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MAJOR ARTICLE

Tuberculosis Disease in Immunocompromised Children and Adolescents: A Pediatric Tuberculosis Network European Trials Group Multicenter Case-control Study

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Background. In high-resource settings, the survival of children with immunocompromise (IC) has increased and immunosuppressive therapies are increasingly being used. This study aimed to determine the clinical characteristics, performance of diagnostic tools, and outcome of IC children with tuberculosis (TB) in Europe.

Methods. Multicenter, matched case-control study within the Pediatric Tuberculosis Network European Trials Group, capturing TB cases <18 years diagnosed 2000–2020.

Results. A total of 417 TB cases were included, comprising 139 children who are IC (human immunodeficiency virus, inborn errors of immunity, drug-induced immunosuppression, and other immunocompromising conditions) and 278 non-IC children as

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controls. Nonrespiratory TB was more frequent among cases than controls (32.4% vs 21.2%; $P = .013$). Patients with IC had an increased likelihood of presenting with severe disease (57.6% vs 38.5%; $P < .001$; odds ratio [95% confidence interval], 2.073 [1.37–3.13]). Children with IC had higher rates of false-negative tuberculin skin test (31.9% vs 6.0%; $P < .001$) and QuantiFERON-TB Gold assay (30.0% vs 7.3%; $P < .001$) results at diagnosis. Overall, the microbiological confirmation rate was similar in IC and non-IC cases (58.3% vs 49.3%; $P = .083$). Although the mortality in children with IC was <1%, the rate of long-term sequelae was significantly higher than in non-IC cases (14.8% vs 6.1%; $P = .004$).

Conclusions. Children with IC and TB in Europe have increased rates of nonrespiratory TB, severe disease, and long-term sequelae. Immune-based TB tests have poor sensitivity in those children. Future research should focus on developing improved immunological TB tests that perform better in patients with IC, and determining the reasons for the increased risk of long-term sequelae, with the aim to design preventive management strategies.

Keywords. tuberculosis; immunodeficiency; immunosuppression; Europe; immune-based tests.

Tuberculosis (TB) remains a pressing global health concern, with children accounting for an estimated 10%–20% of the annual cases of TB. In 2021, the European Centre for Disease Prevention and Control recorded 6556 new cases in European children (<15 years), representing 4% of the total burden [1]. There are growing concerns in Europe that previous gains in TB control could be lost because of underdiagnosis during the coronavirus disease 2019 pandemic [2] and because of the increasing number of migrants to Europe from high-burden settings [3], including a recent surge in migration from Ukraine, one of the highest TB incidence countries in Europe [4].

The immune status plays a pivotal role in shaping the progression from *Mycobacterium tuberculosis* infection to TB [5, 6], and significantly influences disease severity [7]. Notably, in Europe, North America, and other high-income regions, there are growing populations of children with immunocompromise (IC) because of underlying chronic health conditions or immunosuppressive (IS) treatment [5, 7, 8]. Previous data suggest that children with Inborn Errors of Immunity (IEI), particularly those with T-cell defects, have an increased risk of infection and severe disease [7, 9–12], as do children with human immunodeficiency virus (HIV). During the past decade, the use of immunosuppressive drugs for rheumatological and autoimmune conditions, particularly of biological agents, has increased dramatically. Two types of biological agents, antibodies targeting tumor necrosis factor-α (TNF-α) and those targeting interleukin-1, have been shown to increase the risk of progression from *Mycobacterium tuberculosis* infection to TB several-fold compared with the general population, and therefore *M. tuberculosis* infection screening before treatment initiation is imperative [13–15].

Immunocompromised patients with TB tend to present with milder, nonspecific symptoms [16, 17], and more commonly have nonrespiratory TB [5]. In addition, there are in vitro and in vivo data showing that immune-based TB tests, including the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), perform worse in individuals with IC, which could result in delays in establishing a diagnosis of TB [6, 16, 18, 19]. Previous data also suggest that patients with IC are more likely to experience side effects related to TB treatment [5, 6, 16], and that they are at substantially higher risk of developing long-term morbidity and fatal outcome [6, 16, 17, 20]. However, most of the existing data originate from small adult studies, often focused solely on HIV co-infection, and have typically been conducted at single centers in resource-constrained regions, where some diagnostic TB tests are not available in routine clinical practice [21, 22].

This study aimed to describe the clinical manifestations, disease severity, and treatment outcome of TB in children with IC in Europe, with comparisons to children with TB without known IC from the same setting. Additionally, the study aimed to assess the performance of immune-based and microbiological TB tests in both patient populations.

METHODS

We conducted a retrospective multicenter case-control study within the Pediatric Tuberculosis Network European Trials Group (ptbnet) [23], the largest research network dedicated to pediatric TB globally, comprising 416 members across 52 countries as of May 2023.

Inclusion Criteria

Patients younger than age 18 years at the time of their TB diagnosis, who had been diagnosed or treated at a European collaborating center between 2000 and 2020, were included in the study. Cases were defined as patients with IC with TB disease, whereas controls consisted of patients with TB disease without known IC (non-IC) (ie, no primary or secondary immunodeficiency and not receiving immunosuppressive treatment at the time of the TB diagnosis). For each IC case, 2 controls were matched in a 1:2 ratio. Matching criteria included sex and age, with age categories stratified as follows: <2 years, ≥2–10 years, and ≥11 years.

Data Source

The data were sourced from the ptbnet database, a registry launched in 2017 to gather both retrospective and prospective data on children and adolescents <18 years who had TB contact, *M. tuberculosis* infection, or TB disease and received care at a participating healthcare center. The ptbnet database

is managed using REDCap electronic data capture tools [24], hosted at Gregorio Marañón Hospital in Madrid, Spain. This database captures comprehensive data covering demographics, clinical presentation, diagnostic tests, treatment modalities, and outcomes.

Definitions

We adhered to established consensus criteria for defining TB disease [25]. Patients with signs/symptoms of TB and a microbiological confirmation by culture and/or nucleic acid amplification tests (NAATs) were classified as confirmed TB. Unconfirmed TB was defined as a patient lacking microbiological confirmation but meeting at least 2 of the following criteria: (1) symptoms suggestive of TB, (2) chest radiograph consistent with TB, (3) known TB exposure or immunologic evidence of *M. tuberculosis* infection, and (4) response to TB treatment.

The anatomical site of TB disease was classified as respiratory TB, involving lung parenchyma, intrathoracic lymph nodes, larynx, trachea, bronchus, or pleura, or nonrespiratory TB, representing TB at any other site. Patients who had a respiratory disease focus and simultaneously had evidence of TB disease at other sites (eg, intra-abdominal lesions) were classified as having both respiratory TB and nonrespiratory TB. Miliary TB was defined as the acute hematogenous dissemination of miliary TB, evidenced by radiologic millet-like lung nodules, or by the isolation *M. tuberculosis* in blood/bone marrow.

Disease severity at diagnosis was classified as nonsevere TB in patients aged 3 months to <17 years, negative smear microscopy in respiratory samples, no rifampicin-/multidrug-resistance, and 1 of the following forms of disease: intrathoracic lymph node disease without airway obstruction, TB confined to a single lung lobe, noncavitary disease, nonmiliary pattern, uncomplicated pleural effusion, or uncomplicated peripheral lymphadenitis. Conversely, severe TB comprised patients not meeting those criteria according to established standards [26].

Immunocompromised was stratified into the following subgroups: (1) IEI, (2) HIV infection, (3) treatment with IS drugs (ie, conventional IS, biological agents or chemotherapy), (4) severe acute or chronic malnutrition (z score of <-3 or <60% weight for age or mid-upper-arm-circumference <115 mm), (5) other inborn diseases affecting immunity (eg, trisomy 21, sickle cell disease), and (6) other chronic diseases that impair immunological function (eg, renal failure, diabetes mellitus). Children with malnutrition and HIV infection were categorized as children with HIV.

Outcome data were stratified as cure, probable cure, or death [27]. Cure was defined as successful completion of prescribed treatment leading to the resolution of clinical symptoms, radiological improvement, and culture conversion. Probable cure consisted of the same criteria as cure, without documented culture conversion. Regarding death, we distinguished between patients who died because of TB and those who died from another cause. Finally, we used poor outcome to categorize patients who died or developed chronic sequelae resulting from TB.

Statistical Analysis

A comprehensive analysis comparing clinical presentation, diagnostic performance, and outcomes between cases and controls was performed. Subgroup analyses focused on patients with IC, particularly children with HIV and those with drug-induced IC. Qualitative data were described using absolute frequencies and percentages, whereas quantitative data were summarized using mean, standard deviation, median, and interquartile range (IQR). The chi-square test was used for qualitative variables, and the Mann-Whitney U test for quantitative variables. For analyses related to the QuantiFERON-TB Gold assay (QFT; Qiagen, Hilden, Germany), results categorized as indeterminate or negative were collectively considered as "not positive."

In the multivariate analyses, a backward stepwise binary logistic regression model was used with poor outcome as the dependent variable. Independent variables were those deemed clinically relevant and those with statistical significance on univariate analysis. All statistical tests used a 2-tailed approach and a significance level of 0.05, using IBM SPSS (version 27; IBM, Armonk, NY, USA).

Ethics

The study received approval from the Ethics Committee of each participating center. No identifiable information was collected. Written informed consent was obtained from the parents/guardians and/or of children aged ≥12 years, depending on local/national regulations.

RESULTS

A total of 417 participants were included in the study, comprising 139 cases with IC and 278 controls. Spanish centers contributed the largest number of participants (n = 150), followed by centers in Italy (n = 59), Germany (n = 50), Portugal (n = 47), Ukraine (n = 37), Russia (n = 25), United Kingdom (n = 20), Lithuania (n = 17), Sweden (n = 4), Bulgaria and Latvia (n = 3, each), and Austria (n = 2). Table 1 summarizes the demographic characteristics of the cases and the controls. Within the IC group, the largest subgroups were children with HIV and children receiving IS drugs (Table 2). Among children with HIV, the median CD4 count at the time of TB diagnosis was 292 cells/mm^3 (IQR 71–493). For patients with drug-induced IS, the most commonly used medications were chemotherapy (16/37; 43.2%), corticosteroids (8/37; 21.6%), and anti-TNF-alpha agents (6/37; 16.2%).

Clinical Presentation and Disease Severity

With the exception of cough, all clinical symptoms/signs were more prevalent in IC than in non-IC patients (Table 3).

Table 1. Baseline Characteristics of the Study Population Comprising Immunocompromised (IC) Patients and Nonimmunocompromised (Non-IC) Controls

	Non-IC (n = 278)	IC (n = 139)	*P* Value
Age, y, median [IQR]	8.6 [4.1–14.4]	10.3 [6.2–13.5]	.362
Sex (female)	138 (49.6)	69 (49.6)	1.000
BMI, median [IQR]	16.6 [15.2–19.6]	15.5 [13.7–17.5]	**<.001**
BCG-vaccinated (n = 364)	99/250 (39.6)	58/114 (50.9)	.088
Migration status—immigrant (n = 405)	69/270 (25.6)	50/135 (37.0)	**.017**
WHO region of birth (n = 407)			
European	212/273 (77.7)	89/134 (66.4)	**0.016**
African	22/273 (8.1)	23/134 (17.2)	
Eastern Mediterranean	23/273 (8.4)	6/134 (4.5)	
Region of the Americas	11/273 (4.0)	11/134 (8.2)	
South-East Asia	4/273 (1.5)	5/134 (3.7)	
Western Pacific	1/273 (0.4)	0/134 (0.0)	
Ethnic background (n = 410)			
White Caucasian	154/276 (55.8)	66/134 (49.3)	.3216
Black/African American	39/276 (14.1)	28/134 (20.9)	
Latin American	25/276 (9.1)	16/134 (11.9)	
Asian	16/276 (5.8)	9/134 (6.7)	
Arab or Berber	19/276 (6.9)	6/134 (4.5)	
More than 1 ethnicity	7/276 (2.5)	4/134 (3.0)	
Other	16/276 (5.8)	5/134 (3.7)	
Other comorbidities (n = 359)			
Prematurity	3/226 (1.3)	6/133 (4.5)	.066
Cardiovascular	5/226 (2.2)	8/133 (6.0)	.066
Respiratory	7/226 (3.1)	7/133 (5.3)	.319
Neurological	6/226 (2.7)	12/133 (9.0)	**.008**
Gastrointestinal	0/226 (0.0)	11/133 (8.3)	**<.001**
Rheumatological	2/226 (0.9)	12/133 (9.0)	**<.001**
Nephrological	2/226 (0.9)	9/133 (6.8)	**.002**
Hematological disorders	3/226 (1.3)	28/133 (21.1)	**<.001**

Data shown are numbers and percentages unless stated otherwise. Data shown refer to the 417 patients included in the study, unless the number of patients with available data is specified in the denominator. Bold values represent the statistically significant results.

Abbreviations: BCG, Bacillus Calmette–Guérin; BMI, body mass index; IC, immunocompromised; IQR, interquartile range.

Table 2. Subgroups of Immunocompromised Patients

	Number (%)
Inborn errors of immunity	5/139 (3.6%)
Chronic granulomatous disease	2
Mendelian susceptibility to mycobacterial disease	1
Hypogammaglobulinemia/CD16 deficiency	1
IFN-gamma/IL-17 release deficit	1
HIV infection[a]	41/139 (29.5%)
Immunosuppressive drugs[b]	37/139 (26.6%)
Chemotherapeutic agents	16
Steroids	8
Anti-TNF-α agents	6
Methotrexate	3
Azathioprine	2
Cyclosporine	1
Malnutrition[c]	25/139 (18.0%)
Other inborn diseases affecting immunity[d]	20/139 (14.4%)
Trisomy 21	10
Sickle cell disease	10
Other chronic conditions[e]	19/139 (13.7%)

Data shown are numbers and percentages unless stated otherwise.

Abbreviations: IFN, interferon; HIV, human immunodeficiency virus; IL, interleukin; TNF, tumor necrosis factor.

[a]Three children with HIV were also malnourished.

[b]Among children receiving immunosuppressive drugs, 3 received >1 drug; the specific drug was unknown in 2.

[c]Eleven children with malnutrition had other conditions (HIV n = 3, chronic conditions n = 7, inherited disorders n = 1).

[d]Five children with other inborn diseases affecting immunity had other conditions (drug-induced IC n = 4, malnutrition n = 1).

[e]Chronic conditions: diabetes mellitus (n = 10), chronic renal failure (n = 3), Duchenne (n = 1), severe cerebral palsy (n = 1), idiopathic CD4 lymphocytopenia (n = 1), solid organ tumor (n = 1), rheumatologic conditions (n = 2).

In both groups, the most commonly prevalent symptoms/signs were fever, cough, weight loss and asthenia. Similar proportions of IC and non-IC patients had respiratory TB (95.0% vs 91.4%). However, nonrespiratory disease was significantly more common in the IC than in the non-IC group (32.4% vs 21.2%). Also, the proportions of patients with miliary/disseminated TB, TB meningitis, and abdominal TB were significantly higher in the IC group than in the non-IC group (Table 3). Patients with IC also had an increased likelihood of presenting with severe disease (57.6% vs 38.5%; $P < .001$; odds ratio [95% confidence interval], 2.073 [1.37–3.13]).

Comparisons between non-IC patients and 4 IC subgroups (Supplementary Table 1), showed that miliary/disseminated TB was significantly more common in patients with IEI, patients with HIV, patients with drug-induced IC, and patients with malnutrition than in non-IC patients. All 4 IC subgroups also had higher proportions of severe TB disease than the group of non-IC patients.

Diagnostic Test Results

Chest radiograph findings were documented in 412 (98.8%) children and 272 (65.2%) underwent a computed tomography scan. Similar proportions of patients with IC and non-IC had abnormal findings on chest radiograph and/or chest computed tomography (Table 4). There were no significant differences in the radiological abnormalities identified between both groups, with the exception of miliary changes, which were significantly more common in the IC group.

False-negative TST results (<5 mm) were significantly more common in patients with IC than in those without (31.9% vs 6.0%; $P < .001$; Table 4 and Figure 1). Children with IC also had smaller TST indurations on average than children without IC (12 mm vs 15 mm; $P < .001$). Similarly, the proportion of false-negative QFT results was far higher in the IC than in the non-IC group (30.0% vs 7.3%; $P < .001$); in contrast, the proportion of indeterminate QFT results did not differ significantly between both groups.

Table 3. Reason for TB Screening, Clinical Characteristics at Presentation, Site of Disease, Disease Severity, and Outcome of Immunocompromised (IC) and Nonimmunocompromised (Non-IC) Study Participants

	Non-IC (n = 278) n (%)	IC (n = 139) n (%)	*P* Value n (%)
Reason for TB screening (n = 406)			
Contact tracing	109/271 (40.2)	27/135 (20.0)	**.002**
TB signs/symptoms	142/271 (52.4)	81/135 (60.0)	.254
Migrant screening	20/271 (7.4)	2/135 (1.5)	.169
IC screening	0 (0)	25/135 (18.5)	**<.001**
Clinical symptoms at presentation (n = 413)	192/277 (69.3)	120/136 (88.2)	**<.001**
Fever (n = 411)	109 (39.2)	72 (51.8)	**<.001**
Cough (n = 398)	120 (44.3)	60 (47.2)	.580
Respiratory distress (n = 387)	20 (7.7)	25 (19.7)	**<.001**
Weight loss (n = 389)	76 (29.0)	60 (47.2)	**<.001**
Asthenia (n = 391)	80 (30.4)	61 (47.7)	**<.001**
Vomiting (n = 307)	7 (3.4)	11 (11.1)	**.007**
Other GI symptoms (n = 339)	21 (9.1)	18 (16.5)	**.047**
Hepatomegaly (n = 386)	3 (1.1)	23 (16.5)	**<.001**
Splenomegaly (n = 387)	7 (2.5)	16 (11.5)	**<.001**
Headache (n = 381)	6 (2.3)	10 (8.2)	**.008**
Peripheral lymphadenopathy (n = 385)	28 (10.7)	24 (19.5)	**.018**
Site of TB (n = 416)			
Respiratory disease	254 (91.4)	132 (95.0)	.184
Non-respiratory disease[a]	59 (21.2)	45 (32.4)	**.013**
Miliary/disseminated TB	13 (4.7%)	33 (23.7%)	**<.001**
TB meningitis	6 (2.2%)	17 (12.2%)	**<.001**
Abdominal TB	10 (3.6%)	18 (12.9%)	**<.001**
Peripheral lymph node TB	25 (9%)	14 (10.1%)	.721
Osteoarticular TB	18 (6.5%)	11 (7.9%)	.586
Genitourinary TB	1 (0.4%)	1 (0.7%)	.616
Disease severity and outcome			
Severe TB at diagnosis	107 (38.5)	80 (57.6)	**<.001**
Poor outcome (n = 392)	16/263 (6.1)	20/129 (15.6)	**.002**

Data shown are numbers and percentages unless stated otherwise. Data shown refer to the 417 patients included in the study unless the number of patients with available data is specified in parentheses. Bold values represent the statistically significant results.

Abbreviations: CNS, central nervous system; GI, gastrointestinal; IC, immunocompromised; IQR, interquartile range; LN, lymph node; TB, tuberculosis.

[a]73 participants with nonrespiratory disease also had respiratory disease.

Table 4. Immune-based, Microbiological, and Radiological Tests in the Study Population

	Non-IC (n = 278)	IC (n = 139)	*P* Value
TST; median [IQR][a]	15 [12–20]	12 [5–17]	**<.001**
TST <5 mm	11/183 (6.0)	22/69 (31.9)	**<.001**
TST ≥5 mm	172/183 (94.0)	47/69 (68.1)	**<.001**
Categorical QFT result			
Negative	14/191 (7.3)	21/70 (30.0)	**<.001**
Indeterminate	9/191 (4.7)	2/70 (2.9)	**<.732**
Positive	168/191 (88.0)	47/70 (67.1)	**<.001**
TB microbiological confirmation			
Confirmed TB	137 (49.3)	81 (58.3)	.083
Culture-positive[b]	116/252 (46.0)	70/129 (54.3)	.128
NAAT-positive[b]	96/220 (43.6)	58/96 (60.4)	**.006**
Chest x-ray findings	222/274 (81.0)	105/138 (76.1)	.243
Hilar lymphadenopathy	105/215 (48.8)	40/103 (38.8)	.094
Parenchymal opacities	142/220 (65.0)	60/101 (59.4)	.323
Calcifications	10/178 (5.6)	4/82 (4.9)	.790
Cavities	27/211 (12.8)	8/100 (8.0)	.211
Miliary pattern	8/210 (3.8)	25/102 (24.5)	**<.001**
Chest CT findings	167/172 (97.1)	97/100 (97.0)	.965
Hilar lymphadenopathy	106/163 (65.0)	55/94 (58.5)	.298
Parenchymal opacities	111/164 (67.7)	62/94 (66.0)	.777
Calcifications	28/143 (19.6)	13/76 (17.1)	.655
Cavities	30/159 (18.9)	12/88 (13.6)	.295
Miliary pattern	10/158 (6.3)	26/90 (28.9)	**<.001**

Data shown are numbers and percentages unless stated otherwise. Data shown refer to the 417 patients included in the study unless the number of patients with available data is specified in denominators. Bold values represent the statistically significant results.

Abbreviations: CT, computed tomography; IC, immunocompromised; NAAT, nucleic acid amplification test; QFT, QuantiFERON-TB Gold; TST, tuberculin skin test.

[a]TST induration was not recorded in 83 participants.

[b]Both culture and NAAT were positive in 119 participants.

Subgroup analyses (Supplementary Table 1) showed that the rate of false-negative TST results (<5 mm), was significantly higher in patients with HIV, drug-induced IC, or malnutrition than in non-IC patients. Also, the rate of false-negative QFT results was substantially higher in all 4 IC subgroups than in the non-IC group. The highest proportion of indeterminate QFT results (16.7%) was observed in the subgroup of patients with malnutrition.

TST and QFT agreement was assessed in 163 children, comprising 30 IC and 133 non-IC patients. Among non-IC patients, there was a positive agreement (TST+/QFT+) in 87.1%, negative agreement (TST−/QFT−) in 3.8%, TST+/QFT− discordance in 7.6%, and TST−/QFT+ discordance in 2.3%. In contrast, the IC group showed a positive agreement in only 53.3% of the patients, negative agreement in 23.3%, TST+/QFT− discordance in 13.3%, and TST−/QFT+ discordance in 10.0%.

Children with IC exhibited a higher proportion of microbiologically confirmed TB compared with non-IC patients (58.3% vs 49.3%; $P = .083$; Table 4), with a significantly higher proportion of patients having positive NAATs results in the former group (60.4% vs 43.6%; $P = .006$). Children with HIV had a lower microbiological confirmation rate than children in the other IC subgroups (43.9% vs 64.3%, $P = .026$) (Supplementary Table 2).

There were no statistically significant differences in the microbiological yield of different sample types between IC and non-IC patients: gastric aspirates (43.8% vs 43.8%, $P = .990$), spontaneous sputum (50.0% vs 68.8%, $P = .082$), induced sputum (33.3% vs 36.8%, $P = .788$), and fine-needle aspiration (72.7% vs 55.0%, $P = .332$).

Treatment and Outcome

On average, patients with IC received longer courses of anti-TB treatment compared with non-IC patients (8.5 months [IQR:

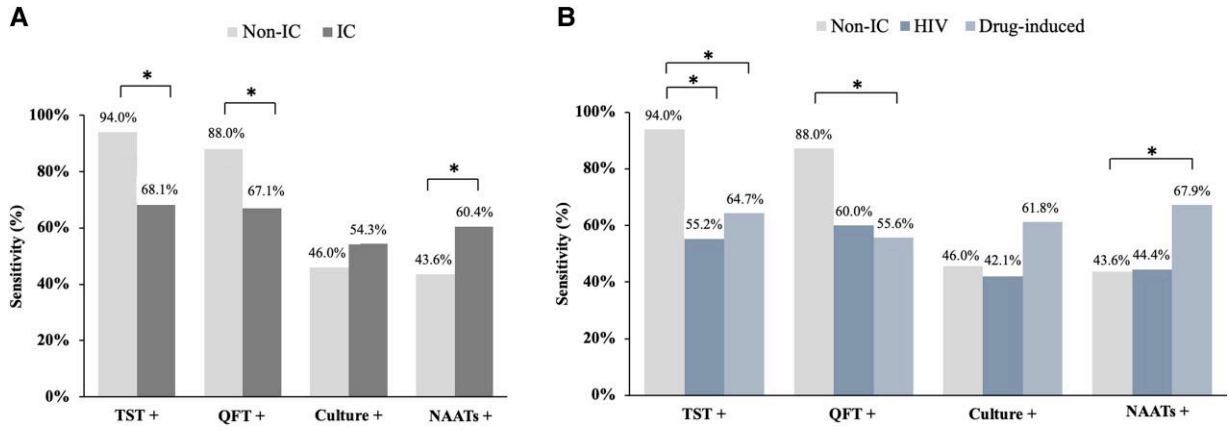

Figure 1. Sensitivity of immunological and microbiological tests according to immune status. Bar chart showing sensitivity of immunological and microbiological tests in nonimmunocompromised (non-IC) and immunocompromised (IC) patients (*A*), and non-IC patients, patients with HIV, and patients with drug-induced immunocompromise (*B*). Comparisons were made with chi-square tests; statistically significant differences ($P < .05$) are indicated by *. Abbreviations: IC, immunocompromised; HIV, human immunodeficiency virus; NAATs, nucleic acid amplification tests; QFT, QuantiFERON-TB Gold; TST, tuberculin skin test.

6–12] vs 6.3 months [IQR: 6–9], $P < .001$). Drug-related adverse events occurred in 82 children (32.4% [36/111] of IC and 24.2% [46/190] of non-IC patients, $P = .207$), with the most frequent events being elevation of liver enzymes (36.4%) and gastrointestinal symptoms (24.2%). Adherence to treatment was good overall, with no significant difference between IC and non-IC patients (94.7% vs 93.7%, $P = .680$); almost all children completed the prescribed course of treatment, except for 8 cases (4 IC and 4 non-IC patients).

Outcome data for 392 children revealed a probable cure rate of 72.7% in IC versus 80.7% in non-IC patients, and cure rates of 26.6% and 19.3%, respectively. The IC group had a higher rate of poor outcome (ie, death or chronic sequelae) compared with the non-IC group (15.6% vs 6.1%, $P = .002$). There was only 1 reported death—a 10-year-old girl with severe malnutrition and epilepsy who died of miliary TB 1 month after treatment initiation. Long-term sequelae were significantly more common in IC than in non-IC patients (14.8% vs 6.1%; $P = .004$), with the most common types comprising respiratory (7.8% vs 1.4%; $P = .003$), osteoarticular (3.9% vs 2.3%; $P = .358$), and neurologic sequelae (2.3% vs 0.8%; $P = .335$).

In the multivariate analyses related to outcome (Table 5), IEI and malnutrition were identified as IC conditions associated with poor outcome (IEI: odds ratio, 9.54 [1.50–60.34], $P = .017$; malnutrition: odds ratio, 3.87 [1.39–10.78], $P = .009$). Other factors associated with poor outcome were non-European origin (odds ratio, 3.3 [1.64–6.64], $P < .001$), presence of respiratory distress at presentation (odds ratio, 4.24 [1.67–7.31], $P = .002$) and nonrespiratory TB (odds ratio, 8.71 [3.85–19.73], $P < .001$). Finally, having a negative QFT result at presentation was also associated with poor outcome (odds ratio, 9.41 [2.27–38.99]; $P = .002$).

DISCUSSION

This European case-control study currently represents the largest multicenter study focusing on TB disease in children with IC in middle- to high-income countries, and provides valuable contemporary data related to this high-risk patient group. HIV infection and drug-induced IC were the predominant conditions in this cohort, the latter reflecting the increasing prevalence of autoimmune-mediated diseases in high-resource countries [28].

In concordance with previous studies in people with HIV and studies focusing on TB in patients with drug-induced IS, we found that children with IC had significantly higher rates of nonrespiratory TB and disseminated/miliary TB [5, 16]. Further analyses also revealed that all IC subgroups—children with IEI, children with HIV, children with drug-induced IS, children with malnutrition—were at increased risk of severe TB disease compared with non-IC controls. Both observations can be explained by the reduced ability to contain *M. tuberculosis* in patients with IC, which requires a complex functioning interaction between innate immune cells and T cells [29].

Our study also highlights the limitations of immune-based TB tests in children with IC. Overall, close to one third of the patients had false-negative TST (at the 5-mm cutoff) and/or QFT results. In contrast to some previous studies, in our cohort, the sensitivity of the QFT assay was not greater than that of the TST [30, 31]. Consequently, although in children with IC presenting with features consistent with TB, a positive TST or QFT result can be useful to support a putative diagnosis of TB; negative results should not distract from further investigations, including imaging and microbiological tests. Considering that TST/IGRA discordance is not uncommon in children with TB disease, especially in those with IC, we believe that both tests should be done in parallel to increase the

Table 5. Multivariate Analyses of Factors Potentially Associated With Poor Outcome

	Good Outcome (n = 356)	Poor Outcome (n = 36)	*P* Value	OR (95% CI)	*P* Value
IC disorder					
Inborn errors of immunity	3/5 (60.0)	2/5 (40.0)	.069	**9.54 (1.50–60.34)**	***P* = .017**
HIV infection	32/37 (86.5)	5/37 (13.5)	.338	2.27 (.78–6.62)	*P* = .131
Immunosuppressive drugs	30/33 (90.9)	3/33 (9.1)	1.000	0.61 (.13–2.75)	*P* = .520
Malnutrition	17/23 (73.9)	6/23 (26.1)	**.004**	**3.87 (1.39–10.73)**	***P* = .009**
Other inborn diseases	15/19 (78.9)	4/19 (21.1)	.085	1.72 (.40–7.39)	*P* = .461
Other chronic conditions	17/18 (94.4)	1/18 (5.6)	1.000	2.49 (.80–7.79)	*P* = .115
Non-European[a]	82/100 (82.0)	18/100 (18.0)	**<.001**	**3.30 (1.64–6.64)**	***P* < .001**
Clinical presentation					
Respiratory distress	32/353 (9.0)	10/36 (27.8)	**.002**	**4.24 (1.67–10.77)**	***P* = .002**
Nonrespiratory TB	69/355 (19.4)	26/36 (72.2)	**<.001**	**8.71 (3.85–19.73)**	***P* < .001**
Diagnostic tests					
Negative TST	26/220 (11.8)	5/17 (29.4)	.038	0.60 (.67–7.31)	*P* = .765
Negative QFT result	34/229 (14.8)	8/21 (38.1)	**.006**	**9.41 (2.27–38.99)**	***P* = .002**
Culture confirmation	155/328 (47.3)	19/35 (54.3)	.429	0.69 (.10–4.81)	*P* = .716
NAAT confirmation	126/275 (45.8)	19/28 (67.9)	.026	1.22 (.13–10.90)	*P* = .857

Data shown are numbers and percentages unless stated otherwise. Bold values represent the statistically significant results.

Abbreviations: CI, confidence interval; IC, immunocompromise; NAAT, nucleic acid amplification tests; OR, odds ratio; QFT, QuantiFERON-TB Gold; TB, tuberculosis; TST, Tuberculin skin test.

[a]Region of birth.

diagnostic yield, as also recommend by clinical practice guidelines [32]. We found that overall microbiological confirmation, by both culture and NAATs, is more commonly achieved in children with IC than those without IC. However, subgroup analyses revealed that children with HIV had lower confirmation rates that children with other forms of IC and non-IC children. This finding is in line with previous studies in adults with HIV, which also reported low yields of microbiological investigations in this particular patient group [22, 33].

Previous studies from low-resource settings have highlighted the increased risk of long-term sequelae and fatal outcome in patients with IC, including in people with HIV [34, 35]. In our cohort, only 1 child with IC died, equating to a mortality rate below 1%. This observation is likely explained by the fact that all participating units had access to the full range of radiological and microbiological diagnostics, thereby enabling timely diagnoses, as well as high-level intensive care support. However, despite the availability of those facilities, a substantial proportion (15.6%) of children with IC had a poor outcome. Long-term sequelae resulting from TB were significantly more common in children with IC than in those without IC (14.8% vs 6.1%). Multivariate analyses revealed several risk factors for poor outcome in children with IC, including underlying IEI or malnutrition, presence of respiratory distress at presentation, presence of nonrespiratory TB, and a negative QFT result at presentation. The latter observation is intriguing and may reflect reduced numbers of *M. tuberculosis*–specific T cells in the peripheral circulation or alternatively T-cell energy [36].

Our study has certain limitations. First, because of its retrospective nature some data are missing and there is a risk of selection bias. Also, given the limited number of patients with TB matched by sex and age in some countries, it was not always possible to also match cases and controls according to their country of origin. The diverse management practices in the different participating units may limit the generalizability of our observations to low-income countries. In addition, there is limited access to IGRAs in some participating centers in middle-income countries. Furthermore, not all included patients were microbiologically confirmed, but this is a common issue in pediatric TB studies, in which confirmation rates are typically far lower than in adult studies. Additionally, of the 13 children with HIV who had radiological findings consistent with miliary TB, only 5 had microbiologically confirmed TB; in the remaining 8 the possibility of lymphoid interstitial pneumonitis cannot be excluded with certainty. Last, the relatively small number of children with IEI included in this cohort restricted our ability to conduct robust comparative analysis within this subgroup.

In summary, our study of IC children with TB in Europe found increased rates of nonrespiratory TB, severe disease, and long-term sequelae within this group. Immune-based TB tests had poor sensitivity, with approximately one third of IC children having negative TST and/or IGRA results. Overall, the sensitivity of microbiological tests was similar in children with IC and those without IC, with the exception of children with HIV in whom microbiological confirmation of TB disease was significantly lower. Future research should focus on the development of improved immunological TB tests that have better performance characteristics than existing tests in children with IC. Furthermore, more research is needed to

explore the reasons for the increased rate of long-term sequelae in children with IC, ultimately with the aim to design preventive management strategies to avert adverse outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. R. M., M. T., T. S., L. F. A., and B. S. G. conceptualized and designed the study; P. R. M., L. F. A., and A. H. B. collected data; B. S. G. coordinated and supervised data collection; P. R. M. and L. F. A. drafted the initial manuscript; M. D. A., B. S. G., and P. R. M. carried out the initial analyses. All authors critically reviewed the data and revised the manuscript. All authors approved the final submitted manuscript and agreed to be accountable for all aspects of the work.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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