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Review article: latent tuberculosis in patients with inflammatory bowel diseases receiving immunosuppression—risks, screening, diagnosis and management

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Summary

Background: One quarter of the world's population has latent tuberculosis infection (LTBI). Systemic immunosuppression is a risk factor for LTBI reactivation and the development of active tuberculosis. Such reactivation carries a risk of significant morbidity and mortality. Despite the increasing global incidence of inflammatory bowel disease (IBD) and the use of immune-based therapies, current guidelines on the testing and treatment of LTBI in patients with IBD are haphazard with a paucity of evidence.

Aim: To review the screening, diagnostic practices and medical management of LTBI in patients with IBD.

Methods: Published literature was reviewed, and recommendations for testing and treatment were synthesised by experts in both infectious diseases and IBD.

Results: Screening for LTBI should be performed proactively and includes assessment of risk factors, an interferon-gamma releasing assay or tuberculin skin test and

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chest X-ray. LTBI treatment in patients with IBD is scenario-dependent, related to geographical endemicity, travel and other factors. Ideally, LTBI therapy should be used prior to immune suppression but can be applied concurrently where urgent IBD medical treatment is required. Management is best directed by a multidisciplinary team involving gastroenterologists, infectious diseases specialists and pharmacists. Ongoing surveillance is recommended during therapy. Newer LTBI therapies show promise, but medication interactions need to be considered. There are major gaps in evidence, particularly with specific newer therapeutic approaches to IBD.

Conclusions: Proactive screening for LTBI is essential in patients with IBD undergoing immune-suppressing therapy and several therapeutic strategies are available. Reporting of real-world experience is essential to refining current management recommendations.

1 | INTRODUCTION

Tuberculosis (TB) is a major global health issue and communicable cause of death, accounting for 1.2 million deaths worldwide in persons not infected with the human immunodeficiency virus (HIV) in 2019.[1] After exposure to *Mycobacterium tuberculosis*, the spectrum of natural disease progression varies from immediate organism clearance to primary acute infection. In the majority of infected patients, the host immune response arrests further growth of *Mycobacterium tuberculosis* by the way of granuloma formation, leading to dormant or latent tuberculosis infection (LTBI).[2] Individuals with LTBI are asymptomatic of their infection but remain at risk of reactivation and development of active TB. This is estimated to occur in approximately 5%–10% of the general immunocompetent population over their lifetime.[3] Importantly, LTBI is estimated to affect one quarter of the world's population.[4,5]

Diagnosing LTBI provides a window of opportunity for treatment. Such treatment prevents reactivation and subsequent development of active TB infection, which carries a risk of significant morbidity and mortality.[6] Guidelines recommend screening for and treating LTBI in patients at high risk of reactivation or with a high likelihood of LTBI on the basis of epidemiological risk factors.[7,8] Treatment prevents the transmission of infection and is an essential component of eliminating TB in low-incidence countries.[9] Key determinants to accessing available regimens are geographic location and cost.[9]

A principal risk factor for TB reactivation in those with LTBI is immune suppression or immune incompetence, with the latter including primary immune-deficiency diseases and secondary immunodeficiency.[10] Immunomodulation in patients with IBD is multifactorial but primarily occurs as a function of a patient's medication regimen. IBD patients often require immune-suppressing therapies including corticosteroids, thiopurines, tumour necrosis factor (TNF)-antagonists, non-TNF-targeted biologics and targeted small molecule therapies. These therapies may impact immunological pathways integral to controlling anti-mycobacterial activity.[11] Secondly, malnutrition and disease activity are modifiable risk factors in IBD that can result in an immune-suppressed state and increased risk of opportunistic infection.[11]

Given such risks, it is surprising that guidelines on who and how to screen for and manage LTBI in patients with IBD are somewhat empirical. Further, there appears to be considerable heterogeneity in their implementation regarding, for example, who should be screened, the timing of its administration in relation to commencing immunosuppressive therapy and its duration and subsequent assessments are not uniform. Whether having IBD alone sufficiently warrants screening is not known, but, in clinical practice, the initiation of systemically acting immune-modulating therapies appears to be the trigger for addressing the question of LTBI. Underlying reasons for such haphazard practice include the exclusion of patients with LTBI in stringent research protocols, the genesis of most data from countries where TB is very uncommon, and the paucity of real-world data that inform clinical practice in terms of risk and clinical approach. Thus, this review presents the evidence and its gaps and develops evidence-based standards to guide the management of LTBI in IBD patients.

2 | INDICATIONS FOR SCREENING PATIENTS

A comparison of society and agency guidelines for LTBI screening is summarised in Table 1. The current World Health Organisation (WHO) guidelines recommend screening patients with immunodeficiency diseases such as HIV infection, those with underlying chronic lung diseases such as silicosis, household contacts of persons infected with pulmonary TB and other high-risk population groups such as prisoners, healthcare workers, homeless people, people who inject drugs (PWIDs) and immigrants from high-prevalence countries. Screening is also recommended prior to the commencement of immunosuppressive therapy such as tumour necrosis factor-alpha inhibitors, organ or haematological transplantation, or renal replacement therapy.[9] The national position statement for the management of LTBI in Australia mirrors these recommendations.[12,13]

TABLE 1 Comparison of guidelines addressing issues in screening, diagnosis and timing of therapy for latent tuberculous infection

Issue	European Crohn's colitis organisation (ECCO)[11]	British Society of Gastroenterology (BSG)[158]	British Thoracic Society (BTS)[38]	Anters for disease control and prevention (CDC)[98]	World Health Organisation (W)[8]	Australian Department of Health guidelines[13]
When to screen	If close contact or from an endemic country Consider at diagnosis Always perform prior to anti-TNF therapy	If close contact or from an endemic country Prior to commencing anti-TNF therapy or other biological therapy	If close contact or from an endemic country Prior to anti-TNF treatment, tofacitinib, vedolizumab and ustekinumab	If close contact or from an endemic country People living with HIV or undergoing solid organ transplant People who work in high-risk settings, prisoners, people who use illicit drugs and healthcare workers Prior to immunosuppressive therapy (such as anti-TNF) or systemic corticosteroids ≥5 mg/d prednisolone	If close contact or from an endemic country People living with HIV or undergoing solid organ transplant or living with silicosis Consider prisoners, homeless people, people who use illicit drugs and healthcare workers Patients commencing anti-TNF therapy	If close contact or from an endemic country People living with HIV or undergoing solid organ transplant Australian residents working for prolonged periods in healthcare settings in a high-incidence country Patients commencing anti-TNF therapy
Diagnosis	Patient history, chest X-ray, TST and IGRA Use IGRA in BCG-vaccinated individuals	Clinical risk stratification, chest X-ray and IGRA	Clinical history, examination, chest X-ray and IGRA/TST	Clinical history, examination, chest X-ray and IGRA/TST	Clinical history, chest X-ray and TST/IGRA	Clinical history and TST/IGRA
Timing of anti-TNF and LTBI treatment	When there is latent TB and active IBD, anti-TNF therapy should be delayed for at least 3 weeks, except in cases of greater clinical urgency and with specialist advice When active TB is diagnosed, anti-TB therapy must be started and anti-TNF therapy stopped but can be resumed after 2 months if needed	Latent TB should be treated prior to commencing biologics	Chemoprophylaxis should be given before commencing anti-TNF-α treatment In the case of active TB, minimum of 2 months of full chemotherapy directed by a specialist in TB before starting anti-TNF-α treatment	Not addressed	Not addressed	Not addressed

The risk of LTBI reactivation in patients with IBD is related to patient and treatment factors. The European Crohn's and Colitis Organisation (ECCO) recommends clinicians consider screening on a case-by-case basis at the time of IBD diagnosis according to an individualised assessment.[11] During this assessment, patients should be asked about past TB exposure, symptoms, family history of TB and travel to endemic areas. The American College of Gastroenterology (ACG) advocates for screening consideration in patients with IBD prior to immunosuppressive therapy, if they are judged to have a high risk of previous exposure and undiagnosed LTBI.[14] The high risk of previous exposure includes contacts with people known or presumed to have TB and long-term travellers to endemic countries (3–12 months) (Figure 1). Travellers particularly at risk include those who are in close contact with the local population, have occupational exposure and/or, those who are at higher risk of acquisition including children less than 5 years, people who are immunocompromised, cigarette smokers and patients with chronic kidney disease.

In patients who are at low epidemiological risk of LTBI, the anticipation of the treatment regimen is key to screening consideration. Apart from patients commencing anti-TNF therapy, the role of LTBI screening in IBD is not well defined. Table 2 summarises the risk of TB reaction with different classes of IBD treatments and can be used to risk-stratify patients. Given that immunosuppression is associated with a reduction in the sensitivity of screening tests, the investigation should ideally occur when patients are not pharmacologically immunosuppressed to maximise diagnostic yield.[11,15,16,17] The difficulty with IBD management, however, is that the need and urgency for escalation of therapy cannot always be anticipated. Hence, it is not unreasonable to screen all IBD patients at the commencement of immunosuppression. Where there is a need for escalation of therapy to an anti-TNF, for example, and LTBI screening has been performed distantly, it is also prudent to repeat screening if there is the possibility of new exposures/travel in the intervening period.

3 | DIAGNOSIS OF LATENT TUBERCULOSIS

A diagnosis of LTBI is based on clinical history, immunological assays and imaging (Tables 1 and 3). Firstly, patients should be

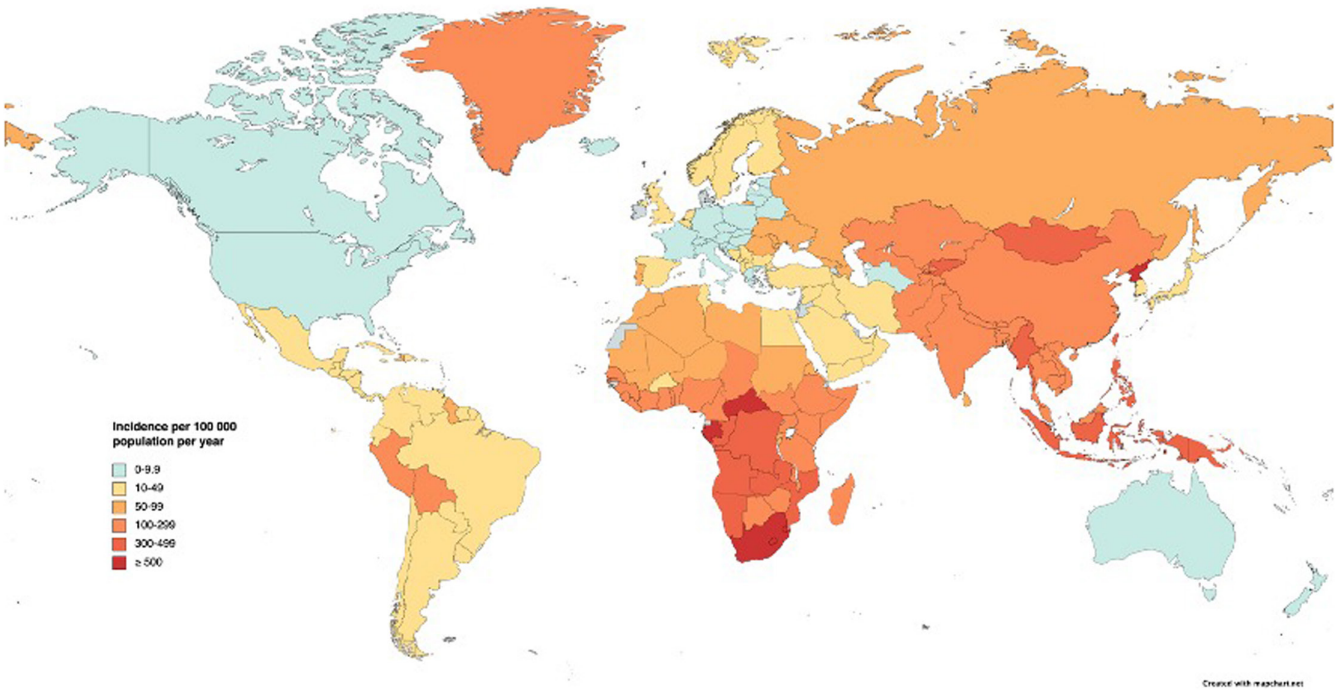

FIGURE 1 Estimated incidence rates of TB. Adapted from https://www.who.int/publications/digital/global-tuberculosis-report-2021/tb-disease-burden/incidence Figure 2.1.5. World Health Organisation; 2021. License: CC BY-NC-SA 3.0 IGO

TABLE 2 Immune modifying agent and risk of TB reactivation

Very low risk	Low risk	High risk
5-aminosalicylates (high-level evidence)	Thiopurines (moderate-level evidence) Methotrexate (moderate-level evidence) Vedolizumab (low-level evidence)	Anti-tumour necrosis factor (high-level evidence) High-dose corticosteroid (high-level evidence) Ustekinumab (low-level evidence) Tofacitinib (low-level evidence) Calcineurin inhibitors (moderate-level evidence)

TABLE 3 Diagnosis, indications and recommendations for LTBI treatment according to IBD therapy

Diagnosis of LTBI	• Use a combination of clinical, radiological and screening tests (TST and/or IGRA).[6,9,13,18] • For indeterminate results repeat testing at 8 weeks post-disease flare or following the cessation of corticosteroids.[23,25] • Involve infectious diseases physicians early where immunosuppressive therapy is emergent
Indications for LTBI treatment	• All decisions regarding LTBI treatment need to be considered in the context of the individual patient. Risks of reactivation with immunosuppressive therapy must be stratified and weighed against the risk of medication side effects, inconvenience of treatment and costs of therapy • By and large, positive test results will be associated with a recommendation to treat, but in some cases, the risk of treatment may be determined to outweigh the benefit • It is important to consider the involvement of an infectious diseases physician in decision-making regarding immunosuppressive therapies and decisions regarding LTBI or active TB infection
Considerations for treatment	• Severity of IBD at diagnosis • Likelihood of requiring escalation to high-risk drugs or combination therapies for IBD • Medication interactions, especially with rifampicin-containing regimens
Management according to a therapeutic agent	
5-aminosalicylates	• Risk of TB reactivation: very low risk • Recommendation: LTBI treatment is not indicated prior to or during treatment • Special considerations: consider potential blood dyscrasias with sulfasalazine and a consequent theoretical risk of reactivation of infection[53-55]
Corticosteroids	• Risk of TB reactivation: very high risk (cumulative dose dependent).[11,59,60,61] • Recommendation: LTBI treatment is indicated in patients commencing prednisolone at a dose of ≥15 mg daily (or its equivalent) for a duration extending beyond 1 month. Ideally, LTBI treatment should be completed prior to corticosteroid commencement. Treatment duration is not impacted by corticosteroid therapy. • Special considerations: corticosteroids are often used in the setting of clinical urgency and, therefore, it is not always possible to complete a course of anti-tuberculosis therapy prior to corticosteroid initiation. In this setting, anti-tuberculosis therapy should be commenced prior to, or at least concomitantly, with corticosteroid initiation and continued until completion. Consider drug interactions when choosing a latent TB treatment regimen
Thiopurines and Methotrexate	• Risk of TB reactivation: low risk[11,71] • Recommendation: LTBI treatment should be commenced prior to or alongside thiopurines/methotrexate. Delaying thiopurine or methotrexate therapy is not warranted. Prioritise LTBI treatment in patients on combination therapy with an anti-TNF. LTBI treatment duration is not impacted by thiopurine or methotrexate therapy. • Special considerations: caution with methotrexate and concurrent anti-mycobacterial treatment due to drug interactions and potential hepatotoxicity[10,78,79,80,81,119]
Tumour necrosis factor inhibitors and anti-interleukin 12/13 (ustekinumab)	• Risk of TB reactivation: very high risk (lower risk in IL-12/23 therapy than with anti-TNF therapy[110,111]) • Recommendation: ideally LTBI treatment should be completed prior to anti-TNF and anti-IL-12/23 commencement.[11,14] In more urgent settings, it is recommended that anti-TNF/anti-IL-12/23 therapy should be delayed for at least 3 weeks of anti-tuberculosis treatment • Special considerations: in the setting of the imminent need for biological therapy, infectious diseases specialist consultation should be sought, but concomitant commencement of LTBI treatment and anti-TNF or anti-IL-12/23 therapy where clinically required can be considered. Anti-tuberculosis therapy should be continued until completion, and treatment duration is not impacted by anti-TNF or anti-IL-12/23 therapy
Anti-integrin (vedolizumab)	• Risk of TB reactivation: low risk.[107,108] • Recommendations: LTBI treatment should be commenced prior to or alongside vedolizumab, especially in individuals using combination therapy. Treatment with vedolizumab should not be delayed in order to commence LTBI treatment
Janus kinase (JAK) inhibitors (tofacitinib)	• Risk of TB reactivation: very high risk • Recommendation: ideally, LTBI treatment should be completed prior to tofacitinib use. In more urgent settings, tofacitinib therapy should be delayed for at least 4 weeks of LTBI treatment with close monitoring for potential drug interactions • Special consideration: in the setting of the imminent need for tofacitinib use, infectious diseases specialist consultation should be sought, but the treatment of LTBI can be considered concurrently with tofacitinib commencement where clinically indicated. The anti-tuberculosis therapy should be continued until completion and treatment duration is not impacted by tofacitinib therapy. Consider drug interactions when choosing a latent TB treatment regimen
Calcineurin inhibitors (cyclosporine, tacrolimus)	• Risk of TB reactivation: very high risk • Recommendation: ideally, LTBI treatment should be completed prior to CNI use. In more urgent settings, CNI therapy should be delayed for at least 3 weeks of LTBI therapy with close monitoring for potential drug interactions • Special consideration: in the setting of the imminent need for CNI use, infectious diseases specialist consultation should be sought, but the treatment of LTBI can be considered concurrently with calcineurin inhibitors where clinically indicated. The anti-tuberculosis therapy should be continued until completion, and treatment duration is not impacted by calcineurin inhibitor therapy. Consider drug interactions when choosing a latent TB treatment regimen

screened for risk factors for past exposure including symptoms, personal history and travel history to endemic areas. LBTI is suggested by evidence of sustained immunological response to *Mycobacterium tuberculosis* antigens, by tuberculin skin test (TST) or interferon-gamma release assay (IGRA), in the absence of active TB infection either clinically or radiographically.[18] Screening may vary slightly depending on whether the patient resides in TB-endemic or non-endemic areas (see Figures 1 and 2a,b).

3.1 | Testing for LTBI

There is no gold standard test for the diagnosis of LTBI; TST and IGRA each have their own advantages and disadvantages.[6,9,12,18]

3.2 | Tuberculin skin test

This involves the intra-dermal injection of tuberculin-purified protein derivative (PPD). This induces a T-cell-mediated hypersensitivity response in patients with prior TB exposure, leading to an area of induration at the injection site within 48–72 h. The diameter of the induration is then measured by a trained clinician.[19] Threshold values for a positive test are based on the patient's pre-test probability of LTBI as well as their likelihood of progressing to active TB. Accepted diagnostic values are[8,12,19]:

- ≥5 mm in children <5 years old and immunosuppressed individuals (i.e. infected with HIV or on immunosuppressive therapy, including those on TNF inhibitors, chemotherapy and prednisolone >15 mg day)

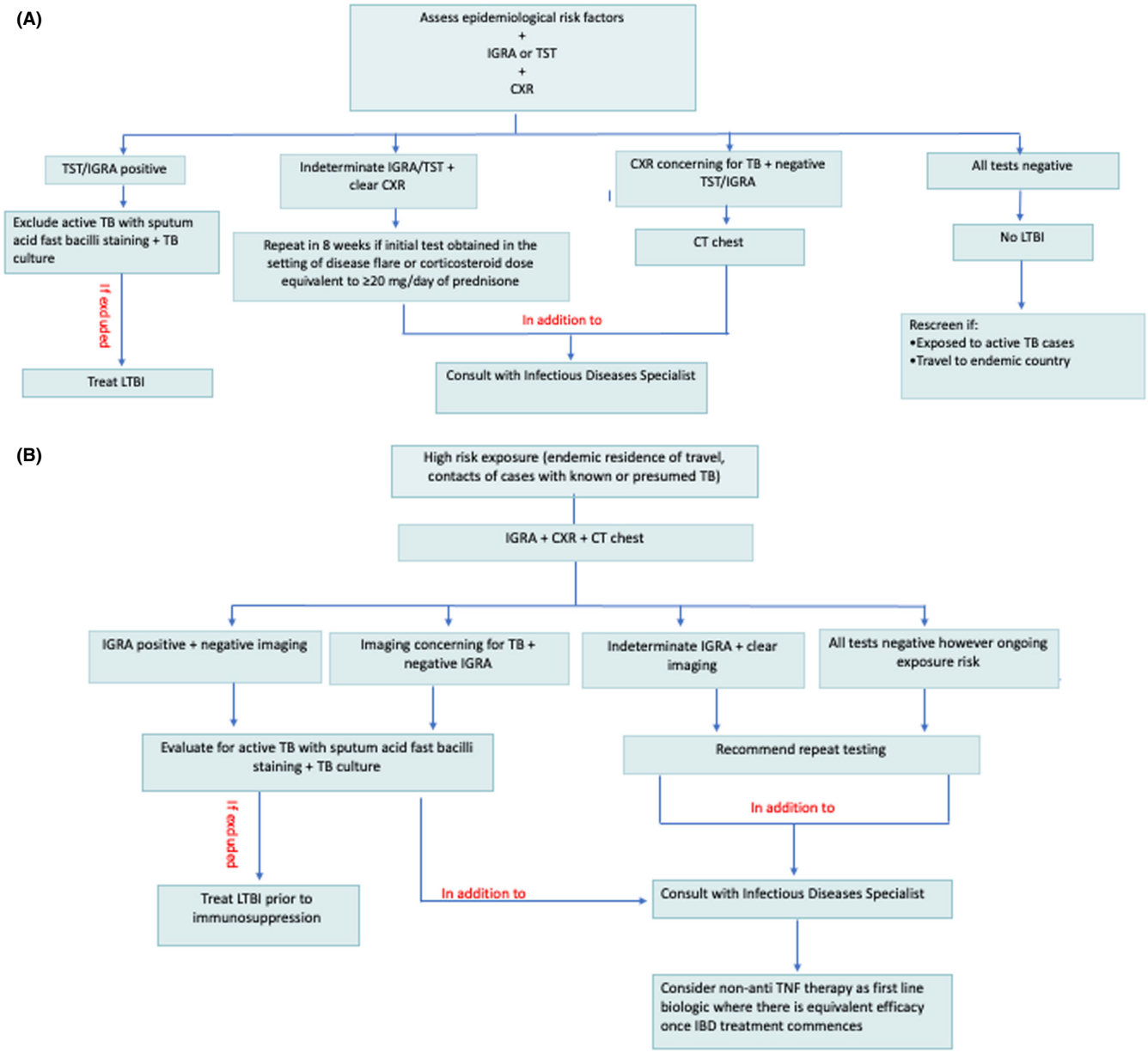

FIGURE 2 Detection of LTBI in IBD patients. (a) Detection of LTBI in non-endemic areas. (b) Detection of LTBI in endemic areas

- ≥5 mm but <10 mm in patients who are likely to be infected and have a high risk of progression.
- ≥10 mm but <15 mm in patients who are likely to be infected and have a low to intermediate risk of progression.
- ≥15 mm in patients who are unlikely to be infected.

Disadvantages to the TST method include the requirement for trained personnel to perform the test, risk of clinician subjectivity in interpreting the test and the requirement for a follow-up visit to assess the response to PPD injection. False-positive results may occur when an individual has a non-TB mycobacterial infection or has previously received vaccination with Bacillus of Calmette and Guerin (BCG). Conversely, false-negative results can occur in those with pharmacological immunosuppression or immunodeficiency, recent vaccination for measles, mumps and rubella (MMR) or those with recent TB exposure.[19]

3.3 | Interferon-gamma release assay

This involves testing a patient's blood for T-cell response with interferon-gamma release to antigens specific to *Mycobacterium tuberculosis*.[18,20] IGRA is more expensive than TST and requires venepuncture. Two different IGRAs have been marketed: The QuantiFERON Gold (In-Tube and Gold Plus) and the T-Spot TB. The QuantiFERON tests use specialised blood collection tubes containing specific TB antigens and then measure interferon-gamma production from circulating T-lymphocytes.[27,28] The T-Spot TB uses enzyme-linked immunoassays (ELISPOT) to count T-lymphocytes sensitised to TB antigens, producing a count of the number present in collected samples.[21] Both tests measure T-cell sensitisation to TB antigens via interferon-gamma responses and are here considered effectively equivalent.

IGRA may return indeterminate results. This refers to a failure of the positive or negative mitogen control to elicit the expected interferon-gamma response. The two possibilities making the test uninterpretable include a strong response to the negative control or weak response to the positive control.

Having a diagnosis of IBD in itself does not appear to lead to an increased likelihood of an indeterminate result, but patients who are experiencing an IBD flare or are actively immunosuppressed (particularly with prednisolone doses equivalent to ≥20 mg/day) appear to be at a greater risk.[22-24] A large study evaluating 3002 patients undergoing testing with IGRA showed indeterminate or equivocal results in 107 patients (3.6%). Indeterminate results were more likely in individuals tested prior to initiation of biological therapy compared to other groups, which may reflect concurrent immunosuppressive medication or the influence of underlying disease activity.[25] On repeat testing within 6 months, 52% returned negative, 13% positive, 23% equivocal and 9% indeterminate, highlighting the difficulty in interpreting these results.

There are two strategies that can be followed after an indeterminate IGRA test. First, the IGRA should be repeated once using the same test initially performed. Ideally, repeat testing should be performed after the resolution of a disease flare and/or after corticosteroids have been ceased, and no sooner than 8 weeks after initial testing. However, high-risk patients should be referred to an infectious diseases consultant for the guidance in management. The second option is to perform a TST after an indeterminate IGRA. Although this is a valid screening method and TST is reliable following an IGRA test, it is important to note that an IGRA result is not reliable after TST as TST may 'boost' the immune response after 3 days.[26]

3.4 | Comparison of assay performances

Studies directly comparing TST and IGRA in the same populations have failed to definitively conclude that one is superior to the other.[27-31] A meta-analysis including IBD patients demonstrated a moderate to strong concordance between TST and IGRA at 85% (95% confidence interval [CI] 77%–90%).[32] Recommendations vary between guidelines, with older guidelines recommending the use of TST,[33-38] while more recent guidelines endorse the use of IGRA.[39-41] The World Health Organisation recommends TST or IGRA as equivalent options, with local practical factors determining which test should be used.[9] Some guidelines suggest both should be used to maximise diagnostic yield with acceptance of the likely higher false-positive rate.[6,12,42,43,44,45]

3.5 | Imaging

Screening for TB also includes performing a clinical examination and chest x-ray.[9,11,18,35] Chest X-ray has good sensitivity but poor specificity; in patients with radiological features of TB on chest X-ray chest, computed tomography can be used to delineate between active and LTBI[46] and to identify false-positive results[47,48] (see Figure 2a). CT chest is also used as a screening tool in place of CXR in many TB-endemic countries or in cases where suspicion of LTBI is high where the risk of false-negative results is of higher concern (see below: Management of LTBI in TB-endemic countries) (see Figure 2b). The rationale for this is highlighted in a retrospective study of IBD patients in China which 28% had LTBI on CT chest with concordance between serological assay and imaging fallible.[49] Further, a recent study from India suggests that in TB-endemic areas, the high risk of TB reactivation upon commencing anti-TNF therapy can be significantly reduced with a stringent screening strategy that includes all the clinical history, TST, IGRA, CXR and CT chest.[50]

4 | INDICATIONS FOR TREATMENT OF LTBI

The general indications for LTBI treatment include persons with a high risk of TB reactivation or those with a high pre-test probability with indeterminate or negative results.[51] Guidelines advocate

preventative treatment in patients who require anti-TNF therapy (Tables 1 and 3). However, there is no consensus as to whether all patients diagnosed with IBD and LTBI should undergo empiric anti-mycobacterial treatment, nor is it standard clinical practice. Although immunosuppressive therapy is avoided or minimised where possible, the current treatment paradigm in IBD heavily emphasises the importance of escalating therapy to achieve early remission and long-term maintenance of remission. The individual likelihood of requiring a biological agent and/or combination therapy needs to be considered when determining whether or not to treat LTBI.

It is important to be cognizant of the nature of IBD as a progressive or relapsing condition, whereby an acute disease relapse may warrant the urgent need for escalation of management. This may include high-dose corticosteroid use. Hence, early LTBI therapy may be warranted, so as to ensure relatively urgent immunosuppression is not precluded or complicated. Additionally, such a 'pre-emptive' strategy may reduce the potential risk of commonly encountered drug interactions between anti-tuberculous and immunosuppressive therapies.

Indications for LTBI treatment are summarised in Table 3.

5 | TREATMENT OF LTBI

The drugs available for the treatment of LTBI, the recommended duration of therapy, advantages and disadvantages and side effects are shown in Table 4. Current national and international guidelines vary, and these are outlined in Table 5.

6 | MANAGEMENT OF LTBI ACCORDING TO THERAPEUTIC AGENT

The risk of TB reactivation with the various IBD immune modifying agents is summarised in Tables 2 and 3. The recommendations around LTBI treatment according to therapy are summarised in Table 3. The timing around IBD medication initiation and treatment of LTBI is summarised in Figure 3.

6.1 | 5-aminosalicylates

5-aminosalicylates (5-ASAs) and their pro-drug, sulfasalazine, are considered first-line therapies in the induction and maintenance of mildly to moderately active ulcerative colitis.[52] Their exact mechanism of action is not clear, but is likely to be multi-modal. A key function is believed to be the local anti-inflammatory effect on the intestinal mucosa through inhibition of secretion and synthesis of pro-inflammatory cytokines, leukotrienes and prostaglandins.[53]

Large cohort studies evaluating the safety profile of 5-ASAs do not demonstrate an increased risk of serious or opportunistic infections.[54] No association between 5-ASA use and TB reactivation has been described. However, blood dyscrasias are recognised as idiosyncratic adverse drug reactions (ADR). These most commonly present as a mild transient leukopenia, but fatal agranulocytosis has been reported with sulfasalazine use.[55] This could speculatively lead to an increased risk of serious infections and the reactivation of opportunistic infections such as TB.[54]

Given the overall absence of excess risk of TB reactivation in patients using 5-ASAs, there are no current guidelines recommending the initiation of LTBI therapy in 5-ASA users.

6.2 | Corticosteroids

Short-term corticosteroids are frequently prescribed in active IBD to reduce inflammation by way of impairing cellular immune response through multiple pathways.[56,57] They are effective in inducing remission but are not recommended as maintenance therapy.[58]

A dose-dependent relationship between the risk of TB reactivation in patients receiving corticosteroids is well established,[59,60] but the specific threshold above which the risk of infection is notably increased remains unknown. In a large multicenter prospective evaluation of patients with Crohn's disease (CD) from the TREAT registry, the incidence of serious infections was 1.7%, with the strongest independent predictor being corticosteroid use (OR 2.21).[60] A case–control study based on a large general practice cohort that included 497 new cases of TB compared with 1977 controls reported an odds ratio of 4.3 for the diagnosis of TB in patients exposed to corticosteroids.[59] The risk was increased in current users and was greatest in patients receiving prednisolone at a dose of ≥15 mg daily. At a physiological dose of 7.5 mg daily, there was a trend towards increased risk, but this did not reach statistical significance. There was also no clear association with prolonged duration or cumulative dose.[70] However, a more recent evaluation of 3806 patients from the Taiwan National Health Insurance Research Database[61] demonstrated that higher cumulative corticosteroid dosage was associated with an increased risk of TB reactivation. ECCO guidelines, consistent with the American Thoracic Society and the U.S. Centers for Disease Control and Prevention (CDC), recommend the treatment of LTBI in patients receiving corticosteroids at a dose equivalent to prednisolone 15 mg/day for at least 1 month.[11,19]

Regarding the timing of treatment, it is important to note that the absolute risk of progressing to active TB even while receiving high-dose corticosteroids in the short term is low; the absolute risk of TB reactivation over 2 years of follow-up in a rheumatological cohort of patients with LTBI who were treated with oral corticosteroids for at least 4 weeks was approximately 5%.[62] The cumulative and daily mean prednisolone doses 1 month prior to TB reactivation were 1 g and 15 mg respectively. Therefore, although infectious diseases consultation is recommended, it is reasonable that where clinical urgency dictates, anti-tuberculosis therapy be commenced concomitantly or just prior to corticosteroid initiation. Prospective evaluation to validate this strategy is desirable.

TABLE 4 Agents available for the treatment of latent tuberculosis

Drug regimen	Pharmacokinetic properties and bioavailability	Advantages	Disadvantages	Side effects	Cost	References
Six months of isoniazid monotherapy (6H[a])	$C_{max:}$ 1–2 h $T_{1/2}$: 0.7–4 h (faster for rapid acetlyators) Bioavailability: 90% Effect of food: reduced absorption and C_{max} Metabolised extensively by the liver. 5%–30% renally excreted (lower for rapid acetylators)	Long-term clinical experience	Hepatotoxicity Peripheral neuropathy (requires pyridoxine supplementation) Poor compliance Emerging resistance	Hepatotoxicity Asymptomatic elevation of serum liver enzymes[ba] Peripheral neuropathy (preventable with pyridoxine co-administration) Dizziness Reduced alertness, mild drowsiness Hypersensitivity reactions Seizures (infrequent)	$	51,158,159
Four months of rifampicin monotherapy (4R)	$C_{max:}$ 1–4 h $T_{1/2:}$ 1.5–5 h Bioavailability: 90%–95% Effect of food: delayed absorption (−36%) and C_{max} ([b]103%), particularly high fatty foods[160] Metabolised 60%–80% by liver 15%–30% renally excreted	Enhanced adherence compared to isoniazid Use in isoniazid resistance	Bodily fluid discolouration Lower risk of hepatotoxicity compared to isoniazid monotherapy Drug interactions common	Orange discolouration of urine, tears, saliva, semen, contact lenses (harmless) Cutaneous reactions Gastrointestinal intolerances Thrombocytopenia Haemolytic anaemias Renal failure Hypersensitivity reactions Flu-like symptoms with intermittent use	$	161-165
Three months of rifapentine–isoniazid combination therapy (3HP)	Rifapentine $C_{max:}$ 4.83–6 h $T_{1/2}$: 13 h Bioavailability: 70% Effect on food: increases AUC and C_{max} by 40%–50% 17% renally excreted	Enhanced adherence compared to isoniazid monotherapy Greater potency and longer half-life compared to rifampicin	Hypersensitivity reactions Lower risk of hepatotoxicity compared to isoniazid monotherapy Drug interactions common	As with rifampicin and isoniazid	$$$	161,166,167
Four months of rifampicin–isoniazid combination therapy (3HR)		Enhanced adherence compared to isoniazid monotherapy. Used in paediatric setting	Hepatotoxicity Peripheral neuropathy (requires pyridoxine supplementation) Drug interactions common	As with rifampicin and isoniazid but combination increases the risk of hepatotoxicity compared to monotherapy	$$$	161,162,168

Time to maximum concentration (C_{max}); elimination half-life ($T_{1/2}$).

[a]Isoniazid (also known as isonicotinic acid hydrazide) is denoted as H in WHO and MSF guidelines.

[b]10%–20% of patients in the first few months of therapy but it can occur at any time.

TABLE 5 Treatment options for latent tuberculosis as per current guidelines (adult dosing)

Drug regimen	Australian therapeutic guidelines	WHO (9)	CDC (19, 98)	NICE
Isoniazid monotherapy (6H)	✓ 10 mg/kg, up to 300 mg daily for 6–9 months	✓ 5 mg/kg/day for 6 months	✓σ 5 mg/kg/day, up to 300 mg daily for 6–9 months OR 15 mg/kg up to 900 mg twice weekly *under* **DOT** for 6–9 months	✓ 10 mg/kg up to 300 mg daily for 6 months
Rifampicin monotherapy (4R)	✓ 10 mg/kg up to 600 mg daily for 4 months	✓ 10 mg/kg/day for 4 months	✓ 10 mg/kg up to 600 mg daily for 4 months	✘
Rifapentine–isoniazid combination therapy (3HP)	✓ Rifapentine: Adult >50 kg: 900 mg weekly × 12 doses Adult ≤50 kg: 750 mg weekly × 12 doses Isoniazid: 15 mg/kg, up to 900 mg weekly × 12 doses	✓*under* **DOT** Rifapentine: 900 mg weekly × 12 doses Isoniazid: 900 mg weekly × 12 doses	✓ under **DOT** Rifapentine: Adult >50 kg: 900 mg weekly × 12 doses. Adult: 32.1–49.9 kg: 750 mg weekly × 12 doses Isoniazid: 15 mg/kg, up to 900 mg weekly x 12 doses	✘
Rifampicin–isoniazid combination therapy (3HR)	✓ Rifampicin: 10 mg/kg up to 600 mg daily for 3 months Isoniazid: 5 mg/kg, up to 300 mg daily for 3 months	✓ Rifampicin: 10 mg/kg/day for 3 months Isoniazid: 5 mg/kg/day for 3 months	✓ Rifampicin: 10 mg/kg up to 600 mg daily for 3 months Isoniazid: 5 mg/kg, up to 300 mg daily for 3 months	✓ Rifampicin: up to 600 mg daily for 3 months if >50 kg, up to 450 mg if adult <50 kg Isoniazid: up to 300 mg daily for 3 months

✓ recommended.

DOT recommendation with directly observed therapy (DOT).

✘ Not recommended.

σ CDC guidelines preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.

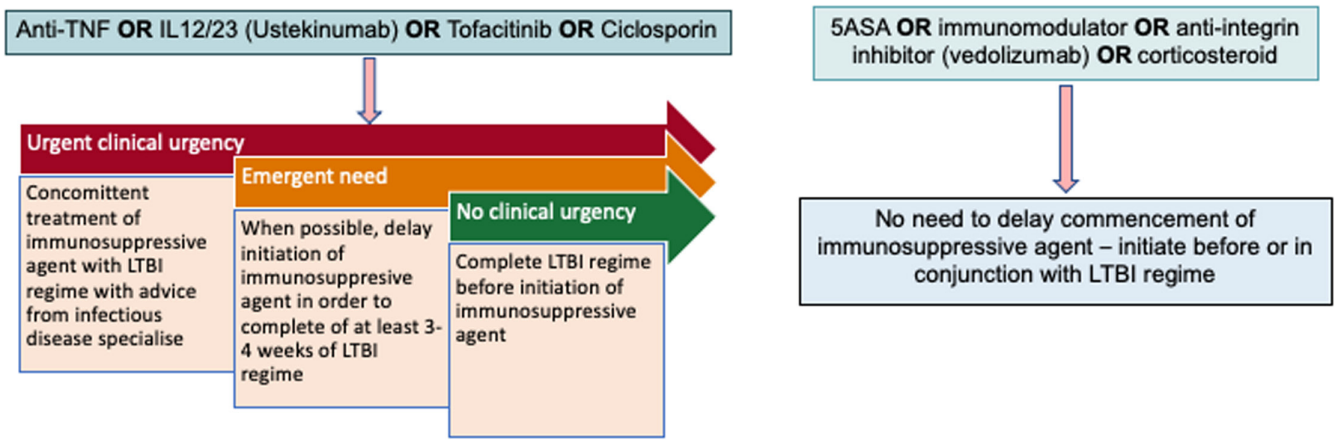

FIGURE 3 Initiation of immunosuppressive treatment with LTBI in IBD

The pharmacokinetic effects of rifampicin on corticosteroid clearance and bioavailability are important to consider. Rifampicin increases the plasma clearance of prednisolone by up to 45% and reduces the amount of drugs available to the tissues by up to 66%. Thus, doubling the prednisolone dose in order to achieve therapeutic concentrations can be considered or a rifampicin-free regimen may be offered.[63]

6.3 | Immunomodulators

6.3.1 | Thiopurines

Thiopurines (including mercaptopurine and its pro-drug azathioprine) are purine analogues that have cytotoxic effects on dividing cells, therefore impairing adaptive immune responses.[64,65] These

immunomodulators are frequently used as maintenance therapy for patients with moderate to severe IBD.[66] Due to their delayed onset of action and time to maximal pharmacodynamic effect, immunomodulators often require concomitant induction medication administration for the first 6–8 weeks of therapy.[67] Importantly, when considering the risk of TB reactivation, they are also often used synergistically with biological agents to increase efficacy and reduce immunogenicity.[68,69]

In addition to their therapeutic immune-modulating effects, thiopurines induce dose-dependent myelosuppression, with an increased risk of infections.[70,71] Thiopruines appear to particularly reduce the immune response to viruses, with their use associated with up to a fivefold increase in the risk of herpes simplex virus lesions and significant worsening of viral warts.[72] The literature is, however, conflicting regarding the specific risk of thiopurine-associated respiratory tract infections or pulmonary infections. In a large registry, the risk of opportunistic infections with thiopurine monotherapy was lower than that of placebo.[59,60] However, in a cohort study of 3806 Taiwanese patients, the risk of TB reactivation was increased in association with a high cumulative thiopurine dosage (50 mg/day for more than 1 year) (HR = 3.6, 95% CI: 1.7–7.3).[61] The SONIC and UC-SUCCESS trials compared thiopurine therapy alone or in combination with an anti-TNF in patients with Crohn's disease and ulcerative colitis, respectively, and did not demonstrate an increased risk of opportunistic infections with combination therapy compared to monotherapy. However, these studies were limited by the exclusion of patients at high risk of infections and short follow-up periods.[68,69] A recent systematic review comprising 40 randomised controlled trials reported that the highest risk of TB reactivation was associated with combination therapy compared to controls (OR 54; 95% CI 5.3–88) and with anti-TNF monotherapy (OR 13.3; 95% CI 3.7–100).[10]

Thiopurines have also demonstrated in vitro dose-dependent antibacterial activity against *M. paratuberculosis*. The capacity of the drugs to limit the growth of *M. paratuberculosis* was more pronounced with mercaptopurine than that of azathioprine, but neither agent was bactericidal.[73]

There are no current guidelines advocating for the treatment of LTBI in patients treated with thiopurines.

6.3.2 | Methotrexate

Methotrexate is most commonly used in patients with Crohn's disease who are intolerant or refractory to thiopurines or, in CD and UC, in combination with anti-TNF agents.[74-76] Its immunosuppressive activity results from the inhibition of nucleic acid synthesis in activated T cells.[77]

An association between methotrexate and an increased risk of serious and opportunistic infections has not been consistently demonstrated in the literature. In particular, no recognised association with TB reactivation exists. However, when used in combination with anti-TNF therapy, a substantially increased risk of TB reactivation has been reported. This risk is greater than the additive risk of both therapies.[10,78]

There are no current guidelines detailing recommendations to treat LTBI in patients treated with methotrexate.

Both methotrexate and anti-mycobacterial therapeutic agents are associated with hepatotoxicity.[79,80] Using these medications in combination has the potential to cause significant morbidity.[81] Additionally, since rifampicin may reduce the serum concentrations of methotrexate, the use of a rifampicin-free regimen should be considered.[82]

6.4 | Tumour necrosis factor-alpha inhibitors (anti-TNF)

Anti-TNF therapy is recommended for induction and maintenance of moderately to severely active IBD in patients who are steroid-dependent or steroid-resistant and/or refractory to immunomodulators[68,83,84,85] and as primary induction therapy for perianal fistulizing Crohn's disease.[86,87] TNF-dependent chemokines play a critical role in the process of granuloma formation.[88] The presence of TNF-alpha within macrophage-rich granulomas confers immunological and physical constraints on the *M. tuberculosis* infection. Thus, impairing granuloma formation with anti-TNF therapy increases susceptibility to reactivation as well as early dissemination and extra-pulmonary site involvement.[89-91]

While individual randomised controlled trials did not recognise an increased risk of opportunistic infections with anti-TNFs, subsequent real-world use was associated with an increased incidence of active TB, including miliary TB, across North America and Europe.[85,92,93] An increased risk of opportunistic infections, including TB, associated with anti-TNF therapy was demonstrated in large observational cohorts of patients with rheumatoid arthritis, including in countries with low TB prevalence.[89,91,94,95] In a systematic review and meta-analysis that included 14,683 patients from 40 randomised controlled trials, there was a higher incidence of active TB in patients on anti-TNF monotherapy compared to controls (2/5769 vs 0/4673, OR 4; 95% CI 0.2–15.7). The risk was more substantial in the anti-TNF group that included patients on combination therapy (OR 24.8; 95% CI 2.4–133).[10] Although there are no head-to-head trials, observational studies have not shown significant differences in the risk of TB reactivation comparing the different anti-TNF agents used in IBD.[89] Not surprisingly, concomitant prednisolone is a consistent predictor of TB reactivation.[96]

Several guidelines recommend completing treatment of LTBI prior to the commencement of an anti-TNF agent where possible.[9,11,14,19,97] When this is not possible, guidelines vary in terms of the duration of anti-tuberculous therapy required prior to commencing anti-TNF but the majority recommend completing between 1 and 2 months despite the lack of clinical evidence justifying these time frames.[37,40] ECCO guidelines recommend delaying anti-TNF therapy until 3 weeks of antituberculosis therapy has been completed,[11] ACG clinical guidelines recommend 'several weeks or months'[97] and

WHO guidelines do not specify details on timing.[9] In cases of greater clinical urgency, accepted earlier institution of immunosuppressive agents is advised, but only once active TB has been adequately excluded.

In patients requiring urgent anti-TNF therapy, infectious diseases consultation is recommended where possible. Additionally, although there are no IBD-specific data on this, indirect evidence suggests that a strategy of concomitant commencement of LTBI therapy and severe immunosuppression is safe. For example, in patients undergoing bone marrow and solid organ transplantation who simultaneously start LTBI and immunosuppressive therapy, TB reactivation risk is very low.[98-100]

Importantly, the implementation of guidelines to identify and empirically treat LTBI in anti-TNF exposed patients has demonstrated efficacy.[101] Published data extracted from the BIOBADASER (Spanish Society of Rheumatology Database on Biological Products) cohort showed an impressive reduction in rates of active TB when comparing pre- and post-implementation of LTBI treatment guidelines (IRR 0.22, 95% CI 0.03–0.88; $p = 0.008$).[101] Extrapolation of such findings to the IBD population seems entirely reasonable.

There does not appear to be any interaction between anti-TNF therapies and anti-mycobacterial treatment.

6.5 | Anti-integrin

Vedolizumab is a humanised anti-$\alpha_4\beta_7$ integrin monoclonal antibody recommended for induction and maintenance of moderately to severely active IBD in patients who are refractory to first-line therapies.[102-104] The $\alpha_4\beta_7$ integrin binds mucosal addressing cell adhesion molecule-1 expressed on mucosal endothelial cells to facilitate the homing of gastrointestinal T-lymphocytes, which is inhibited by the integrin antagonist.[105] Vedolizumab has minimal systemic toxicity owing to its gastrointestinal tract selective mode of action.[105,106]

Initial randomised controlled trials demonstrated favourable safety profiles in the short term, particularly in relation to the risk of serious and opportunistic infections.[102,103] However, there may be a small increase in the risk of gastrointestinal infections.[107] Larger phase 4 cohorts including post-marketing surveillance confirm a low incidence of serious infections in the long term with vedolizumab.[108] Pooled data from 2830 patients treated with vedolizumab from six randomised controlled trials identified only four cases of TB. However, patients with LTBI were excluded from screening.[104,107] These cases were, therefore, considered likely or possible primary infections, as they had negative screening tests on study entry. Importantly, all these patients were on concomitant immunosuppressive therapy.

There are no current guidelines available advising management of LTBI in patients requiring or receiving vedolizumab. While its gut-selective actions might theoretically reduce the risk of reactivation, there is a paucity of information about the use of vedolizumab in such patients. Likewise, there is no evidence guiding the timing of concomitant LTBI therapy and vedolizumab therapy, and an ongoing review of the literature in this area is required.

There does not appear to be any interaction between vedolizumab and anti-mycobacterial therapies.

6.6 | Anti-IL-12/23

Ustekinumab is a humanised anti-p40 monoclonal antibody recommended for inducing and maintaining remission in patients with moderate to severe IBD.[109] P40 is a protein subunit shared by two cytokines, IL-12 and IL-23. IL-12 and IL-23 are important in the host defence against intracellular pathogens including *Mycobacteria*.[110,111] Thus, theoretically, the risk of reactivation of TB is similar to that of anti-TNF therapy.

Despite this theoretical concern, there was only one case of TB in the Crohn's disease registration (UNITI) trials for ustekinumab, and this occurred 10 months after the administration of a single dose of 130 mg of ustekinumab intravenously.[109] There are case reports describing TB reactivation in patients on ustekinumab, but only in patients not receiving concomitant anti-tuberculosis therapy.[112] Safety data of 3177 psoriasis patients integrated from five randomised controlled trials included patients with LTBI if treatment was initiated before or at the same time as the first administration of the study drug. No cases of LTBI reactivation occurred in patients who received isoniazid treatment prior to, or concomitantly with, initiation of ustekinumab.[113,114]There are no current guidelines or real-world data available guiding the management of LTBI in patients requiring or receiving ustekinumab, so due to a lack of adequate data, recommendations follow those for anti-TNF agents. Thus, completion of latent TB treatment prior to commencement of ustekinumab is ideal where possible or ustekinumab initiation should be delayed in order to complete at least 3 weeks of anti-tuberculosis treatment. However, this window can be shortened when clinically necessary, although infectious diseases consultation is recommended.

There does not appear to be any interaction between anti-IL-12/23 agents and anti-mycobacterial therapies.

6.7 | Janus kinase inhibitors

This family of orally administered targeted small molecules selectively inhibit interleukin-mediated intracellular signal transmission. Tofacitinib is the first agent available in this class and it is indicated as an induction and maintenance therapy in UC.[115-117]

Increased overall rates of infection are reported with its use, including a consistently reported increased risk of Herpes zoster infection across trials in UC, CD and RA patients. Although no cases of tuberculosis occurred in the initial IBD induction trials, patients with LTBI were excluded from enrolment.[117-119] Pooled safety data have been published from two long-term open-label extension studies evaluating tofacitinib at a dose of 5 or 10 mg

twice daily in 6194 patients RA patients up to 8.5 years.[120] The incidence ratio (IR) for tuberculosis was 0.2 (0.1–0.3), with no notable difference with longer duration exposure. For the statistical analysis, TB rates were stratified by geographical background rates, and 28/36 cases of TB occurred in endemic regions. Out of the 301 rheumatoid arthritis patients with latent TB infection at screening prior to commencing tofacitinib, 23 were considered to be untreated and were, therefore, retreated for 4 weeks prior to study commencement. None of these patients developed active TB.[121]

There are no current guidelines or real-world evidence available to guide the management of LTBI in patients requiring or receiving tofacitinib. However, given its systemic action and association with an increased risk of infection,[120] patients should undergo LTBI screening and treatment if positive prior to initiating tofacitinib. There is no evidence guiding time frames but, as mentioned above, clinical trials required 4 weeks of LTBI treatment before initiation of Janus kinase (JAK)-inhibitor therapy without any cases of reactivation and this seems a reasonable time interval.

Notably, in patients requiring treatment for LTBI who will have concomitant JAK-inhibitor therapy, rifampicin may reduce the serum levels of tofacitinib.[122] Therefore, the use of a rifampicin-free regimen should be considered.

6.8 | Calcineurin inhibitors

The calcineurin inhibitors (CNI), cyclosporine and tacrolimus, are indicated for inducing remission in moderate to severe steroid-refractory IBD.[123-127] Tacrolimus is also used as maintenance therapy[128] and in suppository and enema formulation for patients with proctitis.[129] Tacrolimus has a more favourable pharmacokinetic and side-effect profile compared to cyclosporine. However, according to international guidelines, both these agents should be used only as a bridge to a proposed maintenance therapy agent and discontinued within 6 months due to the risk of side effects.[130]

In post-transplant cohorts, CNI is known to increase the risk of active TB infection.[131,132] A retrospective study reported a 2.5 times higher ($p = 0.0311$) risk of early post-transplantation TB with cyclosporine therapy compared to patients treated with a combination of corticosteroids and azathioprine.[133,134] However, patients undergoing bone marrow and solid organ transplantation who simultaneously start LTBI and immunosuppressive therapy have a very low risk of TB reactivation.[98-100]

The risk of CNI-related serious and opportunistic infections in non-transplant settings is lower,[135,136] which likely reflects dosing and concomitant immunosuppressive agents. The dose range for most rheumatological and dermatological conditions is 2.5–5 mg/kg, which is much lower than the doses used in the transplant setting. In IBD, the initial dose of cyclosporine is 2 mg/kg, which has been compared directly to 4 mg/kg demonstrating no difference in efficacy.[137]

There are no current guidelines regarding the management of LTBI in IBD patients receiving CNI therapy. However, patients receiving CNI prior to or following solid organ or haematological transplantation are recommended to undergo LTBI screening and treatment. Despite the lower dose used for IBD patients, CNI has systemic immunosuppressive action and therefore LTBI treatment should ideally be completed before initiation of CNI therapy. Where this is greater clinical urgency, as per the recommendations for anti-TNF-based therapies, delaying CNI therapy until at least 3 weeks of anti-tuberculosis treatment would be a reasonable approach.

Notably, in patients requiring treatment for LTBI who will have concomitant CNI therapy, rifampicin may reduce the serum levels of the CNI.[138] Therefore, the use of a rifampicin-free regimen should be considered.

7 | MONITORING DURING LTBI TREATMENT

Close follow-up during LTBI treatment is essential. Monitoring for adverse effects, including hepatotoxicity and neurotoxicity, is prudent and should be performed according to the individual patient's risk. Patients with risks or cofactors for liver injury, including excessive alcohol consumption (all patients should be counselled to minimise alcohol intake during treatment), female sex, age >65, malnutrition, hepatotoxic medications (such as methotrexate and thiopurines), concomitant viral hepatitis or underlying liver disease, warrant at least monthly liver function tests. This is particularly important with isoniazid, or when baseline liver function tests are abnormal.[139]

Patient education is required on the need for avoidance of alcohol consumption and medications that induce livery injury, and immediate reporting of symptoms should they arise.[140] Symptoms of hepatotoxicity may include fatigue, nausea, right upper quadrant pain, pruritis and jaundice.

Treatment interruption is required, with a modified or alternative regimen instituted, when liver function test derangement meets the following criteria: alanine aminotransferase (ALT) >3× upper limit of normal (ULN) with symptoms or >5× ULN in asymptomatic patients.[139] Drug-induced liver injury secondary to anti-tuberculous medications can progress to fulminant hepatic failure in approximately 1% of cases, particularly when drug-induced hepatitis is recognised late, reinforcing the need for vigilant monitoring.[141,142]

Additionally, 'directly observed therapy' can be implemented to ensure adherence to particular regimens such as rifapentine–isoniazid combination therapy. Directly observed therapy involves patients being provided with and observed taking their medications each day. This strategy is used to prevent relapse and the development of

resistance.[143] Directly observed therapy has been shown to improve the likelihood of completing anti-TB therapy courses but is not warranted in all patients. Rather, this strategy should be considered in individuals with a high risk for non-adherence.[143,144]

8 | DRUG INTERACTIONS

Anti-mycobacterial agents interact with other medications as well as among themselves (Table 6). Additionally, the use of drug

TABLE 6 Drug–drug interactions and toxicity risk between anti-mycobacterial agents and IBD therapies

	Isoniazid	Rifampicin	Rifapentine Given rifapentine is a moderate CYP3A4 inhibitor, similar effects but to a lesser extent are expected with drugs compared to rifampicin, a strong CYP3A4 inhibitor
5-ASA	🟠	🟠	🟠
Methotrexate	🟣 Hepatotoxicity Both agents have the potential to increase liver function tests. Monitor blood	🟣 Hepatotoxicity	🟣 Hepatotoxicity
Thiopurines	🟠 Hepatotoxicity Both agents have the potential to increase liver function tests. Monitor blood and consider that raised liver enzymes at beginning of isoniazid could be thiopurine related to those patients on thiopurines	🟠	🟠
Infliximab	🟠	🟠	🟠
Adalimumab	🟠	🟠	🟠
Golimumab	🟠	🟠	🟠
Vedolizumab	🟠	🟠	🟠
Ustekinumab	🟠	🟠	🟠
Tofacitinib	🟠	🔴 Tofacitinib is ↓ AUC reduced by about 85% and C_{max} reduced by about 75%. Consider alternative IBD therapy	🟣 Tofacitinib is ↓ Likely to be significant, recommend avoid
Prednisolone	🟣 Isoniazid is ↓	🔴 Prednisolone is ↓ AUC reduced by about 60%, half-life decreased by 40%–60%.[169] Maximum interaction by day 14. Interaction disappears 14 days after rifampicin withdrawal.[63] Consider increasing prednisolone by two–three-fold	🟣 Prednisolone is ↓
Opioids	🟠	🔴 Opioids are ↓ Decrease in morphine AUC by 28%, C_{max} by 41%. Decrease in oral and IV oxycodone AUC by 53% and 86%, respectively, and reduced oral bioavailability from 69% to 21%.[170,171]	🟣 Opioids ↓
Calcineurin inhibitors	🟠	🔴 Calcineurin inhibitors are ↓ Tacrolimus and cyclosporine are reduced through the induction of CYP450 with rifapentine. Monitor calcineurin levels carefully	🔴 Calcineurin inhibitors ↓ Reduction of calcineurin levels is less marked with rifapentine compared to rifampicin. However, careful monitoring of calcineurin levels is still recommended

🟠 Nil interactions.
🟣 Consider monitoring and theoretical interaction.
🔴 Interaction expected, dose adjusted as appropriate.

combinations to enhance efficacy and reduce the emergence of resistance, as well as the protracted courses of treatment, increase the likelihood of patients requiring the use of concomitant medications.

9 | LTBI MANAGEMENT REQUIRING IMMINENT IMMUNOSUPPRESSION

There are particular circumstances when patients with IBD require immediate commencement of immunosuppressive therapy. First-line therapy during a severe IBD flare is usually institution of high-dose corticosteroid therapy. In patients with acute severe ulcerative colitis inadequately responding to 72 h of corticosteroid therapy, guidelines recommend initiation of rescue immunosuppressive therapy with either anti-TNF therapy or cyclosporine.[145] Therefore, patients who have not previously been tested for LTBI or have had possible TB exposure since testing should undergo LTBI screening on admission to expedite results.

There are no data available handling TB-reactivation risk in this specific setting in patients with LTBI. However, there is some literature evaluating outcomes of other cohorts of patients needing urgent immunosuppressive therapy who are simultaneously diagnosed with latent or active TB, including patients undergoing bone marrow and solid organ transplantation. The evidence overall supports the simultaneous commencement of active and LTBI therapy with immunosuppressive therapy.[98-100] However, collaborative specialist physician-driven management for both IBD and TB is required in these settings.

Other complicating factors to carefully consider are the drug interactions that exist between rifampicin and rescue immunosuppressive medications. Rifampicin lowers the drug concentrations of calcineurin inhibitors (cyclosporine and tacrolimus) and corticosteroids. A combination of immunosuppressive and anti-TB therapy also increases the risk of adverse drug events. Alternatives, such as the use of rifabutin, may be considered given the lesser degree of interaction with immunosuppressive medications.

In the event that a patient requires urgent immunosuppression and LTBI screening for is positive or indeterminate, referral to an infectious disease physician is essential. These complex clinical scenarios require multidisciplinary teams to carefully consider each individual case.

10 | MANAGEMENT OF IBD IN TB-ENDEMIC COUNTRIES

The approach to the investigation and management of LTBI in IBD patients is similar between TB-endemic and non-endemic countries. However, the prevalence of LTBI in these countries is evidently higher, and thus injudicious anti-TNF use may pose a serious health risk.

Due to the high prevalence of tuberculosis in these countries, chest radiographs combined with the TST or IGRA may be insufficient to screen for tuberculosis.[48] Therefore, chest computer tomography has sometimes been recommended as an adjunctive to IGRA before commencing immunosuppressive therapies,[146,147] including prior to biological agents and small molecule inhibitors, in high-prevalence regions.[46] Supporting this, a recent study from India demonstrated that stringent screening for LTBI prior to anti-TNF therapy that includes clinical history, TST, LTBI, CXR and CT chest can significantly mitigate the risk of TB reactivation.[50] In this study by Kumar et al,[50] 112 patients were screened between January 2005 and January 2019 with a less stringent regimen of clinical history and TST plus or minus an IGRA, CXR and/or CT chest at the discretion of the treating physician. Their outcomes were compared to 59 patients screened after January 2019 with the stringent screening strategy. Patients were commenced on chemoprophylaxis if any of the tests were positive. On the follow-up, 17% developed TB in the earlier less stringent screening group compared to only 1.7% in the later stringent screening cohort, suggesting the benefit of complete screening that includes CT chest in patients from high risk, endemic areas. Increasing the diagnostic yield of testing is considered particularly important in more urgent settings such as acute severe ulcerative colitis, during which the cost and risk of radiation is outweighed by the need to identify and treat cases of LTBI. However, clinical practice varies significantly as this remains an almost evidence-free zone.

Furthermore, patients with negative baseline LTBI tests on immunosuppressive therapy who have an ongoing high risk of TB exposure may be considered for repeat testing, although there is limited evidence to guide recommendations.

Finally, the management of IBD in TB-endemic countries should follow the same principles as in non-TB-endemic countries. However, when selecting immunosuppressive therapies, the ongoing risk of TB infection should be taken into account. Where there is equivalent efficacy, non-anti-TNF therapies may be chosen as the first-line biological therapy.

11 | SURVEILLANCE OF LTBI DURING IMMUNOSUPPRESSION

Existing guidelines vary in terms of ongoing surveillance for exposure to, and acquiring, TB infection during immunosuppression.[33,37,40,43,148] It is recommended that clinicians should take a clinical history and perform a respiratory examination at each review. However, this is not consistent with clinical practice nor is it always possible as fewer face-to-face appointments are being conducted with the increasing use of telehealth in the COVID-19 era. Routine laboratory or imaging surveillance is not recommended but should be considered if a patient reports a new exposure.

A prospective trial over 3 years demonstrated that IGRA conversion commonly occurred in areas with intermediate TB burden and that IGRA levels higher than 4.00 IU/ml were independently associated with the development of active TB (incidence rate ratio 42.2, 95% CI 17.2–99.7, $p < 0.001$).[149] This study suggests the potential role of serial IGRAs during immunosuppressive therapy, supporting

the guidelines that advise annual TB screening.[33,40,148] However, this recommendation is not universally purported.[37,43]

12 | REPEAT TESTING FOR PATIENTS TRAVELLING TO ENDEMIC COUNTRIES

A recent global survey of 305 IBD physicians assessed clinicians' management strategies for patients on immunosuppressive therapies visiting TB-endemic areas. Great variability in practice was demonstrated. This may reflect the absence of current guidelines on how to approach the management of these patients prior to and during their travel.[150]

There are three phases of travel risk assessment during which travel medicine practitioners may institute risk-reducing measures, defined as pre-travel, during travel and post-travel.

12.1 | Pre-travel

Pre-travel risk assessment consists of a thorough history exploring the likelihood of TB exposure and ascertaining the relative susceptibility of the individual. Countries being visited and the length and location of stay should be evaluated according to the background incidence of TB, as well as multi-drug-resistant TB, in the region. Recreational and work activities may expose additional occupational hazards such as for healthcare workers. As previously mentioned, those at higher risk include patients visiting friends and relatives, children less than 5 years old, immunocompromised individuals (HIV infection, anti-TNF and corticosteroid therapy), cigarette smokers and patients with chronic kidney disease.[151]

For persons at high risk of exposure or those who are at greater risk of developing active TB following initial infection, testing with LTBI should be initiated prior to travel with either IGRA or TST. A baseline negative test is useful for comparison post-exposure. If a person is found to have LTBI, then consideration of treatment should be made on a case-by-case basis. The presently available BCG vaccination has an approximated efficacy of only 50%. Routine practice includes vaccinating high-risk persons travelling to high-prevalence countries for over 1 month including children younger than 5 years old and healthcare workers. Unfortunately, BCG is contraindicated in the setting of immunodeficiency/immunosuppression.[152]

12.2 | During travel

Risk reduction interventions should be recommended to travellers who will be in prolonged contact with people infected with TB, particularly those working or living in confined spaces. This has been addressed in previous publications.[153] Personal protective wear such as appropriately ventilated masks can be taken. Alternatively, seeking guidance from local practitioners regarding the availability of personal protective equipment should be encouraged.

12.3 | Post-travel

In a returned traveller, the post-travel assessment should focus on identifying signs and symptoms suggestive of active TB. If there is any suspicion of a pulmonary tuberculous infection, the patient should immediately be referred for expert evaluation. For asymptomatic persons with a known or high likelihood of exposure, assessment for LTBI is recommended with either IGRA or TST, usually 8–10 weeks after return. Although delayed testing may increase the risk of missing early seroconverts and those who fail to attend, this represents the time at which the result becomes more reliably positive.[154] In the setting of recent exposure and conversion from a negative to a positive test for LTBI, treatment should be considered, as the risk of progression to active disease is most significant in the first few years post-exposure.[153]

13 | SURVEILLANCE OF PATIENTS PREVIOUSLY TREATED FOR LTBI

Cure rates with completed therapy are as high as 90% depending on the regimen and duration of therapy. However, protracted courses reduce adherence rates, which can increase the risk of reactivation, supported by increased relapse rates that occur with therapy duration reduction.[155] However, it is very much dependent on the regimen used as randomised controlled trials evaluating a shortened fluoroquinolone containing regimen to 4 months was non-inferior to 6 months.[156,157] Therefore, early discontinuation of some regimens may not impact relapse rates.

Unfortunately, there are no clinical tests available for assessing the risk of relapse or to identify re-exposure in patients who have previously been treated for LTBI given that IGRA and TST do not reliably become negative and frequently remain positive long term after treatment. It is imperative that patients who have previously been exposed and/or treated are educated about their risk of recurrent infection to avoid further exposure where possible. In the setting of incomplete treatment or likely re-exposure, such as in a returned traveller from an endemic country, clinical history, physical examination and imaging with either a chest X-ray or a CT scan must be performed with clinicians maintaining a low threshold for active disease.

14 | GAPS IN EVIDENCE

The literature is limited with regard to LTBI screening, diagnosis and treatment indications in the IBD population. There are no clinical trials evaluating the timing of LTBI therapy in relation to the use of immunosuppressive therapies or duration of anti-TB therapy, resulting in guidelines that have major methodological gaps in their recommendations for this cohort. Additionally, the risk of exposure and acquisition of LTBI in IBD patients following travel or migration to high-prevalence countries is not well characterised in the literature.

As such, the capacity to develop evidence-based guidelines to advise these patients, as well as to screen and treat them, is limited.

15 | CONCLUSION

TB infection is of paramount relevance to the IBD population given the increasing likelihood of immunosuppression. Therefore, proactive screening in all patients with IBD is recommended.[11,14] Summarised is a suggested approach to screening, diagnosis and management of LTBI in the setting of IBD and the frequently used medications. Ongoing surveillance for LTBI is advised in patients with IBD throughout the course of their disease, particularly following travel to endemic countries, high-risk exposures and in the context of drug therapy escalation. Active collaboration with infectious diseases clinicians, especially in complex cases such as those requiring emergent immunosuppression, is imperative. There remain major gaps in evidence in many situations, particularly in association with specific newer therapeutic approaches. Reporting of real-world experience will be important in changing current recommendations that aim to mitigate the detrimental effects of LTBI on achieving IBD control and vice versa.

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