according to the scientific quality. Grade I recommendation based on at least one well-designed, controlled, RCT Grade II recommendation based on at least one well-designed, but not RCT, cohort studies, multiple time-series studies or very evident results in uncontrolled trials Grade III recommendation based on the opinion of experts, descriptive studies or clinical experience

l. Category A At least one RCT or meta-analyses of RCTs, or reviews if these contain category A references Category B At least one controlled trial without randomization or at least one other type of experimental study, or extrapolated recommendations from RCTs or meta-analyses Category C Non-experimental descriptive studies, such as comparative studies, correlational studies, and case-control studies, which are extrapolated from RCTs, non-randomised controlled studies, or other experimental studies Category D Expert committee reports or opinions or clinical experience of respected authorities. Also includes all abstracts

m. I Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, II Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, III Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, IV Descriptive studies, expert opinions and narrative reviews

n. A Randomised, controlled clinical trials (therapeutic or diagnostic) and metaanalyses of randomised, controlled clinical trials or systematic reviews, B Prospective and controlled but nonrandomised investigations (cohort studies); diagnostic testing evaluated by direct methods, OR Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods, C Descriptive studies, expert opinions and narrative reviews

o. 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. 12 Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias. 2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal. 2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal. 22 Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal. 3 Non-analytical studies (e.g. case reports, case series). 4 Expert opinion

p. A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results. B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+. C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+. D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

q. Strong recommendation for use of an intervention: Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator, Weak recommendation for the use of an intervention: Risks and benefits of the intervention are finely balanced; many patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected, No recommendation: Insufficient evidence to support any recommendation, Strong recommendation against the use of an intervention: Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the interventions

r. A Evidence is from end-points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made Category A requires substantial numbers of studies involving substantial numbers of participants, B Evidence is from end-points of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent, C Evidence is from outcomes of uncontrolled or non-randomised trials or from observational studies, D This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories The Panel consensus is based on clinical experience or knowledge that does not meet the criteria listed above

s. A high, B moderate, C low, D very low

t. Level 1: we recommend, level 2: we suggest, no grade: used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence

u. A: guidelines are supported by at least one large published RCT or more, B: guidelines are supported by large open trials or smaller trials with consensus results; C: guidelines are derived from small or controversial studies, or represent the opinion of the group of experts

v. I Evidence from at least one well-executed randomised, controlled trial; II Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments; III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

w. A Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered; B Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. Should generally be offered. C Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences, (e.g., drug toxicity, drug interactions), or cost of the chemoprophylaxis or alternative approaches. Optional. D Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered. E Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered

x. I. At least one properly randomised trial with clinical endpoints II. Clinical trials either not randomised or conducted in other populations III. Expert opinion

y. A Preferred; should generally be offered B Alternative; acceptable to offer C Offer when preferred or alternative regimens cannot be given D Should generally not be offered E Should never be offered

z. I evidence from at least one RCT, II evidence from 1) at least one well-designed clinical trial, without randomization, 2) cohort or case-controlled analytic studies 3) multiple times series 4) dramatic results from uncontrolled experiments III evidence from opinions of respected authorities on the basis of cumulative public health experience, descriptive studies, or reports of expert committees

aa. A highly recommended in all circumstances, II recommended; implementation might be dependent on resource availability, C might be considered under exceptional circumstances

bb. A Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal. B Level 2++, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 1++ or 1+. C Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 2++. D Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus *or* extrapolated from level 2 clinical evidence supplemented with health economic modelling. D (GPP) A good practice point (GPP) is a recommendation based on the experience of the GDG.

Table 2: Grade of recommendation

Guideline name	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)	Weighted Kappa Scores (Quadratic)	95% CI
ARA 2010[1]	75	31	10	67	25	0	0.74	0.56-0.92
Aguado et al 2009[3]	72	28	24	72	29	58	0.76	0.62-0.90
CDC 2016[9]	89	89	81	75	77	83	0.29	-0.14-0.71
WHO 2015[10]	97	94	88	89	92	88	0.67	0.27-1.00
Beglinger et al 2007[15]	75	42	23	67	25	0	0.72	0.54-0.91
Cantini et al 2015[16]	89	53	55	89	56	38	0.80	0.63-0.97
Doherty 2008[17]	92	44	75	86	71	58	0.55	0.19-0.91
Duarte et al 2012[18]	86	44	31	83	52	0	0.67	0.46-0.89
Fonseca et al 2008[19]	92	72	73	86	60	4	0.74	0.53-0.95
Hodkinson et al 2013[20]	83	83	56	75	71	25	0.00	-0.27-0.27
Kavanagh et al 2008[21]	64	33	29	67	15	0	0.61	0.39-0.82
Keith et al 2014[22]	83	42	45	50	19	42	0.61	0.27-0.92
Koike et al 2007[23]	78	33	28	56	10	29	0.41	0.08-0.75
Lichauco et al 2006[24]	89	69	67	78	65	0	0.64	0.27-1.00
Mir Viladrich et al 2016[26]	81	42	29	75	40	42	0.66	0.44-0.88
Mok et al 2011[27]	69	36	28	53	27	33	0.53	0.24-0.82

Nordgaard-Lassen et al 2012[28]	78	39	48	64	35	0	0.75	0.60-0.90
Salmon et al 2002[25]	72	42	13	64	0	0	0.76	0.55-0.97
BTS 2005[29]	92	69	91	89	71	63	0.32	-0.05-0.70
Smith et al 2017[30]	94	61	80	83	65	75	0.77	0.51-1.00
Solovic et al 2010[31]	69	33	35	81	44	38	0.66	0.41-0.92
Carrascosa et al 2016[32]	67	42	46	61	21	83	0.71	0.56-0.87
Bumbacea et al 2012[33]	69	44	43	81	40	67	0.48	0.13-0.84
KDIGO 2009[34]	100	78	67	75	65	92	0.21	-0.07-0.48
Meiji et al 2014[35]	64	25	28	72	25	38	0.67	0.43-0.89
EBPG 2002[36]	86	67	68	89	77	75	0.18	-0.05-0.41
Subramanian 2013[37]	75	42	42	78	54	42	0.31	-0.10-0.71
Tomblyn et al 2009[38]	81	58	43	69	35	17	0.44	0.15-0.74
Pozniak et al 2011[39]	81	42	38	64	56	0	0.73	0.51-0.95
SA 2010[40]	78	19	10	78	69	0	0.91	0.85-0.98
Santin et al 2016[42]	92	58	74	83	67	88	0.73	0.49-0.97
Al Jahdali et al 2010[42]	83	58	32	75	46	0	0.58	0.35-0.81
ECDC 2011[43]	72	31	33	69	29	17	0.41	0.14-0.67

Mazurek et al 2010[44]	78	72	71	72	60	8	0.57	0.33-0.81
Taylor et al (CDC 2005)[45]	75	44	28	58	38	0	0.26	0.09-0.47
CTC 2008[46]	83	50	52	69	40	46	0.29	0.01-0.58
Japanese Society for Tuberculosis 2014[47]	56	11	26	67	60	0	0.67	0.52-0.82
NICE 2016[48]	100	97	93	92	69	83	0.52	0.09-0.96

ARA Australian Rheumatological Association, CDC centre for disease control, WHO World Health Organisation, BTS British Thoracic Society, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence

Table 3: Summary of recommendations

Guidelines	Population	Screening process				Treatment method	Treatment duration	Timing before immunosuppression
		History	TST	IGRA	CXR			
ARA 2010[1]	Biological therapy		X	X	X	Isoniazid[a]	6-9 months	1-2 months
Aguado et al 2009[3]	Transplant recipients	X	X		X	Isoniazid	9 months	Before transplant
CDC 2016[9]	HIV patients		X	X		Isoniazid	9 months	NS
WHO 2015[10]	low-middle income countries		X	X		Isoniazid	6 months	NS
Beglinger et al 2007[15]	Biological therapy	X		X	X	Isoniazid OR rifampicin	NS	1 month
Cantini et al 2015[16]	Biological therapy	X	X	X		Isoniazid	9 months	1 month
Doherty 2008[17]	Psoriasis patients	X	X		X	Isoniazid	9 months	1-2 months or longer
Duarte et al 2012[18]	Biological therapy	X	X	X		Isoniazid	9 months	1-2 months
Fonseca et al 2008[19]	Biological therapy	X	X		X	Isoniazid	6-9 months	1 month
Hodkinson et al 2013[20]	Patients with rheumatoid arthritis	X	X	X	X	Isoniazid	9 months	1 month
Kavanagh et al 2008[21]	Biological therapy	X	X		X	Isoniazid	9 months	Pre-immunosuppression
Keith et al 2014[22]	Bullous dermatosis		X	X		NS	NS	NS

Koike et al 2007[23]	Biological therapy	X	X		X	Isoniazid	NS	NS
Lichauco et al 2006[24]	Biological therapy		X		X	Isoniazid	9 months	1 month
Salmon et al 2002[25]	Biological therapy		X		X	Rifampicin and pyrazinamide	2 months	3 weeks
Mir Viladrich et al 2016[26]	Biological therapy	X	X	X		Isoniazid	9 months	4 weeks
Mok et al 2011[27]	Biological therapy		X			Isoniazid	9 months	4 weeks
Nordgaard-Lassen et al 2012[28]	Biological therapy			X		Isoniazid	9 months	4 weeks
BTS 2005[29]	Biological therapy	X	X		X	Isoniazid	6 months	Concurrent
Smith et al 2009[30]	Biological therapy			X	X	Isoniazid OR Isoniazid and rifampicin	6 months OR 3 months	2 months
Solovic et al 2010[31]	Biological therapy	X	X	X	X	Isoniazid	9 months	4 weeks
Carrasoca et al 2016[32]	Methotrexate therapy		X	X	X	Isoniazid	NS	NS
Bumbacea et al 2012[33]	Transplant recipients		X	X		NS	NS	Before transplant
KDIGO 2009[34]	Renal transplant	X	X			Isoniazid	9 months	NS
Meiji et al 2014[35]	Transplant recipients		X	X		Isoniazid	9 months	NS
EBPG 2002[36]	Renal transplant recipients	X	X		X	Isoniazid	9 months	NS

Subramanian 2013[37]	Transplant recipients	X	X	X	X	Isoniazid	9 months	Before or after transplant
Tomblyn et al 2009[38]	HCT recipients	X	X	X		Isoniazid	9 months	NS
Pozniak et al 2011[39]	HIV patients		X	X		Isoniazid	6 months	NS
SA 2010[40]	HIV patients		X			Isoniazid	6 months	NS
Santin et al 2016[41]	HIV patients	X	X	X		NS	NS	NS
	Biological therapy	X	X	X		NS	NS	NS
	Transplant recipients	X	X	X		NS	NS	NS
Al Jahdali et al 2010[42]	Susceptible populations		X	X		Isoniazid	9 months	NS
ECDC 2011[43]	Immunocompromised		X	X		NS	NS	NS
Mazurek et al 2010[44]	Susceptible populations	X	X	X	X	NS	NS	NS
Taylor et al (CDC 2005)[45]	Susceptible populations	X	X	X		Isoniazid	NS	NS
CTC 2008[46]	Immunocompromised		X	X		NS	NS	NS
Japanese Society for Tuberculosis 2014[47]	Susceptible populations	X		X	X	Isoniazid	6-9 months	3 weeks before immunosuppression NS for transplant
NICE 2016[48]	Susceptible populations	X	X	X		Isoniazid OR Isoniazid and	6 months OR 3 months	NS

	rifampicin

TST tuberculin skin test, IGRA interferon gamma release assay, CXR Chest X ray, ARA Australian Rheumatological Association, CDC centre for disease control, HIV human immunodeficiency virus, NS not specified, WHO World Health Organisation, BTS British Thoracic Society, KDIGO Kidney Disease Improving Global Outcomes, EBPG European Best Practice Guideline Expert Group on Renal Transplantation, SA South Africa, ECDC European Centre for Disease Prevention and Control, CTC Canadian Tuberculosis Committee, NICE National Institute for Health and Care Excellence

a. Where isoniazid is used, it is always provided concurrently with pyridoxine prophylaxis

Figure 1: Database search strategy
The medical databases EMBASE, PsychINFO and Medline were searched for articles relevant to tuberculosis in an immunosuppressed setting, using the search strategy described in Appendix 1. A total of 9467 articles were found and compiled into the EndNote software (Clarivate Analytics 2017, version X7), of which 1130 articles were duplicate articles. From the remaining articles, 6121 articles were excluded by abstract review, primarily because they were irrelevant. A further 2056 articles were removed during a second review of titles and abstracts. 160 articles were reviewed in full of which 122 were excluded as they did not fulfil guideline or relevance criteria. 38 articles were included in our final review

Disclosures

Ethics was not required for this work

There are no external sources of funding for this work

This manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted and all discrepancies have been explained

Data sharing – data are available on request

Conflicts of interest
SC reports grants from MSD Australia, outside the submitted work

Author contributions:
Tasnim Hasan
- Database search, selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

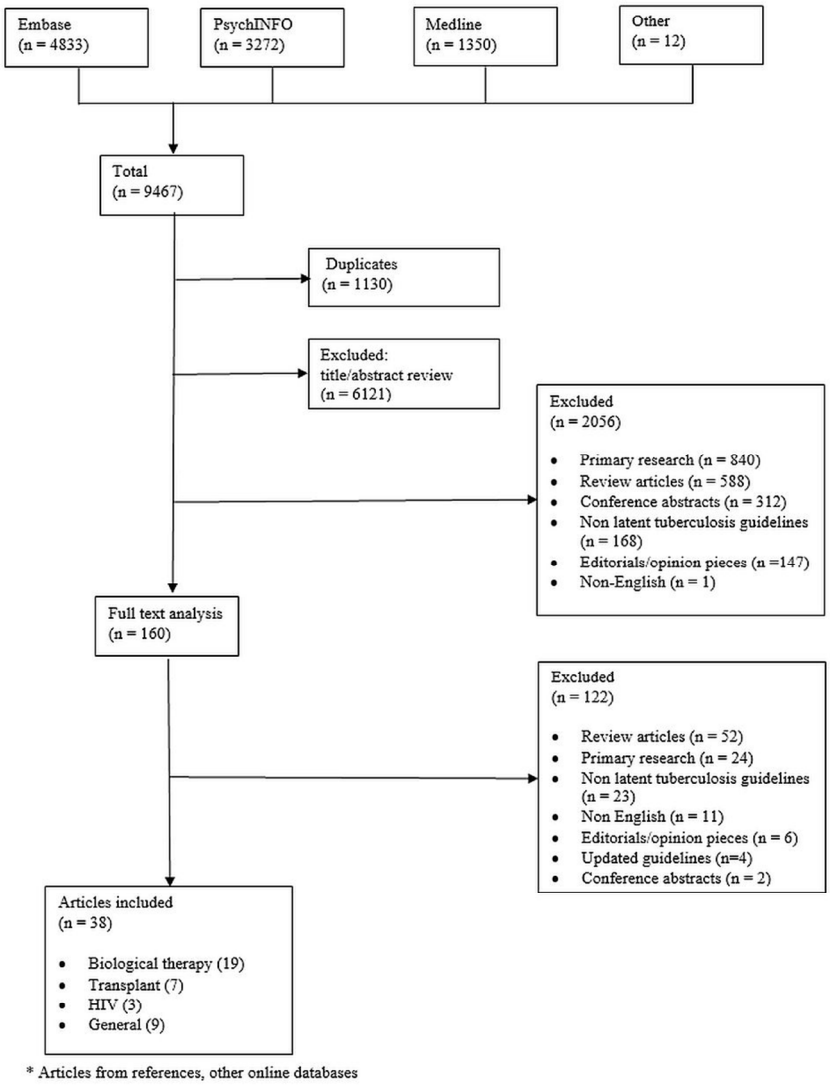
Eric Au
- Selection of guidelines
- Grading of guidelines, assessing quality, interpretation
- Preparation of manuscript and editing

Sharon Chen
- Preparation of manuscript and editing

Allison Tong
- Preparation of manuscript and editing

Germaine Wong
- Preparation of manuscript and editing

Figure 1: Database search strategy



Database search strategy

90x115mm (300 x 300 DPI)

Appendix 1: Search strategy

1. TB
2. Tuberculosis
3. Mycobacteria
4. 1 OR 2 OR 3
5. Immunosuppression
6. Immunocompromised
7. Immunodeficient
8. Immunosuppressed
9. Immunosuppress
10. Steroids
11. Chemotherapy
12. TNF
13. Tumor necrosis factor
14. Transplant
15. HIV
16. Human immunodeficiency virus
17. Biologic
18. Monoclonal
19. Lupus
20. Autoimmune
21. Rheumatoid
22. Vasculitits
23. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. Guideline
25. Position
26. Consensus
27. Recommendations
28. Recommendation
29. Clinical practice
30. 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 4 AND 23 AND 30

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Thematic analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	36
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12,15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	nil

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