# Severe disseminated tuberculosis in HIV-negative refugees

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**In high-income countries, the presentation of tuberculosis is changing, primarily because of migration, and understanding the specific health needs of susceptible populations is becoming increasingly important. Although disseminated tuberculosis is well documented in HIV-positive patients, the disease is poorly described and less expected in HIV-negative individuals. In this Grand Round, we report eight HIV-negative refugees, who presented with extensively disseminated tuberculosis. We discuss the multifactorial causes, such as deprivations during long journeys, precarious living conditions, and the experience of violence, which might add to nutritional factors and chronic disorders, eventually resulting in a state of predisposition to immune deficiency. We also show that disseminated tuberculosis is often difficult to diagnose when pulmonary symptoms are absent. Communication difficulties between refugees and health-care workers are another major hurdle, and every effort should be made to get a valid patient history. This medical history is crucial to guide imaging and other diagnostic procedures to establish a definite diagnosis, which should be confirmed by a positive tuberculosis culture. Because many of these patients are at risk for multidrug-resistant tuberculosis, drug susceptibility testing is imperative to guide therapy. In the absence of treatment guidelines for this entity, clinicians can determine treatment duration according to recommendations provided for extrapulmonary tuberculosis and affected organs. Paradoxical expansion of tuberculous lesions during therapy should be treated with corticosteroids. In many cases, treatment duration must be individualised and might even exceed 12 months.**

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## Introduction

With an estimated 1·6 million deaths associated with the disease in 2017, tuberculosis is a global health emergency that is difficult to control.[1] In indigenous residents of high-income countries, tuberculosis incidence is steadily declining and most cases are now seen in minority groups, particularly in newly arrived immigrants and refugees from high-burden countries, who often congregate in deprived communities and refugee shelters.[2] Because of widespread conflict areas, natural disasters, and economic globalisation, migration has greatly increased since the 1980s.[3] This increase has had a major effect on middle-income countries such as Brazil, Russia, India, China, and South Africa, whose health-care systems, which are still vulnerable, have to cope with large numbers of migrants from low-income countries.[4] Additionally, neighbouring countries or nations with armed conflicts and civil wars have seen a sharp increase in tuberculosis incidence, as shown in Lebanon, a country hosting a substantial number of Syrian refugees.[5]

However, migration not only changes the epidemiological figures of tuberculosis, but also seems to affect the clinical presentation of the disease. Extrapulmonary forms of tuberculosis that are difficult to diagnose and treat are emerging in European countries where pulmonary tuberculosis had been by far the most common form of the disease.[6] Clinicians increasingly have to manage complicated forms of tuberculosis in refugees (panel).[6] Although disseminated tuberculosis is well known as an opportunistic infection in HIV-positive individuals, the infection might be less expected in HIV-negative individuals (panel). Clinical symptoms of extrapulmonary and disseminated tuberculosis are less specific than in pulmonary tuberculosis, often leading to diagnostic delay in these patients. We present eight cases of severe disseminated tuberculosis in HIV-negative refugees with no apparent immunological defect explaining this extensive mycobacterial spread to several organs and body sites. We discuss and review the literature regarding diagnostic and therapeutic challenges of disseminated tuberculosis as well as the potential effect of migration, malnutrition, and post-traumatic stress on immunological host defence.

### *Panel*: Definitions of terms

#### Disseminated tuberculosis

Although definitions of disseminated tuberculosis vary slightly, many experts would agree that the diagnosis can be made when the infection involves the blood stream, bone marrow, liver, or two or more non-contiguous body sites.[7–10] Miliary tuberculosis is a disseminated form of tuberculosis. Pulmonary involvement is not a prerequisite for the diagnosis of disseminated tuberculosis, and extrathoracic or extrapulmonary involvement is typical. Disseminated tuberculosis can be further differentiated into bacteraemic and non-bacteraemic disease. Bacteraemic disease is a hallmark of patients co-infected with HIV and a predictor of mortality.[7]

#### Migrant populations

There is considerable heterogeneity in the use and definition of the terms refugee, asylum seeker, and migrant.[11] The conceptual problems in defining these terms have been discussed extensively elsewhere.[12] In this Grand Round, we decided to primarily use the term refugee to describe individuals who make an involuntary choice to leave their country of origin.

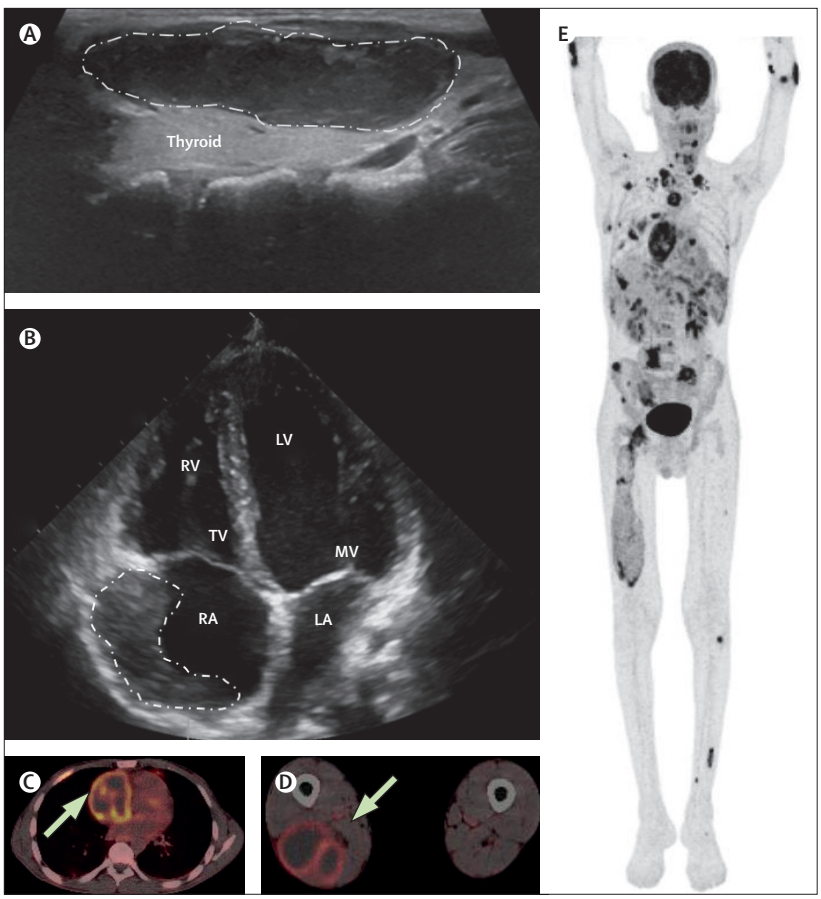


***Figure 1:*** **$^{18}$F-FDG PET with CT, echocardiography, and ultrasound in patient 5**
(A) Sagittal ultrasound neck view showing an abscess in the left thyroid (circled). (B) Apical four-chamber view with ultrasound visualising the right atrial lesion (circled) close to the TV. (C) Fusion $^{18}$F-FDG PET with CT with a section through the heart showing right atrial involvement (arrow). (D) Fusion $^{18}$F-FDG PET with CT on the level of the thighs, visualising a soft tissue abscess (arrow). (E) $^{18}$F-FDG PET as maximum intensity projection showing multiple FDG-avid tuberculous lesions involving the thyroid, bones, lymph nodes, lungs, heart, peritoneum, and soft tissues. Physiological uptake can be seen in the brain, the kidneys, and the bladder. TV=tricuspid valve. $^{18}$F-FDG=$^{18}$F-fluorodeoxyglucose. RA=right atrium. LA=left atrium. MV=mitral valve. LV=left ventricle. RV=right ventricle.

## Case description

Between May 2016 and July 2018, eight HIV-negative refugees with severe disseminated tuberculosis were treated at University Hospital Cologne. We describe one patient (patient 5) in detail. Clinical features of the remaining seven patients are provided in the appendix.

See Online for appendix

In February 2018, a 32-year-old Eritrean patient presented to a German primary care hospital with recurrent fever (40°C), pain in the back, legs, and arms. Assessment of patient history was barely possible because of language barriers. Physical examination of the cachectic patient (body-mass index [BMI] 15·1 kg/m$^2$) revealed palpable tumours in the right upper arm, the back of the upper left thigh, the inguinal region, and the upper back. Laboratory tests showed an elevated C-reactive protein concentration (105 mg/L), erythrocyte sedimentation rate (94 mm/h), and an elevation of γ-glutamyltransferase (400 U/L). Results of a chest x-ray were normal and sputum smears were negative for acid-fast bacilli. Results of a QuantiFERON-TB Gold-In Tube test were negative. Multiple blood cultures and serologies for other infectious diseases (malaria, HIV, Q-fever, syphilis, and leishmaniasis) were negative. Because of the presence of fever and elevated C-reactive protein concentration, empirical antibiotic treatment (piperacillin with tazobactam, or doxycycline) was started with no improvement of clinical symptoms. A biopsy of the right upper arm revealed a necrotising granulomatous inflammation on histopathological examination.

See Online for video 1

See Online for video 2

The patient was transferred to University Hospital Cologne. Assessment of patient history with an interpreter revealed unintentional weight loss (more than 8 kg), chronic cough, which had persisted for several months, and a stay in a hospital in Sweden due to an abdominal tumour of unknown origin. A chest CT showed multiple small pulmonary cavities in the upper parts of the lungs. A bronchoalveolar lavage was done and samples were positive for acid-fast bacilli. A positive PCR specific for *Mycobacterium tuberculosis* established the diagnosis of pulmonary tuberculosis. GeneXpert testing was negative for rifampicin resistance and a standard four-drug regimen was started (450 mg rifampicin daily, 200 mg isoniazid daily, 1500 mg pyrazinamide daily, and 800 mg ethambutol daily). Fully drug sensitive tuberculosis was later confirmed by phenotypic testing. Ultrasound examination revealed multiple abscesses of the thyroid, liver, and spleen (figure 1A, 2C, 2D). A puncture aspirate of the thyroid abscess was positive for *M tuberculosis* culture and PCR. A transthoracic echocardiography showed a large mass inside the right atrium (3·5×3·0×1·0 cm) suspicious for a tuberculoma (figure 1B, video 1). To understand fully the extent of the disease, PET combined with CT using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) was done, showing extensively disseminated tuberculosis with lesions in muscles and bones of all four extremities (figure 1C, 1D, 1E, video 2). Additional manifestations were confirmed in the thyroid, pericardium, both lungs, diaphragm, peritoneum, spleen, and the liver. The tumour in the right atrium showed FDG enhancement, indicating a tuberculoma and ruling out a thrombus of the heart.

Serology for HIV-1 and HIV-2 was repeatedly negative and CD4 cell count was in the normal range. The only finding associated with immune deficiency was lymphocytopenia (0·59×1×10$^9$/L lymphocytes) and severe vitamin D deficiency. The patient then received Vitamin D supplementation. For academic reasons, a second QuantiFERON-TB Gold-In Tube test was done, which also showed a false-negative result.

2 weeks after initiation of anti-tuberculous treatment, the patient reported worsening of symptoms and severe pain in the extremities and in the back. Clinical examination and ultrasound showed an enlargement of the cardiac tuberculoma and several other lesions. A paradoxical reaction was diagnosed despite persistent lymphocytopenia, and adjunct treatment with prednisolone (60 mg daily) was started, resulting in rapid

and sustained improvement of pain, fever, and lesion size. After 12 months of anti-tuberculous treatment, we observed sustained clinical improvement with regard to weight gain, body temperature, and pain. A second $^{18}$F-FDG PET with CT showed a decrease of FDG enhancement and reduction of all lesions, including the atrial tuberculoma. Blood tests showed sustained improvement of lympho-cytopenia and inflammatory markers.

## Review and discussion

Our patients highlight the multiple challenges in the management of severely ill refugees with disseminated tuberculosis. Routine laboratory findings were unspecific in all patients and there was no cardinal symptom allowing for rapid diagnosis. Most (seven of eight) of our patients were sputum smear negative, and proper diagnosis was difficult to achieve and delayed by false negative interferon-γ release assay (IGRA) results. We discuss diagnostic and therapeutic challenges and possible ways to overcome these. We also review the literature on the many causes for immunosuppression in refugees, which may explain the extensive forms of disseminated tuberculosis we report here.

### Disseminated tuberculosis

*Epidemiology*

Because of differences in case definitions and substantial heterogeneity in study populations, exact data concerning the incidence of disseminated tuberculosis is scarce. Disseminated tuberculosis is estimated to occur in 1–5% of all tuberculosis cases.[9,13] The epidemiology of disseminated tuberculosis is strongly linked with its pathophysiology. Dissemination requires haematogenous or lymphogenous bacterial spread from the primary site of infection, which leads to manifestation of the disease in several organ sites. This spread occurs more frequently in immuno-compromised patients, as shown by the high rate of disseminated tuberculosis in HIV-infected patients (up to 31% of patients).[8,9] Other risk factors for disseminated disease include diabetes, cancer (mostly haematological malignancies), receipt of immuno-suppressive drugs, chronic renal failure, and alcohol misuse.[7,9]

Reports from high-income countries indicate an increase in the proportion of extrapulmonary tuberculosis, which is primarily seen in non-native patients.[14,15] Most of these studies do not describe the extent and localisation of the disease and do not distinguish between different forms of extrapulmonary tuberculosis.

*Access to care*

The social background of refugee patients adds to the multiple clinical challenges and complicates patient care and containment of tuberculosis in contagious forms of the disease. Because of regulatory barriers (eg, social insurance systems) and structural problems (eg, transport to health-care provider), refugees have considerable difficulties in accessing health care in their host countries.[11]

Having overcome these barriers, taking a comprehensive clinical history is crucial but frequently hampered by missing medical records.[16] Refugees and doctors face language barriers, which negatively affect the reporting of somatic and psychiatric symptoms.[16,17] Professional interpreters can help to overcome these challenges, but are not used as much as needed in many cases.[18] Different perceptions of medicine and inadequate health literacy

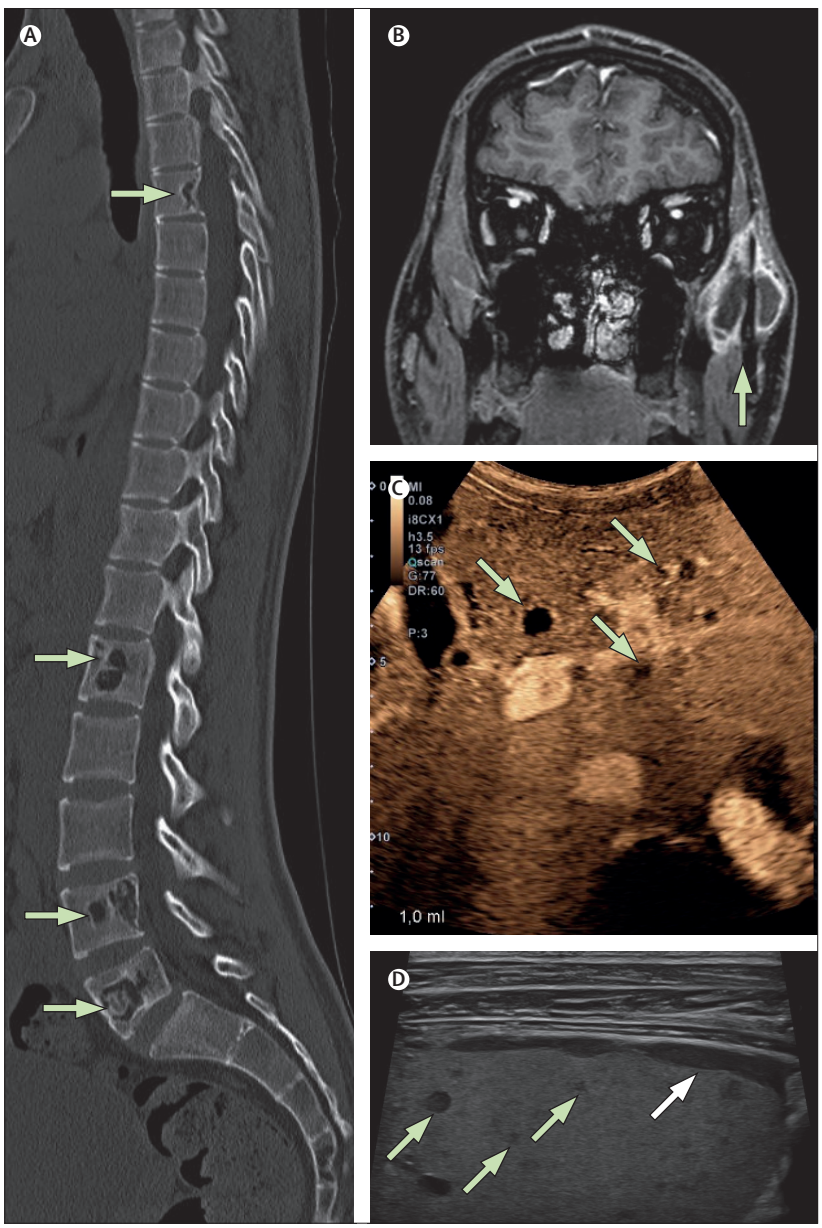


***Figure 2*: Various diagnostic modalities for the visualisation of tuberculosis lesions in three patients**
(A) CT of the spine with multiple osseous lesions (patient 3). (B) MRI of the head showing a contrast-enhancing lesion periorbital left infiltrating the temporal muscle (patient 6). (C) Late-phase washout of small lesions in the liver in contrast-enhanced ultrasound (arrows; patient 5). (D) Multiple hypoechoic lesions in the spleen (green arrows) and hypoechoic peritoneal thickenings (white arrow; patient 5).

affect the success of patient–doctor interactions.[11,19] The disruption of continuity of medical care due to frequent relocations is another problem.[20]

*Laboratory tests*

IGRAs are extensively used for the diagnosis of tuberculosis by measuring interferon-γ release in response to *M tuberculosis* antigens secreted by T-cells. The most frequently used assay is the ELISA-based QuantiFERON-TB Gold In-Tube test.[21] IGRAs are indicated for diagnosis of latent *M tuberculosis* infection. The test systems detect previous sensitisation to *M tuberculosis* and cannot differentiate active disease from latent tuberculosis infection. Given the scarcity of rapid and reliable diagnostic tests, clinicians often tend to use the assay for the diagnosis of patients with suspected active tuberculosis.

Studies investigating the accuracy of IGRAs in the diagnosis of culture-positive tuberculosis found a sensitivity ranging from 78% to 83%.[22,23] Multiple factors leading to false-negative IGRA results have been identified, and these include young or old age,[22–24] low BMI,[22] extrapulmonary or disseminated disease,[25] and lymphocytopenia and malignancies.[24] Notably, three out of six tested patients had false-negative QuantiFERON-TB Gold In-Tube test results (appendix).

The Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is an automated PCR test, which accurately detects pulmonary tuberculosis and rifampicin resistance when used on sputum specimens. The test also works well in some non-sputum samples, and WHO recommends its use with cerebrospinal fluid in patients with suspected tuberculosis meningitis.[26] According to WHO, the test can also be used with other non-respiratory samples. The assay showed a pooled sensitivity of 83·7% if lymph node biopsies or fine needle aspirates were used as test material.[26] Sensitivity for tissue samples other than a lymph node varies substantially and clinicians might expect a considerable number of false-negative test results. Xpert MTB/RIF Ultra, the next generation test system, which is expected to have improved sensitivity, is now increasingly installed and tested in tuberculosis laboratories. One study showed good specificity and high sensitivity for this test in a large variety of extrapulmonary samples and overall recommendations might change with more studies done.[27] Generally, any material that is accessible by biopsy should be examined for the presence of *M tuberculosis*-specific DNA with a modern PCR-based assay, in-house nucleic acid amplification test, or Xpert MTB/RIF, or both. Gastric aspirates, ascitic fluid, urine, and stool can also be tested with PCR-based techniques and usually show satisfactory sensitivity and specificity, especially in immunocompromised patients.[8,27]

In patients with suspected disseminated tuberculosis who are sputum-smear negative, other tests such as the urine lipoarabinomannan point-of-care test, which is commercially available, can be an approach to identify active tuberculosis in a subset of HIV-positive patients with CD4 counts below 100 cells per μL.[28] In these severely immunocompromised patients, the test is capable of detecting a surface glycan that is highly *M tuberculosis*-specific, which is released into the urine during active tuberculosis.[29] In HIV-negative patients with disseminated disease, sensitivity is low.[30] In the future, sensitivity of the assay in HIV-negative patients might be substantially increased (>95%) by applying a copper complex dye within a hydrogel nanocage that captures and concentrates lipoarabinomannan before detection.[31] A positive IGRA, PCR, or urine lipoarabinomannan assay requires additional efforts to isolate viable bacteria from affected body sites for confirmation of the diagnosis and, most importantly, for drug sensitivity testing.

In immunocompromised patients with sputum smear-negative tuberculosis, blood culture for mycobacterial culture should either be inoculated directly into BACTEC Myco/F Lytic bottles (Becton Dickinson, Franklin Lakes, NJ, USA), BacT/ALERT MP bottles, or Isolator 10 lysis centrifugation tubes (Wampole Laboratories, Waltham, MA, USA). If inoculated with an adequate volume of blood and incubated for 42 days, a sensitivity of 32–47% can be achieved in HIV-positive patients.[7,8] These studies indicate that blood cultures can play a role in the diagnosis of disseminated tuberculosis when diagnostic procedures cannot isolate the bacteria from diseased organs, primarily in HIV co-infected patients. Positive blood culture and a positive urine lipoarabinomannan test are independent predictors of mortality in tuberculosis patients.[7,8,30]

*Imaging*

Radiological investigations play a crucial role in the diagnosis of disseminated tuberculosis. Imaging modalities of choice are CT, ultrasound, and MRI. Additionally, bone scanning can be done in cases of suspected skeletal involvement. The advantages and disadvantages of these techniques have been extensively discussed elsewhere.[32]

PET is based on the imaging of $^{18}$F-FDG uptake in inflamed tissue. In combination with CT scans, the technique provides a powerful, non-invasive tool to locate and quantify lesions in patients with tuberculosis, which has been extensively shown for pulmonary tuberculosis.[33,34] Being a non-specific tracer, which also accumulates in malignant lesions, sarcoidosis, or HIV-associated lymphadenopathy, $^{18}$F-FDG PET with CT is not useful for the primary diagnosis of tuberculosis. Brain or kidney involvement can be difficult to detect because of the physiological uptake and urinary excretion of $^{18}$F-FDG. So far, few studies have examined PET with CT in the context of disseminated tuberculosis.[35] Lefebvre and colleagues studied PET with CT in 18 patients with definite (n=11) or probable (n=seven) lymph node tuberculosis.[35] PET with CT revealed previously undetected visceral lesions in eight patients, and splenic and bone marrow $^{18}$F-FDG-uptake in seven other patients.

Identification of these lesions led to the correct diagnosis of disseminated tuberculosis with accurate pre-therapeutic mapping. In five patients, the technique was used to guide biopsies. PET with CT might be a valuable diagnostic procedure early during patient workup.

*Rare manifestations of tuberculosis*

Extrapulmonary tuberculosis comprises about 20% of all tuberculosis cases, with lymphatic extrapulmonary tuberculosis being the most prevalent manifestation of Extrapulmonary tuberculosis.[36,37] Pleura, bones, joints, the genitourinary tract, and the CNS are other sites that can be affected by *M tuberculosis*. Although virtually any organ can be involved in active tuberculosis, manifestations at other sites are rare.

Among the refugees with disseminated tuberculosis in this Grand Round, we found highly unusual manifestations, which might be due to difficulties in access to care and a delayed diagnosis. A 2006 review of thyroid tuberculosis found only 76 cases in the literature,[38] rarely causing abnormal thyroid function.[39] In tuberculosis that involves the heart, pericarditis is the most prevalent condition. Tuberculoma of the right atrium, which was present in one of our patients, is an unusual manifestation and has rarely been observed in the context of disseminated tuberculosis.[40,41]

Ocular tuberculosis is of special importance because it can lead to blindness if the infection is not properly diagnosed and treated. Virtually any part of the eye can be affected, primarily after haematogenous spread of the bacteria in disseminated forms of the disease.[42] The prevalence of ocular involvement in disseminated tuberculosis in immune compromised patients is estimated to be 5–20%,[43] but the condition has also been described in immune competent patients with disseminated tuberculosis.[44] The diagnosis of ocular tuberculosis is challenging and requires specific expertise.[45] Some forms of ocular tuberculosis such as anterior uveitis and paradoxical worsening of eye lesions after initiation of anti-tuberculous treatment must be treated with corticosteroids to prevent permanent damage. Therefore, ophthalmological examination in patients with suspected or proven disseminated tuberculosis is paramount.[46]

*Treatment and infection control*

In drug-susceptible tuberculosis, treatment for extrapulmonary or disseminated tuberculosis often needs longer treatment courses than the standard 6-month regimen for pulmonary tuberculosis,[47–49] and duration often has to be modified according to individual clinical response. The recommendations concerning treatment duration are guided by the involved organ and should be 9–12 months for tuberculosis of the bones and joints,[47] 6–9 months for lymph node tuberculosis, 6 months for tuberculous pericarditis,[47–49] 12 months for tuberculous meningitis,[50,51] and 6 months in peritoneal or intestinal tuberculosis.[47] For tuberculous meningitis and CNS tuberculosis, several studies found a survival benefit if adjunctive corticoisteroids were administered.[48–50,52] Corticosteroids can be used in tuberculosis pericarditis, but there are conflicting study results regarding a beneficial effect.[49,53] Corticosteroids should be used selectively in patients who develop inflammatory complications during treatment, not routinely in all patients.[47]

No specific guidelines exist for patients with multidrug-resistant (MDR) tuberculosis presenting with extrapulmonary or disseminated infection.[54,55] Treatment durations of 18–24 months are standard for these severely ill patients, and the choice of drugs should be guided by phenotypic and genotypic sensitivity testing. A shortened treatment regimen of 9–12 months that is promoted for pulmonary tuberculosis (the so-called Bangladesh regimen)[55] is not recommended for patients with extrapulmonary or disseminated tuberculosis. Extrapulmonary tuberculosis can be infectious when diagnostic or therapeutic procedures are done that result in the formation of aerosols. Protection against aerosol formation requires the use of N95 or FFP2 face masks. Laryngeal tuberculosis is highly contagious and requires full protective equipment similar to that required for smear-positive pulmonary tuberculosis.[56]

*Treatment response and outcome*

A feasible treatment response biomarker similar to sputum conversion used for pulmonary tuberculosis is not available in most cases of extrapulmonary tuberculosis or sputum-negative disseminated tuberculosis. Unspecific inflammation markers such as C-reactive protein concentration and erythrocyte sedimentation rate can help to assess early treatment response.[57] However, neither established criteria for cure and relapse nor parameters to guide treatment duration exist.[55] As a result, long-term treatment response must be thoroughly assessed on the basis of patients' clinical signs (eg, weight gain), laboratory findings, and by imaging.

Radiographical investigations such as CT and ultrasonography for tuberculous lymphadenopathy,[58] MRI for CNS tuberculosis,[59] and MRI or CT for musculoskeletal regions[32] are used. Treatment response is primarily assessed on the basis of lesion size, which can be problematic because pre-existing lesions might persist after termination of treatment or might enlarge during treatment, which is referred to as paradoxical reaction.[60] Residual lymph nodes or other residual lesions do not necessarily indicate unfavourable outcomes at the end of treatment because radiological improvement can lag behind considerably. Repeat biopsies are usually not required.[61] When treatment is terminated, lesions identified in imaging studies should be in steady state—ie, not have changed upon sequential examinations.

One retrospective study found a correlation between cure and a complete response using $^{18}$F-FDG PET with

CT in patients with lymph node tuberculosis and disseminated tuberculosis.[35] However, the sample size was small (18 patients) and the follow-up $^{18}$F-FDG PET with CT was done fairly late during or after treatment. Another study in HIV-negative patients with pulmonary tuberculosis found no reliable association between cure or relapse and $^{18}$F-FDG PET with CT results when done at the end of the 6-month treatment period.[34] More prospective studies are needed to investigate a possible role of $^{18}$F-FDG PET with CT in extrapulmonary and disseminated tuberculosis.

Extensive research into the identification of non-invasive blood biomarkers predicting tuberculosis treatment outcome and cure is ongoing. These methods, which are not yet implemented in routine clinical practice, are discussed elsewhere.[62,63] Refugee populations have an increased risk for treatment non-adherence and special interventions supporting improved adherence might be required (eg, directly observed therapy).[64]

*Immunosuppression in HIV-negative refugees*

Stressful conditions, social deprivation, and poor access to health care during migration, flight, and expulsion can contribute to the development of infectious and non-infectious diseases in refugees.[4,65] These conditions continue to affect the health status of refugees well beyond the process of migration and displacement.[65,66] These factors might be linked to high prevalence and increased severity of tuberculosis in children and young to middle-aged refugees without any obvious immune defect.[67,68]

An important contributor to disease is malnutrition, which is frequently observed in refugee children and adolescents entering high-income countries. One in five refugees younger than 18 years entering the US state of Georgia were anaemic, primarily because of iron deficiency, or malnourished.[69] Similar observations were made in 388 refugee children aged 16 years or younger on arrival to Canada between January 2009 and December 2014.[70] More than half of these refugees (53·5%) had vitamin D deficiency (25-hydroxyvitamin D [25OHD] <20 ng/mL). Studies revealed that severe vitamin D deficiency (25OHD <10 ng/ml) is also highly prevalent in adolescent and adult refugees coming to Europe.[71] Although there is some evidence that the risk of *M tuberculosis* infection or progression to active tuberculosis is increased in individuals with vitamin D deficiency, a protective role of vitamin D supplementation is a matter of debate and clinical studies regarding this issue are ongoing.[72] Clinicians should consider quantification of vitamin D (25OH-cholecalciferol) concentrations in the plasma of newly arrived refugees who are diagnosed with active tuberculosis and supplementation in case of severe deficiency. Another contributor to impaired host defence is co-infection with helminths.[73] Chronic parasitic infections cause widespread immune dysregulation, a dominant Th2 cytokine immune profile, and an immune hyporesponsiveness, which, in turn, might abrogate a robust antimycobacterial immune response.[74] Additionally, intestinal helminth infections are well known contributors to malnutrition, anaemia, and vitamin deficiencies.[74] Epidemiological studies done in high-incidence countries, such as Ethiopia, show that up to 24·4% of tuberculosis patients were co-infected with intestinal helminths.[75] The prevalence of potentially pathogenic parasites among refugees who resettle in Europe and North America is equally high.[69,76] Thus, presumptive screening of refugees for intestinal parasites and consecutive therapeutic measures are recommended by health organisations.[76]

A complex factor that might contribute to immune imbalances and increased severity of tuberculosis is post-traumatic stress. Most refugees experience traumatic events before or during migration, which can lead to post-traumatic stress disorder (PTSD). According to a meta-analysis, PTSD is prevalent in 19·0–52·7% of young refugees coming to Europe.[77] Although no studies exist linking PTSD to incidence or severity of tuberculosis, there is clear evidence that PTSD affects the function of the immune system. A meta-analysis identified 20 studies, which found increased plasma levels of proinflammatory cytokines, such as tumour necrosis factor-α and interferon-γ in individuals with PTSD, indicating chronic low grade inflammation in these patents.[78] These cytokines are important mediators of a potent antimycobacterial immune response. However, proinflammatory cytokine imbalances can also lead to increased tissue damage and bacterial spread as seen in patients with disseminated tuberculosis.[79] These aspects might best be addressed by host-directed therapies, an emerging research topic in tuberculosis control.[80]

### Search strategy and selection criteria

Data for this article were identified by searches of Medline, PubMed, and electronic databases such as Google Scholar. References from relevant articles using the search terms "extrapulmonary tuberculosis", "disseminated tuberculosis", "latent tuberculosis" , "tuberculosis diagnostics", and "tuberculosis treatment" were used. Only articles published in English between Jan 1, 2000, and July 31, 2018, were included. Web material was cited for epidemiological data not yet published in PubMed listed journals.

## Conclusion

Proper management of disseminated tuberculosis in refugees requires a heightened awareness among physicians, comprehensively taking medical history even in the presence of language barriers, and a multidisciplinary team approach involving health-care workers, social workers, nutritionists, and clinical psychologists. The application of appropriate diagnostic

procedures will result in the use of efficacious treatment regimens, often to be applied for prolonged periods of time. The mechanisms that lead to disseminated tuberculosis in the absence of HIV infection are not well understood and should be the subject of further research.

#### Contributors

JR, GF, SF, and IS initiated the idea and developed the first draft outline. Subsequent drafts were developed by CL, DM, RR, NJ, MS, NJ, RR, AB, and GP. All authors were involved in patient treatment. All authors contributed to all sections relevant to their experience and helped finalise the text and content.

#### Declaration of interests

We declare no competing interests.

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