Mycobacterial infections in adults with haematological malignancies and haematopoietic stem cell transplants: guidelines from the 8th European Conference on Infections in Leukaemia

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Mycobacterial infections, both tuberculosis and nontuberculous, are more common in patients with haematological malignancies and haematopoietic stem cell transplant recipients than in the general population—although these infections remain rare. Mycobacterial infections pose both diagnostic and therapeutic challenges. The management of mycobacterial infections is particularly complicated for patients in haematology because of the many drug–drug interactions between antimycobacterial drugs and haematological and immunosuppressive treatments. The management of mycobacterial infections must also consider the effect of delaying haematological management. We surveyed the management practices for latent tuberculosis infection (LTBI) in haematology centres in Europe. We then conducted a meticulous review of the literature on the epidemiology, diagnosis, and management of LTBI, tuberculosis, and nontuberculous mycobacterial infections among patients in haematology, and we formulated clinical guidelines according to standardised European Conference on Infections in Leukaemia (ECIL) methods. In this Review, we summarise the available literature and the recommendations of ECIL 8 for managing mycobacterial infections in patients with haematological malignancies.

Introduction

Compared with the general population, haematopoietic stem cell transplant (HSCT) recipients and patients with haematological malignancies are at increased risk of developing infections, including tuberculosis and infections by nontuberculous mycobacteria (NTM). These infections mainly affect the lungs but can be disseminated. The diagnosis of mycobacterial infections is frequently delayed because recognition requires a high degree of clinical awareness and specific laboratory investigations. The management of mycobacterial infections is particularly complicated for patients in haematology, because of the many drug-drug interactions between antimycobacterial agents and haematological and immunosuppressive treatments. The risk-benefit balance of treatment options must be carefully weighed up, especially in the case of dormant infections due to *Mycobacterium tuberculosis*. In 2019 and 2021, a working group within the eighth European Conference on Infections in Leukaemia (ECIL 8) addressed the issue of mycobacterial infections in HSCT recipients and patients with haematological malignancies. First, management practices for latent tuberculosis infection (LTBI) in haematology centres in Europe were surveyed. Second, a review of the literature on the epidemiology, diagnosis, and management of latent tuberculosis infection, tuberculosis, and nontuberculous mycobacteria infections among patients in haematology was performed, and clinical guidelines were formulated according to standardised ECIL methods (appendix p 3).

Tuberculosis of patients in haematology

Epidemiology and risk factors

Tuberculosis is an infectious disease caused by *M tuberculosis* that is spread through bacilli-containing aerosol droplets, which are mainly released through coughing. Epidemiology in the haematology setting is closely linked to general tuberculosis epidemiology, which identifies geographical regions according to their tuberculosis burden using variable and evolving definitions.[1–3] We found that the definitions that classify countries as low, intermediate, or high tuberculosis burden best stratify the risk assessment of developing active tuberculosis.[1] In the reviewed studies, the reported tuberculosis frequency in HSCT recipients and patients with haematological malignancies was 2·7% (range 1·5%–16·0%) in eight studies from regions of high tuberculosis incidence (≥100 cases per 100 000 population); 2·2% (range 0·2%–8·5%) in 12 studies from regions of intermediate tuberculosis incidence (20–99 cases per 100 000 population); and 0·7% (range 0·4%–2·3%) in three studies from low tuberculosis incidence regions (<20 cases per 100 000 population).[4–22] Active tuberculosis can be due either to reactivation of *M tuberculosis* in patients previously infected, or primary infection in the case of *M tuberculosis* exposure. Immune suppression increases the risk for active tuberculosis, especially when the anti-tuberculosis immune response is impaired (ie, the quality of the T-cell response and the IFNγ immune axis). The risk of developing active tuberculosis is higher in patients with haematological malignancies than in the general population, even in low tuberculosis endemic

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See Online for appendix

countries, although HSCT recipients and patients with haematological malignancies form a heterogeneous population with different types and severity of immunosuppression, which makes the analysis of the literature difficult.[23] In low endemic countries, tuberculosis was shown to be a rare infection after autologous haematopoietic stem cell transplantation, and even more so after allogeneic haematopoietic stem cell transplantation.[24] The frequency of tuberculosis is lower in HSCT recipients than in solid organ transplant recipients, although all patients are profoundly immunosuppressed in the peri-transplant period, and allogeneic HSCT recipients need to remain therapeutically immunosuppressed for months to prevent and treat graft-versus-host disease.[25] In HSCT recipients and patients with haematological malignancies, previous exposure to *M tuberculosis* is the main risk factor for developing active tuberculosis.[26] Some drugs such as corticosteroids, fludarabine, and anti-CD52 and TNF-alpha antagonists are also associated with tuberculosis.[24] Additionally, JAK inhibitors (ruxolitinib) are associated with an increased risk of tuberculosis,[27] mainly miliary or disseminated forms with an incidence of 0·7–1·0% (although most cases were from high tuberculosis endemic countries).[28,29] In HSCT recipients, the type of transplant, nature of conditioning regimens, underlying haematological malignancies, presence of acute or chronic graft-versus-host disease and invasive fungal infections, use of steroids and tacrolimus, and history of pretransplant tuberculosis (ie, previously treated but inactive at time of transplantation) were associated with subsequent active tuberculosis.[24,26,30] There are several explanations for the lower than expected incidence of tuberculosis in HSCT recipients. One explanation is the type of immune response balance after transplantation. Control of tuberculosis infection is mediated by cellular immunity, which is dependent on Th1 cytokines. After haematopoietic stem cell transplantation, the upregulated Th1 response might lead to a lower susceptibility of progression to tuberculosis.[31] Extensive use of antimicrobial agents that possess activity against tuberculosis is another possible explanation for the lower than expected incidence of tuberculosis in HSCT recipients.

Tuberculosis in haematology

LTBI is the term that has traditionally been used to define a state of persistent immune response to *M tuberculosis* antigens (which are present on live *M tuberculosis* if no treatment had been given) without evidence of clinically active tuberculosis.[31] This state is detected through immune-based tests such as the tuberculin skin test (TST) or Interferon Gamma Release Assays (IGRA). Two commercial IGRA are currently available: T-SPOT-TB assay (ELISPOT) and QuantiFERON-TB Gold In-Tube assay (ELISA). Both assays measure T-cell release of IFN-γ following stimulation by antigens specific to the *M tuberculosis* complex (but also present in *Mycobacterium kansasii*, *Mycobacterium marinum*, and *Mycobacterium szulgai*).[32] Acknowledging that tuberculosis infection is a spectrum of different phases of pathogen-host interactions, and as there is currently no routine test to determine the state of replication of *M tuberculosis*, the term tuberculosis infection has been proposed to supersede LTBI, to reflect a spectrum of different situations including dormant, intermittent, and actively replicating *M tuberculosis*.[32,33] This new term also acknowledges that some patients who are no longer infected by *M tuberculosis* might still be immunoreactive to *M tuberculosis* antigens.[32] However, considering that the reviewed literature used the LTBI term, we will continue to use it throughout the manuscript.

LTBI is common, although there is marked geographical variation. Nearly a quarter of the global population is estimated to be infected with *M tuberculosis*.[34] In the WHO European region, the prevalence of LTBI is 13·7% (95% CI 9·8–19·8), which is approximately 1 in 7 people, and for people older than 50 years, the prevalence is more than 20%.[34] The prevalence of LTBI varies in patients with haematological malignancies (0–15%) and in HSCT recipients (0–45%),[6,20,35,36] and is related to the overall tuberculosis epidemiology of the region.

Management practices of LTBI in haematology centres: survey results

To gain a better insight into the current management practices of LTBI in haematology centres, we circulated a dedicated questionnaire through the ECIL, the European Society for Blood and Marrow Transplantation, the International Immunocompromised Host Society, and the European LeukemiaNet network. The results are provided in the appendix (pp 4–9).

Among the 88 responders, most (54 [61%]) were haematologists, followed by infectious disease specialists (24 [27%]), with 64 (73%) responders caring for HSCT recipients. Although only 32 (36%) responders had a formal LTBI screening in place, 54 (61%) reported that they perform LTBI screening in all or selected haematology populations, of which 78% (42 of 54 responders; 48% of all responders) used an immunological assay, mainly IGRA. LTBI treatment was provided by 81 (92%) of responders, with isoniazid (treatment length of 6–9 months) being the most frequent choice. In case of LTBI treatment, most clinicians started it concomitantly with ongoing chemotherapy. Although 86% (76) of the responders did not know the exact prevalence of LTBI in their centre, 11% reported it to be less than 1%. Active tuberculosis was rare, with 67% of responders having not seen a single case of active tuberculosis in the previous 12 months.

Screening for LTBI in haematology

TST and IGRA are not as sensitive in immunocompromised patients as they are in other patient populations,

so a negative test does not exclude LTBI in these patients.[37–39] In particular, HSCT recipients frequently do not have a persistent immune response against *M tuberculosis* but can harbour dormant *M tuberculosis* bacteria that might reactivate after the transplantation. Although a single IGRA is more costly than a TST, IGRA-based strategy for tuberculosis contact investigation was shown to reduce overall costs compared with TST in several European countries.[40–42] However, there are no available data in the specific setting of haematology. None of the tests currently used for the diagnosis of LTBI have sufficient predictive value for progression to active tuberculosis, although IGRA might better target the patients considered for preventive treatment who have previously been vaccinated with Bacillus Calmette–Guérin (BCG).[37,43,44,45] Overall, there is a low level of agreement between TST and IGRA in HSCT recipients and patients with haematological malignancies,[46–49] independent of BCG vaccine status.[49] Compared with groups of patients with other immunodeficiencies from the same region, IGRA has the lowest frequency of positive test results among HSCT recipients due to a very high frequency of indeterminate results.[44]

The use of TST and IGRA tests in HSCT recipients and patients with haematological malignancies shows discrepancies between studies. T-SPOT-TB was more frequently positive than TST in some studies;[46,47] T-SPOT-TB was more frequently positive than QuantiFERON and each of the IGRA tests was more frequently positive than TST in some studies;[50,51] and in one study, the concordance between TST and QuantiFERON was high, but the level of agreement was low.[48] In HSCT recipients, TST and IGRA showed similar results,[49,52] with low accuracy to predict active tuberculosis for both TST and IGRA. However, in one study, QuantiFERON was more accurate than TST in predicting active tuberculosis.[36] Indeterminate results for IGRA in HSCT recipients and patients with haematological malignancies ranged between 1% and 15%,[36,44,46,49,50] and up to 44% in one study.[53] In pre-transplantation screening, autologous HSCT and underlying diseases (eg, acute myeloid leukaemia, multiple myeloma, and plasmacytoma) were associated with indeterminate results.[49]

The risk of active tuberculosis disease after LTBI depends on several factors, the most important being the immunological status.[45] For the general population, it is estimated that the lifetime risk of an individual with LTBI progressing to active tuberculosis is 5%–15%, being higher in some high-risk populations such as HSCT recipients.[45]

Treatment of LTBI in haematology

Treatment of LTBI (also termed preventive therapy or prophylaxis for active tuberculosis development) to reduce the risk of progression to active disease[45] is a difficult and controversial topic, particularly because there are few data on LTBI treatment in HSCT recipients and patients with haematological malignancies. In none of the studies that we reviewed was there a significantly lower rate of active tuberculosis after haematopoietic stem cell transplantation with the treatment of pre-transplant positive TST and IGRA test patients (appendix pp 10–11). Moreover, there are many biases and limitations—all but one[54] study were retrospective.[6,8,16,18,20,35,55–59] In ten studies, preventive treatment did not significantly decrease the development of tuberculosis after haematopoietic stem cell transplantation (appendix pp 10–11).[6,8,16,18,20,35,54,56,57,59]

In a recent study, there was a trend towards a lower tuberculosis rate among treated versus non- treated IGRA-positive patients (0·0 *vs* 3·6 per 100 person years, p=0·09).[57] Only one small retrospective study (50 patients) conducted in Pakistan in patients with a pre-transplantation negative TST found a benefit of universal tuberculosis preventive treatment, with 0% versus 16% of active tuberculosis post-transplantation (p<0·001).[55]

In most of the studies, the very low rate of tuberculosis reactivation (even in patients who had not been treated for LTBI) makes it difficult to assess the efficacy of tuberculosis prophylaxis.[18,20,35,54,58,59]

Three studies did not have a single case of active tuberculosis post-haematopoietic stem cell transplantation with or without preventive treatment.[6,56,58] One of these studies, conducted in the USA, was the largest study published, with 2531 HSCT recipients included.[6]

The optimal duration and time to start preventive treatment of LTBI in HSCT recipients and patients with haematological malignancies is unknown. The most frequently used regimen includes isoniazid, and the 2009 International Consensus Panel Recommendations advised the use of isoniazid for a minimum of 9 months.[38] In these guidelines, there was a disagreement about the convenience and benefit of routinely screening for LTBI using TST or IGRA in every transplant candidate.[38] Nonetheless, according to WHO, HSCT candidates should be systematically tested and treated for LTBI regardless of the background tuberculosis epidemiology.[60]

In addition to the fact that initiating tuberculosis preventive therapy should not delay haematological malignancy treatment or haematopoietic stem cell transplantation procedure, compliance and tolerance are potential barriers to completing treatment of LTBI. For isoniazid use, the risk of tuberculosis versus the risk of isoniazid toxicity should be assessed, particularly hepatotoxicity grade 3–4 (weighted average risk for prophylaxis with isoniazid is 278 per 100 000 cases).[61] Better adherence and lower rates of adverse events have been shown with shorter duration treatment schemes, although not specifically for HSCT recipients and patients with haematological malignancies.[62–64] Two multicentre, open-label trials evaluating a 4 month regimen of

rifampicin versus a 9 month regimen of isoniazid found similar rates of safety and efficacy, but the rifampicin regimen had a better rate of adherence in children,[65] and a higher rate of treatment completion and better safety in adults.[63] A post-hoc safety analysis based on data from these trials found that rifampicin was safer than isoniazid, suggesting that rifampicin should become a primary treatment option for LTBI on the basis of its safety profile.[66]

Hepatotoxicity of LTBI treatment[67] is a great concern in HSCT recipients and patients with haematological malignancies, as patients frequently suffer a degree of liver damage for a variety of reasons and receive potentially hepatotoxic comedications. Use of isoniazid for LTBI is frequently associated with asymptomatic transient aminotransferase elevation in the general population (20%);[67] however, 0·1%–5·2% of patients develop asymptomatic transient aminotransferase elevation of more than three times the upper limit of normal concentrations at a median treatment duration of 16 weeks.[67,68] Incidence of isoniazid hepatotoxicity in HSCT recipients was 0–4% in three independent studies.[18,20,35] Use of rifampicin for LTBI is associated with a low rate (0·0–0·7%) of grade 3 or 4 liver failure, leading to drug discontinuation.[68] Isoniazid–rifampicin combination therapy increases the rate of hepatotoxicity (2·5%).[69] Peripheral neuropathy is a complication of isoniazid treatment, and seems to be related to interference of isoniazid with metabolism of pyridoxine (vitamin B6).[70,71] Peripheral neuropathy occurs in 2% of patients treated with isoniazid. Additional risk factors for the development of peripheral neuropathy include the use of neurotoxic drugs (eg, bortezomib and thalidomide), alcoholism, HIV, diabetes mellitus, pregnancy, and cancer. Although data on the prevention of peripheral neuropathy are scarce, a pyridoxine supplement should be provided in these risk groups.

	Grading
Patients to target	
Only the high-risk subpopulation of HSCT recipients and patients with haematological malignancies should be considered for treatment preventing active tuberculosis development	AIIu
Factors associated with a high risk of developing active tuberculosis in HSCT recipients and patients with haematological malignancies are:	
Patients from countries or communities with a high incidence of tuberculosis (≥100 per 100 000 population)*	CIII
People referring exposure to a patient with contagious tuberculosis	AIIt
People with pleuro-parenchymal imaging abnormalities (mainly on the upper lobes) suggestive of previous tuberculosis in patients who had not received appropriate anti-tuberculosis treatment	BIIt
Patients who receive ruxolitinib if epidemiological risk factors are substantial (eg, patient history and endemic areas)[27]	BIIu
Special attention should be paid to the risk of primary infection or re-infection throughout the haematological follow-up	AIII
Strategies for management of the risk of tuberculosis infection in high-risk HSCT recipients and patients with haematological malignancies	
Provide preventive therapy without screening	NA
Screen patients with immune-based tests keeping in mind their limitations and:	
Provide preventive therapy to those who scored positive after excluding active tuberculosis	NA
Exclude active tuberculosis in those who scored indeterminate and consider preventive therapy depending on the risk estimation of future active tuberculosis	NA
Do not treat if scored negative after accurate estimation of the risk for active tuberculosis development	NA
Do not screen and do not provide preventive therapy considering the benefit-risk ratio	NA
Other considerations	
For decision of screening and initiating tuberculosis prophylaxis, consider the prognosis of the haematological malignancy and patients' characteristics, especially age	BIII
Preventive therapy should be administered for close and long lasting contact with active pulmonary or laryngeal tuberculosis, regardless of the patient's TST or IGRA status	AIIt
Patients who previously had active tuberculosis that was correctly treated† do not need to be screened or receive a preventive treatment	AIIt
For patients who had previous active tuberculosis that was not treated appropriately, seek expert advice, and consider full tuberculosis treatment or preventive treatment depending on the tuberculosis history	AIIt

IGRA=interferon-γ release assay. TST=tuberculin skin test. See appendix p 3 for more details on grades. *Tuberculosis incidence in European countries can be found at the European Centre for Disease Prevention and Control.[72] †Refer to the treatment of active tuberculosis section.

Table 1: **ECIL recommendations for strategy of screening latent tuberculosis infection**

Recommendations for screening and treating LTBI

ECIL could not identify a preferred strategy on the basis of the available data. Therefore, the ECIL proposed a set of three strategies for screening and treating LTBI in HSCT recipients and patients with haematological malignancies, targeting only those at high risk for developing tuberculosis (table 1).

Our recommendations for treating LTBI are in line with the recently published Center for Disease Control and Prevention guidelines that recommend short course (3–4 month) rifamycin-based treatment regimens over long course (6–9 month) isoniazid monotherapy (table 2).[73]

In case of pleuroparenchymal imaging abnormalities (suggestive of previous tuberculosis in patients who had not received appropriate anti-tuberculosis treatment), high resolution computed tomography (HRCT) of the lung should be performed to differentiate sequelae from active lesions.[74]

Recommendations regarding how to monitor treatment of LTBI are shown in the appendix (p 12).

Active tuberculosis in haematology patients

Clinical diagnosis and outcome

The median time to occurrence of tuberculosis following haematopoietic stem cell transplantation or the diagnosis of haematological malignancy is approximately 6 months, although tuberculosis might be diagnosed early post-transplantation (ie, within the first month).[4,5,7,8,14,18] In three out of four cases, pulmonary tuberculosis is present, but up to 50% of tuberculosis cases can have extrapulmonary or disseminated manifestations.[10,18,75] Clinical symptoms such as fatigue, lack of appetite, and weight loss are not specific to HSCT recipients and patients with haematological malignancies. Those with pulmonary disease can present with a persistent cough, and rarely present with haemoptysis. Imaging (preferably chest HRCT) is the technique of choice to detect,

characterise, and quantify lung complications.[74] CT findings of pulmonary tuberculosis include centrilobular tree-in-bud opacities, ill-defined ground-glass nodules, areas of consolidation, and cavitation (figure).[76] Pulmonary lower lobes localisation of tuberculosis is usually seen in immunocompromised patients and is associated with tuberculosis reactivation, whereas upper lobe cavitary disease in adults is generally characteristic of primary infection.

Microbiological diagnosis

Diagnosis of active tuberculosis can be achieved using various different specimens, but in most cases these will be respiratory samples of early morning sputum sampled three days consecutively, bronchial aspirate, or bronchoalveolar lavage. If tuberculosis is suspected, sputum samples will be evaluated by microscopic examination of a smear, preferably by fluorescent auramine-phenol staining to better identify the acid-alcohol resistant bacilli. Rapid detection of *M tuberculosis*-specific DNA and rifampicin resistance by q-RT-PCR is currently proposed by WHO—eg, by using the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA).[77] All samples are cultured in liquid and solid media and incubated for 8–12 weeks to maximise the chances of detection. Colonies are identified by molecular or phenotypic methods (MALDI-TOF spectrometry), at the complex, species, or subspecies level.[78–80] Drug susceptibility testing (DST) is performed on every isolated mycobacterium.[77] If the strain is susceptible to first-line drugs (ie, isoniazid, rifampicin, ethambutol, and pyrazinamide), DST for second-line drugs is not required, unless rifampicin is not used in the regimen. Comprehensive genotypic testing and DST should be performed in case of multidrug resistant (MDR) isolates.[77]

Treatment for active tuberculosis and follow-up

Drug-susceptible tuberculosis in HSCT recipients and patients with haematological malignancies is treated according to general recommendations—ie, 2 months treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months treatment with isoniazid and rifampicin (appendix p 13). Longer treatment (ie, 9–12 months) is required for rifamycin-free regimens,[81] and it might be appropriate in disseminated tuberculosis and for the most immunocompromised patients, such as those with chronic graft-versus-host disease.[24,82] Reducing ongoing immunosuppressive therapy is recommended whenever feasible, paying attention to the risk of immune reconstitution inflammatory syndrome.[18,83,84] However, clinicians should be aware of undertreating the haematological malignancy, as delay or reduction in chemotherapy has been associated with poor outcomes.[13,75] Treatment monitoring and management of hepatotoxicity are similar to the general recommendations (appendix pp 14–15). Patients should be followed clinically, and as a minimum, sputum should be collected for microbiological examination at baseline, 2 months after therapy initiation, and at the end of therapy. In case of treatment resistance or doubt about treatment adherence, sputum should be collected monthly until repeatedly negative. In case of positive follow-up sputum culture, extension of treatment duration to 9 months should be considered.[85] Liver function should be monitored at least monthly.[67] The ECIL recommendations regarding the management of active tuberculosis are summarised in table 3.

	Grading
How to screen for LTBI	
IGRA should be preferred over TST for patients previously vaccinated with BCG	BIIt
For other patients, either TST or IGRA can be used	CIIu
TST positivity should be defined as an induration of ≥5 mm	BIIt
For IGRAs, either T.SPOT-TB or Quantiferon can be used	BIIu
In case of doubt about the proximity and duration of tuberculosis sporadic contact, IGRA conversion could be helpful and should be repeated after 8–12 weeks from the last exposure, if initially scored negative	BIIt
If the IGRA score is indeterminate, data from populations of HSCT recipients and patients with haematological malignancies do not support repeating IGRA or TST	BIIt
How to treat LTBI	
Before starting preventive therapy, active tuberculosis must be ruled out (investigate clinical symptoms and perform lung imaging)	AIII
Initiating tuberculosis preventive therapy should not delay haematological malignancy treatment or haematopoietic stem cell transplantation	AIII
Recommended drugs:	
Rifampicin, if possible taking into consideration drug-drug interactions (especially cyclosporine and tacrolimus in HSCT recipients); 4 months of daily treatment with 10 mg/kg/day rifampicin (max 600 mg/day)*	BIIt
If rifampicin cannot be used, isoniazid should be administered at a dose of 5 mg/kg/day (maximum 300 mg/day) for 9 months	BIIt
Drug-drug interactions and toxicities should be discussed on a case-by-case basis	AIII
Pyridoxine 25–50 mg/day should be added in case of treatment with isoniazid	BIIt
For patients with pre-existing peripheral neuropathy, increasing pyridoxine dose to 100 mg/day can be considered	BIII
Preventive treatment should be given with caution during HSCT conditioning therapy and antineoplastic chemotherapy	CIII

BCG=bacille Calmette–Guérin. HSCT=haematopoietic stem cell transplant. IGRA=interferon-γ release assay. LTBI=latent tuberculosis infection. TST=tuberculin skin test. *When used together with other drugs that could interfere with rifampicin blood concentrations, or in patients weighing more than 90 kgs, we recommend measuring rifampicin peak drug concentrations 2 h post drug intake if the assay is available.

Table 2: **ECIL recommendations for screening and treatment for latent tuberculosis infection**

Specificities for MDR/XDR in haematology

Multidrug resistant tuberculosis (MDR-TB) is defined by bacillary drug resistance against rifampicin and isoniazid. In addition, the classification of second-line anti-tuberculosis drugs has recently been revised, and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) is now defined by MDR-TB plus additional resistance against a fluoroquinolone, and XDR-TB is defined as pre-XDR-TB plus additional resistance against bedaquiline and linezolid.[86] The treatment of HSCT recipients and patients with haematological malignancies with MDR-TB or XDR-TB should be guided by detailed DST and

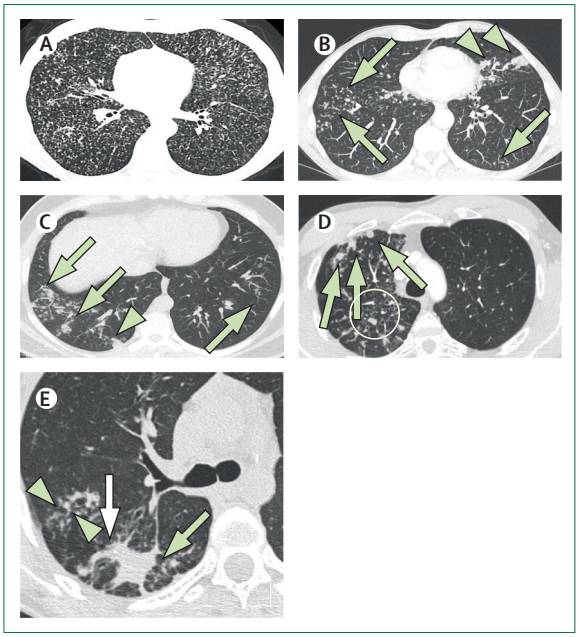

Figure 1: **Imaging findings that can suggest pulmonary mycobacterial infection in an appropriate clinical setting**
(A) Mycobacterial tuberculous infection (miliary form). High-resolution CT (2 mm collimation) image shows innumerable pulmonary nodules scattered throughout both lungs. (B) and (C) Mycobacterium avium–intracellulare complex (MAC) pulmonary disease. CT scan (2 mm collimation) at the level of the lower lungs shows small nodules and branching centrilobular opacities (tree-in-bud pattern) in both lungs (arrows) and focal areas of lobular consolidation in the right lower lobe and lingula (arrowheads). (D) Mycobacterial tuberculous infection. CT scan (2 mm collimation) at the right upper lobe shows multiple peripheral nodules (arrows) and bronchial wall thickening (circle). (E) Mycobacterium avium–intracellulare complex infection. Close-up view of a CT scan (2 mm collimation) at the posterior segment of the right upper lobe shows branching centrilobular opacities (tree-in-bud pattern; arrowheads) and a lobular consolidation (green arrows). Note the associated bronchial wall thickening (white arrow).

according to the WHO guidelines, which are frequently updated (last updated in 2020);[87,88] however, these guidelines do not specifically address the treatment of HSCT recipients and patients with haematological malignancies. Therefore, additional expert consultation is advised.

Management of drug-drug interactions between tuberculosis drugs and drugs used in HSCT recipients and patients with haematological malignancies

As rifampicin-containing drug regimens are the cornerstone to treat active tuberculosis, including in HSCT recipients and patients with haematological malignancies, drug-drug interactions (DDIs) should be checked thoroughly. All rifamycin antibiotics are potent inducers of, among others, the CYP450 enzymes. Rifampicin is considered to be the strongest inducer, followed by rifapentine, and to a lesser extent by rifabutin. An overview of DDIs between rifamycins and drugs commonly used to treat HSCT recipients and patients with haematological malignancies, along with some recommendations, are given in the appendix (pp 16–17). Exposure to specific drugs will be decreased in such a manner that efficacy is no longer guaranteed when associated with rifacycins. For these drugs, combination with rifamycins is contraindicated, and switching to another antituberculosis drug or substrate drug is mandatory. In the case of severe DDIs, therapeutic drug monitoring is highly recommended to ensure exposure of the substrate drugs. If therapeutic drug monitoring is not available, switching to alternative treatment schemes is advised. Isoniazid, ethambutol, and pyrazinamide might also be involved in DDIs (although to a lesser extent), as presented in the appendix (p 18).

Prevention of tuberculosis in HSCT recipients and patients with haematological malignancies

Appropriate isolation should be implemented for contagious patients, and tuberculosis contact investigation should be undertaken. BCG vaccination is contraindicated in HSCT recipients and patients with haematological malignancies.[89]

Nontuberculous mycobacteria

Overall epidemiology in haematology

NTM, which represent over 190 species and subspecies, are common environmental organisms that can cause disease in both non-immunocompromised and immunocompromised patients. NTM species are classified as slow (eg, *Mycobacterium avium* complex) or rapid (eg, *Mycobacterium abscessus*) growing mycobacteria.

There are many biases in the available data regarding NTM infections in HSCT recipients and patients with haematological malignancies. Studies are mainly retrospective and often monocentric, and it is difficult to know whether the interpretation of the results included the internationally recommended criteria, in particular the number of times mycobacteria were found and in which type of sample, along with the potential virulence of the isolate.[78–80]

Prevalence rates range between 0·4% and 10·0% and are 50–600 times more common in HSCT recipients than in the general population (appendix p 19). The most frequent NTM infections in HSCT recipients and patients with haematological malignancies are due to *M avium* complex, *Mycobacterium abscessus-chelonae* complex, and *Mycobacterium haemophilum*.[90] Rapid growers can cause central venous catheter (CVC) infections.[91–97]

Clinical and radiological presentations, risk factors, and outcomes

NTM infections are more frequent in allogeneic than autologous HSCT recipients, especially in those who underwent myeloablative conditioning or T-cell depletion, or who had pulmonary graft-versus-host disease or relapsed leukaemia.[98–100] Known risk factors for NTM infections include chronic kidney disease and neutropenia, but not the type of haematological malignancy.[11] Catheter

infection (40%), skin infection (30%), and pleuropulmonary infection (20%) are the most frequent presentations in HSCT recipients.[100,101] The median time from transplantation to onset of NTM infection is 5 months,[101] but CVC infections will usually occur earlier.[95] Outbreaks of catheter and bloodstream NTM infections have been reported among neutropenic HSCT recipients and patients with haematological malignancies due to water contamination.[96,102,103]

Clinical diagnosis of pulmonary disease is often challenging in clinical practice—the infection must be distinguished from colonisation, which can be transient, intermittent, or persistent. Identification of the infection requires relevant clinical symptoms or imaging abnormalities, consideration of the site of isolation (sterile sample or tissue *vs* respiratory samples), repeated isolation of NTM, and consideration of the pathogenicity associated with the NTM and the immune status of the host.[104] CT findings of NTM pulmonary infection are similar to those of tuberculosis (figure). The presence of a persistent, unexplained fever in severely immunocompromised patients should prompt a blood culture test.

NTM infections in HSCT recipients and patients with haematological malignancies have poor outcomes. Pulmonary disease (mostly reported in HSCT recipients) is associated with a mortality rate of up to 50%, with more than half of deaths not being related to NTM. Prognosis was not associated with any specific NTM species in existing studies.[7,11,98,99,105–108] Since NTM microbiological identification takes several days to weeks, patients could die before a diagnosis is made.[90,98]

Microbiological diagnosis

Microbiological diagnostic techniques for NTM infections are similar to those for *M tuberculosis* infection. Samples showing acid-alcohol resistant bacilli by microscopy should be investigated by molecular methods to rule out tuberculosis. Long term culture up to 9 weeks might be required to detect NTM. The final interpretation, in the context of pulmonary NTM infection, must be carried out in accordance with international recommendations.[78,79,104] Only a few drug combination susceptibility results are correlated with clinical outcome—ie, macrolides and amikacin susceptibility for both *M avium complex* and *M abscessus,* and rifamycin susceptibility for *M kansasii*.[109] Therefore, these combinations are the only ones that should be systematically tested.

Treatment and follow-up

NTM treatment requires an extended combination of at least three drugs (usually including a macrolide), depending on the NTM species or subspecies and the results of drug-susceptibility testing. Azithromycin is preferred over clarithromycin for patients with susceptible NTM due to better tolerance, fewer drug-drug interactions, once daily dosing, and equal efficacy. However, if azithromycin is unavailable, clarithromycin can be used.[104]

Previous treatment with azithromycin, especially for chronic lung graft-versus-host disease, should be noted, as this might be associated with an increased risk for NTM macrolide resistance. Expert guidance is required to confirm indication for treatment and to define optimal strategy according to clinical presentation, causative species, DST if available and reliable, and underlying disease. Management of HSCT recipients and patients with haematological malignancies is further complicated by frequent DDIs with haematological treatments and little evidence on the efficacy of second-line agents.

For NTM pulmonary disease, recent guidelines[79,104,110] recommend at least 12 months of therapy from culture conversion for most species. For NTM extrapulmonary disease,[78] treatment depends on the species and site of infection. CVC-related bloodstream infections are managed by removing the device with or without

	Grading
Treat tuberculosis in HSCT recipients and patients with haematological malignancies similarly to the schema performed in the general population: 2 months of daily isoniazid, rifampicin, ethambutol, and pyrazinamide followed by 4 months of isoniazid and rifampicin for most cases (appendix, p 13)	BIt
Ethambutol can be stopped before 2 months if there is no resistance to isoniazid and rifampicin	BIIt
DDIs between anti-tuberculosis drugs and all other drugs should be carefully considered	AIIu
In case of DDIs, concomitant drugs should be changed when alternatives are available, or the tuberculosis regimen should be modified	BIII
Longer duration treatment must be considered according to the clinical presentation of the disease,* the host's immune status,† or the evolution under treatment‡	AIIt
Longer duration treatment should be considered when rifamycins are not part of the treatment regimen	AIIt
Supplementary pyridoxine is recommended for all HSCT recipients and patients with haematological malignancies treated with isoniazid	BIIt
Treatment of multidrug resistant and extensively drug-resistant tuberculosis must rely on comprehensive phenotypic and genotypic drug susceptibility testing and requires longer treatment; evaluation depends on the choice of drugs and specific schedules to monitor adverse events	AIIt
Careful evaluation of the timing of chemotherapy for the underlying haematological disease with the respect of treatment of active tuberculosis should take into consideration that a delay or reduction of antineoplastic chemotherapy has been associated with poor overall outcome	BIIu
Reduction of the ongoing immune suppression is recommended if feasible, with particular attention to the risk of IRIS, the risk of ruxolitinib withdrawal syndrome, and the need for corticosteroids in case of central nervous system tuberculosis localisation	BIII
For patients with positive sputum cultures, the specimen should be monitored closely by microscopy and culture during therapy until at least two negative culture results are available	BIII
Repeated PCR monitoring is not recommended during therapy	AIIt
If the patient is able to produce sputum, at least a sample should be collected and evaluated by microscopy and culture at baseline, 2 months after therapy initiation, and at the end of therapy; if there is treatment resistance or doubt about treatment adherence, sputum should be collected monthly until sustained culture negativity	BIII
Imaging (preferably a lung HRCT scan in pulmonary tuberculosis) at the end of therapy is helpful as a baseline for possible future evaluation of relapse	CIII

DDIs=drug-drug interactions. HRCT=high-resolution computed tomography. IRIS=immune reconstitution inflammatory syndrome. *Involvement of central nervous systems, bone, joint, or disseminated, or cavitary pulmonary tuberculosis. †In the most severely immunocompromised patients, such as those with GvHD. ‡If sputum culture is still positive at month 2.

Table 3: **ECIL recommendations on the management of active tuberculosis in patients with haematological malignancies**

	Grading
Seek expert advice for management and discuss whether treatment should be initiated	AIII
NTM pulmonary disease	
Differentiating NTM infection from colonisation is a crucial point for treatment decision; consider the pathogenicity of the NTM, clinical and lung CT scan findings, and number and type of NTM-positive samples	AIIt
Do not rely on a single NTM positive sputum to retain the diagnosis of NTM pulmonary disease	AIIt
Repeat sputum or induced sputum or do a bronchoscopy	BIII
Diagnostic criteria for pulmonary NTM should rely on ATS, ERS, IDSA, and ESCMID guidelines; initiation of treatment for NTM is rarely a medical emergency	BIII
Repeated clinical, microbiological, and radiological HRCT evaluations should be considered for decision of treatment	AIIt
A single positive respiratory sample for NTM with no clinical or lung CT scan abnormalities does not require a specific treatment pre-HSCT; however, careful monitoring should be done after HSCT	BIIu
Multidrug treatment regimen against NTM should rely on ATS, ESCMID, ERS, and IDSA recommendations; it should last at least 12 months based on culture conversion	NA
For monitoring the efficacy of treatment, a sputum specimen should be cultured every 1–2 months until the end of therapy, even if these cultures become negative	BIIt
Treatment outcome definition should follow international consensus[105,111]	NA
NTM extrapulmonary disease	
Antimicrobial treatment should be discussed according to the extent of the infection and the causative NTM species	BIII
The duration of treatment for skin and soft tissue NTM infection depends on NTM species and requires expert advice	BIII
In NTM infection of a central catheter, the device should be removed	AIIu
A NTM positive culture from extrapulmonary sterile sites usually requires antimicrobial treatment; *Mycobacterium gordonae* is an exception, as is *Mycobacterium chelonae* in certain circumstances[104,110]	AIIt
Treatment of extrapulmonary NTM should follow the same principles as pulmonary disease (ATS 2007); source control should be provided	AIIt

ATS=American Thoracic Society. BAL=bronchoalveolar lavage. ERS=European Respiratory Society. ESCMID=European Society of Clinical Microbiology and Infectious Diseases. HRCT=high-resolution computed tomography. HSCT=haematopoietic stem cell transplantation. IDSA=Infectious Diseases Society of America. NTM=nontuberculous mycobacteria.

Table 4: **ECIL recommendations on the management of nontuberculous mycobacteria in patients with haematological malignancies**

antimycobacterial treatment.[103,111] Follow-up for NTM pulmonary disease includes regular sputum collection until the end of therapy, even when cultures are negative. In case of bloodstream infection, blood cultures should be performed until negative. ECIL recommendations on the management of NTM in HSCT recipients and patients with haematological malignancies are summarised in table 4.

Interhuman transmission of NTM has not been described; thus, NTM infection does not require specific transmission precautions.

Management of drug-drug interactions

NTM treatment involves several drugs, including macrolides combined with rifamycins, quinolones, and aminoglycosides. DDIs with drugs used for haematological treatment should be evaluated carefully when NTM treatment is initiated, especially when rifamycins are included. DDIs related to the use of rifamycins are presented in the appendix (pp 16–17). DDIs should also be considered when macrolides are administered. As reported in the appendix (pp 20–21), both azithromycin and clarithromycin might prolong the corrected QT interval in a substantial manner, and clarithromycin leads to pharmacokinetic interactions as it acts as a strong inhibitor of CYP3A4.

Search strategy and selection criteria

A group of ten experts—including haematologists, pulmonologists, infectious disease specialists, a microbiologist, a radiologist, and a clinical pharmacist—was selected by the ECIL executive committee. MEDLINE (including MEDLINE in Process) search with no start date (all studies published) until Sept 1, 2019 was performed to identify potentially relevant English language studies related to latent tuberculosis infection, tuberculosis, and nontuberculosis infection infections in haematology and haematopoietic stem cell transplant patients. We did the literature search by using the following indexed terms and free text terms: "bone marrow" OR "h(a)ematopoietic stem cell" OR "peripheral blood stem cell" OR « chronic myeloproliferative disorder », OR « chronic myeloid or myeloproliferative neoplasm », OR « chronic myeloid leuk(a)emia », OR « acute leuk(a)emia », OR « myelodysplastic syndrome », OR « chronic lymphoproliferative disorder », OR « chronic lymphocytic leuk(a)emia », OR « myeloma », OR « lymphoma », OR « Hodgkin's disease » OR « h(a)ematology », AND/OR « tuberculosis », « Mycobacterium tuberculosis », « non-tuberculous mycobacteria », « mycobacterial infections ». Retrieved references were screened for other potentially relevant articles. The relevant studies were analysed with particular attention given to the study design, the population, and the endpoints. We then developed recommendations which were graded according to the European Society of Clinical Microbiology and Infectious Diseases grading systems (appendix, p 3). Results of the literature analysis and proposals for statements to guide clinical management were presented in the plenary session of the ECIL 8 (Sept 20, 2019). The recommendations were discussed and revised until a consensus was reached. The slide set was thereafter made publicly available on the ECIL website on Nov 27, 2019. To include the most up to date information, an additional literature search was done on Sept 1, 2021. Final agreement on the recommendations was reached on Nov 22, 2021. Updating the data has not changed our recommendations.

Conclusion

The frequency of mycobacterial infections in HSCT recipients and patients with haematological malignancies depends largely on the geographical location of the patients. Tuberculosis is less frequent than expected among HSCT recipients. As none of the studies showed a significant reduction in the risk of active tuberculosis with screening and treatment for LTBI in HSCT recipients

and patients with haematological malignancies, this strategy cannot be universally recommended for this setting. The indication for treatment of LTBI should balance the risk of developing tuberculosis versus drug toxicity, and should consider the effect of treatment on haematological management. Innovative tests for tuberculosis infection that are currently under investigation should help to better assess the risk of progression from tuberculosis infection to tuberculosis disease, and thus to better identify patients who require preventive treatment. Although identification of *M tuberculosis* in a respiratory specimen is indicative of tuberculosis that requires treatment, the identification of NTM should call into question the true pathogenicity of the organism, depending on its species. Treatment of mycobacteria in haematology is hampered by DDIs between antimycobacterial drugs and antineoplastic drugs.

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