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The changing epidemiology of tuberculosis in a Spanish tertiary hospital (1995–2013)

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Abstract

Important epidemiological changes and improvement of new diagnostic approaches, mainly molecular tools, might have impacted the management and outcome of tuberculosis (TB) in the last years in industrialized countries. In order to describe the epidemiological trends, and changes in clinical, diagnostic, and therapeutic aspects in patients with TB, an observational study was performed in a tertiary hospital in Western Europe (Madrid, Spain).

All adult patients (>16 years) with a diagnosis of TB in the period 1995 to 2013 were included in the study.

TB was diagnosed in 1284 patients, including 304 (24%) foreign-born and 298 (23.2%) human immunodeficiency virus (HIV)-infected patients. The proportion of foreign-born patients increased significantly, from 7.4% (1995) to 40.3% (2013), $P < .001$, while the proportion of patients with HIV infection decreased (from 41% to 15%, $P < .001$). Extrapulmonary locations of TB increased (from 23.9% to 37.1%, $P < .001$), although the miliary forms were less frequent (from 16% to 5.6%, $P < .001$). Pulmonary involvement remained constant during the period of study (from 50% to 46%, $P = .18$). The yield of microbiological diagnostic methods in different clinical specimens has remained very similar. Only molecular techniques have improved the diagnosis in respiratory, urinary, and peritoneal samples. The global cure rate was 64.8% and mortality rate was 9.1% (6.5% directly attributable to TB). Mortality has decreased significantly during the years of study (from 11% to 2%, $P < .001$).

There has been a significant decline in the number of patients with TB. Changes in HIV coinfection and immigration have conditioned other epidemiological and clinical aspects of the disease, including the clinical presentation, treatment response, and mortality. Only the use of molecular tests has provided an improvement in the diagnosis of pulmonary and extrapulmonary TB.

Abbreviations: AFB = acid-fast bacillus, CI = confidence interval, HIV = human immunodeficiency virus, MDR-TB = multidrug resistant tuberculosis, OR = odds ratio, PCR = polymerase chain reaction, TB = tuberculosis, TST = tuberculin skin test, XDR-TB = extensively drug-resistant tuberculosis.

Keywords: acid-fast bacillus, adenosine deaminase, human immunodeficiency virus, polymerase chain reaction, tuberculin skin test, tuberculosis

1. Introduction

Despite the therapeutic advances of the last century, tuberculosis (TB) continues to be an important cause of morbidity and mortality, with more than 8 million people suffering the disease globally.[1] TB remains a disease of poverty, and some developing high-burden countries endure a devastating impact. In industrialized countries, there has been an important decrease in the number of cases of TB, due to improvements in social conditions

and the availability of effective treatment,[2] but the disease is far from being eradicated.

Spain has one of the highest TB incidence rates in Western Europe.[3] In 2011, 6762 cases of TB were reported, including 1785 (26.4%) with extrapulmonary involvement.[4] In recent years, considerable efforts have been made to gain a deeper understanding of the disease and how to best manage it. TB incidence has been falling since 1995. However, the decrease in the prevalence has slowed down in recent years due to increased immigration from TB-endemic areas.[5] Major changes in the epidemiology of TB have occurred in the last 2 decades that could have modified different features of the diseases during this period.

The present study has been carried out to evaluate the changes in TB during a 19-year period in a tertiary hospital that could help in the design of future strategies for the better control of the disease.

2. Methods

2.1. Study design

This is an observational, retrospective study, performed at the Ramón y Cajal University Hospital in Madrid, Spain. It is a 1200-bed tertiary referral hospital that provides medical care to a population of 500,000 inhabitants. All adult patients with a TB diagnosis during the years 1995 to 2013 were included in the study. Pediatric cases (<16 years old) were excluded from the

González-García et al. Medicine (2017) 96:26

Medicine

analysis. In 1995, a respiratory isolation unit was created for patients referred from different departments. A high rate of patients from the global cohort came from this specific unit.

Patients were identified by crossmatching 3 registries of TB: the Microbiology Department database, the internal server of the center with discharge diagnoses, and Preventive Medicine and Public Health Department registry. Data on all patients were obtained from the medical records. The study was reviewed and approved by the local ethic committee of our institution.

2.2. Definitions

All the patients included in the study had a confirmed or probable diagnosis of TB. Cases of confirmed TB were defined by the presence of positive cultures for *Mycobacterium tuberculosis* complex. Probable TB was considered when there was no isolation of *M tuberculosis* but fulfilled one or more of the following: a positive nucleic acid amplification test with an acid-fast bacilli (AFB) positive smear; histological samples showing the presence of granulomata or caseum in cytological smears; and adenosine deaminase activity in organic fluids higher than 35 U/L (pleural, peritoneal, and pericardial fluid) or 6 U/L (cerebrospinal fluid).

TB was considered to be pulmonary if the organism was isolated in culture of respiratory samples or/and if chest X-ray was suggestive of pulmonary involvement. TB was considered to be extrapulmonary if *M tuberculosis* was isolated from a nonpulmonary source or was histologically confirmed in patients with TB proven by culture. TB was considered to be miliary if chest X-ray showed a miliary pattern, and TB was confirmed by culture of pulmonary or nonpulmonary samples.

2.3. Variables

The following epidemiological, clinical, and microbiological variables were collected in all the patients: demographics: age, gender, and origin; site of disease: pulmonary, extrapulmonary, both, or disseminated; associated risk factors and comorbidities: smoking habit, drug use, alcohol abuse, diabetes, neoplasia, chronic renal disease, liver disease, chronic obstructive pulmonary disease, human immunodeficiency virus (HIV), malnutrition, and previous use of steroids; tuberculin skin test (TST); diagnostic evaluation: AFB smear, polymerase chain reaction (PCR), culture, histological examination, adenosine deaminase, and drug susceptibility testing; and adverse events, treatment adherence, and outcome.

2.4. Laboratory procedures

Clinical samples were processed according to Tacquett & Tison method and inoculated on solid media, Lowenstein Jensen and Coletsos media (Bio Medics SL, Tres Cantos, Madrid, Spain) and, since 1996, in liquid medium (Veersa TREK system, formerly ESP culture System II). *M tuberculosis* complex strains isolates were identified using DNA probes (Gen Probe, San Diego, CA) and phenotypic tests. In vitro susceptibility tests were performed against 1st-line drugs according to Canetti method on Lowenstein Jensen medium and 7H10 agar medium until 1996, and later in liquid medium with antibiotic concentrations according to the manufacturer's protocol (Versa TREK system, formerly ESP culture System II). TB was defined as drug-susceptible when the isolate had a positive susceptibility result for isoniazid and rifampin, independently of resistance to other 1st-line or 2nd-line drugs. Multidrug resistant TB (MDR-TB) was defined when the organism was resistant to at least isoniazid and rifampin. MDR-TB with resistance to a fluoroquinolone and a 2nd-line injectable drug was considered extensively drug-resistant TB (XDR-TB).

Transcription-mediated amplification was applied for molecular diagnosis. The amplified *M tuberculosis* Direct Test (AMTD; Gen-Probe Inc.) is a rapid isothermal (42 °C) method based on the amplification of 16S-rRNA. Reverse transcriptase is used to copy rRNA to a cDNA-RNA hybrid, and the chemiluminescent method is then applied using specific DNA probes. This procedure was directly applied on clinical samples, including sputum, bronchoalveolar lavage, tissue biopsy specimens, and urine.

2.5. Outcome

TB was considered to be cured if correct therapy and follow-up were confirmed, and clinical features showed a favorable outcome. In the case of patients who had abandoned previous therapy and patients who had received more than 1 course of therapy, only the last episode was included for analysis.

2.6. Statistical analysis

The epidemiology of the disease and changes occurring during the study period as well as risk factors associated with isoniazid-resistance, MDR-TB, or XDR-TB was analyzed. Factors related to mortality were analyzed globally or according to the period.

The descriptive statistical analysis included median and range for continuous variables, and frequencies and proportions for categorical variables. The Student *t* test was used to compare continuous data and the chi square test to compare categorical data. Odds ratio (OR), 95% confidence interval (CI), and *P* values were calculated. The difference was considered statistically significant when $P < .05$. Multiple logistic regression analysis was used to determine the independent risk factors associated with different types of resistance and mortality. All variables with a $P < .1$ in the univariate analysis were entered in the multivariate model. Software SPSS Statistics 19 was used for the statistical analyses.

3. Results

3.1. Patients characteristics

From January 1995 to December 2013, 1284 patients were diagnosed with TB. There were 1109 culture-proven, confirmed TB cases (86%). The number of cases decreased from 115 cases in 1995 to 31 cases in 2013 (Fig. 1). Regarding the overall general admissions, TB cases who were hospitalized decreased from 4 per 1000 admissions in 1995 to 1 per 1000 admissions in 2013.

Characteristics of patients, and a comparison of those born in and out of Spain, are shown in Table 1. A total of 821 (63.9%) patients were male, with a male predominance in all the years of the study. The median age was 38 years with a biphasic peak incidence at 30 to 40 and 70 to 80 years. Of the 1284 patients with TB, 304 (24%) were immigrants. The regions of origin were Latin-America (62%), Sub-Saharan Africa (16%), Western Europe (11%), Maghreb (5%), and Asia (4%). The median period of stay in Spain before the diagnosis was 3 (range 1–6) years. Foreign-born patients were younger (34 ± 14 vs 48 ± 18 years, $P < .001$), with a higher proportion of women (46% vs 33%, $P < .001$) and a lower proportion of HIV coinfection (10% vs 27%, $P < .001$). HIV infection at the time of TB diagnosis was present in 298 patients (23.2%). The median CD4+ T cell count
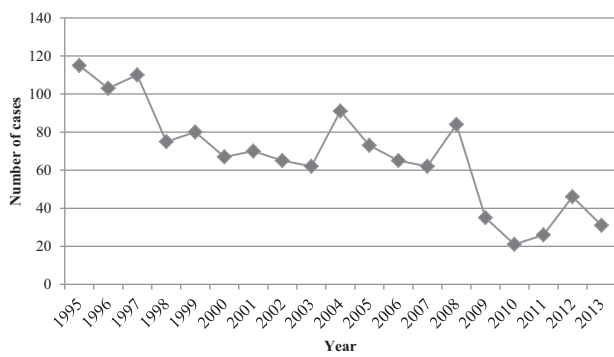
González-García et al. Medicine (2017) 96:26

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Figure 1. Number of patients with tuberculosis diagnosed at Ramón y Cajal University Hospital (1995–2013).

Figure 2. Tuberculosis rate during the years of study according to specific conditions. $P < .001$ for trends in all the conditions shown. HIV = human immunodeficiency virus.

and plasma HIV RNA was 100 cells per cubic millimeter and 100,000 HIV RNA copies per milliliter, respectively.

For purposes of analyzing changes in the epidemiology of TB, the years of the study were divided into 4 periods: 1995 to 1999, 2000 to 2004, 2005 to 2009, and 2010 to 2013. Significant changes were observed (Fig. 2). Median age at diagnosis steadily increased from 41 ± 17 years in 1995–1999 to 47 ± 19 years in 2010–2013 ($P < .001$). The percentage of foreign-born patients also increased significantly from 7.4% in the first period to 40.3% during 2010 to 2013 ($P < .001$). By contrast, the proportion of patients with HIV infection decreased from 41% during 1995–1999 to 15% during 2010–2013 ($P < .001$). Similarly, the proportion of patients with chronic steroid therapy increased from 2.3% in 1995–1999 to 10.5% in 2010–2013 ($P < .001$).

3.2. Clinical manifestations

Among the 1284 cases, pulmonary TB was diagnosed in 918 patients (71.5%). In addition, extrapulmonary involvement was documented in 617 patients (47%), with exclusive extrapulmonary involvement in 366 (28.5%), and both pulmonary and extrapulmonary in 251 cases (19.5%).
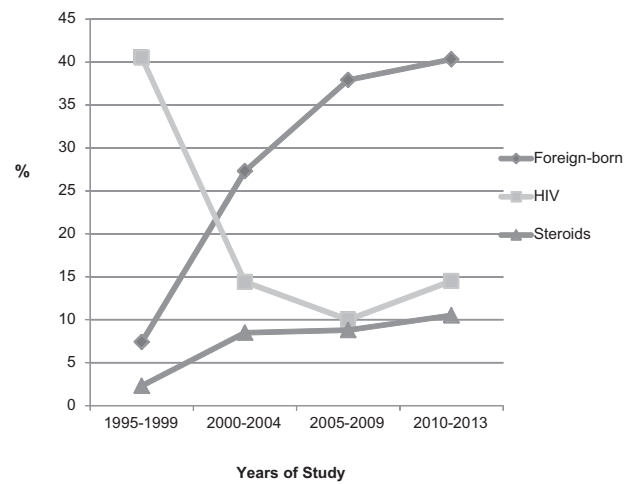
The most frequent sites of extrapulmonary involvement were lymph nodes (248 cases, 19.3%) followed by the pleura (126 cases, 9.8%) (Table 2). A miliary form was documented in 116 cases (9%). The frequency of the individual TB locations has changed throughout the years. Overall forms of extrapulmonary TB increased (from 23.9% to 37.1%, $P < .001$) with no changes in pulmonary involvement (from 50% to 46%, $P = .18$). In particular, a significant decrease was observed in miliary TB (from 16% to 5.6%, $P < .001$) and meningitis (from 5% to 0%, $P < .001$) (Fig. 3).

3.3. Diagnostic methods

In 578 patients a TST was performed. In 445 cases (77%) the TST was positive. The sputum smear was positive in 634 of 886 (72%) in which it was performed and the culture was positive in 786 out of 886 (89%). PCR in sputum was positive in 234 out of 265 (88%). The remaining specimens submitted for microbiological

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Table 1

Main patient characteristics at diagnosis of tuberculosis.

	Overall (n = 1284)	Foreign-born (n = 304)	Spanish (n = 980)	P
Gender, male	821/1284 (64%)	164/304 (54%)	657/980 (67%)	<.001
Age, y	44 (19)	34 (14)	48 (18)	<.001
Smoking	481/1284 (37%)	49/304 (16%)	432/980 (44%)	<.001
Alcohol abuse	271/1284 (21%)	35/304 (11%)	236/980 (24%)	<.001
HIV infection	298/1284 (23%)	30/304 (10%)	268/980 (27%)	<.001
Injection drug use	225/1284 (17%)	3/304 (1%)	222/980 (23%)	<.001
Chronic liver disease	171/1284 (13%)	10/304 (3%)	161/980 (16%)	<.001
Chronic renal disease	38/1284 (3%)	2/304 (0.7%)	36/980 (4%)	<.05
Malnutrition	101/1284 (8%)	13/304 (4%)	88/980 (9%)	<.05
Diabetes mellitus	92/1284 (7%)	5/304 (2%)	87/980 (9%)	<.001
COPD	111/1284 (9%)	2/304 (0.7%)	109/980 (11%)	<.001
Neoplasia	102/1284 (8%)	6/304 (2%)	96/980 (10%)	<.001
Previous TB episode	132/1284 (10%)	26/304 (9%)	106/980 (11%)	.28
Corticosteroids	82/1284 (6%)	6/304 (2%)	76/980 (8%)	<.001
Silicosis	8/1284 (0.6%)	3/304 (1%)	5/980 (0.5%)	.40
Prison history	44/1284 (3%)	0/304 (0%)	44/980 (3%)	<.001
Homeless	80/1284 (6%)	25 (8%)	55 (6%)	.10

Data are reported as number (%) of patients or main value (standard deviation). COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, TB = tuberculosis.

Table 2

Tuberculosis cases by predominant site of disease.

	N	Extrapulmonary (n=617)	Overall (n=1284)
Lymphatic	248	30.3%	19.3%
Pleural	126	15.4%	9.8%
Miliary	116	14.2%	9%
Genitourinary	68	8.2%	5.2%
Abdominal	63	7.7%	4.9%
Bone/joint	47	3.7%	5.7%
Meningeal	40	4.9%	3.1%
Pericardial	19	2.3%	1.5%
ENT	16	1.9%	1.2%
Skin and soft tissues	8	0.9%	0.6
Others	11	1.3%	0.8%

Data are reported as number and percentage of patients respect the overall and the extrapulmonary forms. Others, ocular and adrenal forms. ENT = ear, nose, and throat.

studies and the results are summarized in Table 3. In extrapulmonary TB, the culture yield rates of lymph node (74%) and urine (91%) were the highest. In miliary TB, the culture yield rates in urine were high as well (62%).

The yield rate of examination for lymphatic specimens was 92% with fine needle aspiration and 97% by lymph biopsy. Microbiological studies were done in this specimen reaching higher yield rates of positive cultures by cytological study (74%) than histological (58%). A positive PCR was found in only a modest proportion of histological lymphatic specimens (23%), but in a higher proportion of cytological lymphatic specimens (69%). Positive PCR were observed in 3 out of 3 (100%) abdominal specimen, 30 out of 37 (81%) urinary samples, and 9 out of 11 (82%) bone samples.

The yield of sputum cultures was higher (87.4%) in the early than in the late years (82.2%) ($P<.01$). The yield of the remaining microbiological and biochemical studies was similar. Despite the significant progress in diagnostic procedures during the study period, we did not observe any other remarkable change.

3.4. Antituberculosis drug resistance

Susceptibility testing was performed in 1106 *M tuberculosis* isolates. Resistance to 1 or more drugs was detected in 133 isolates (12%). Global isoniazid resistance was detected in 58 cases (5.2%) and primary isoniazid resistance in 48 (4.2%). MDR-TB was observed in 42 isolates (3.8%) and XDR in 20
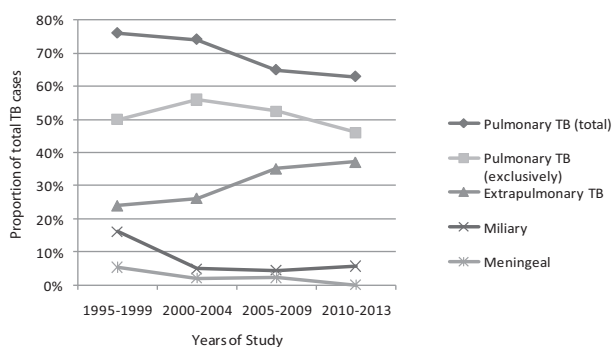

Figure 3. Changes in location of tuberculosis observed during the study periods.

Table 3

Yield of different diagnostic laboratory methods for the diagnosis of tuberculosis.

Specimen	Stain	Culture	PCR	ADA
Sputum	634/886 (72)	786/886 (89)	234/265 (88)	—
Bronchoalveolar lavage	70/116 (60)	94/116 (81)	45/48 (94)	—
Urine	61/459 (13)	109/459 (24)	50/236 (21)	—
Pleural fluid[*]	9/113 (8)	35/113 (31)	3/14 (21)	83/98 (85)
Ascitic fluid[*]	3/23 (13)	10/22 (45)	4/9 (44)	12/14 (86)
Cerebrospinal fluid[*]	3/35 (9)	16/35 (46)	2/5 (29)	25/29 (86)
Pericardial fluid[*]	1/6 (17)	3/6 (50)	2/5 (40)	2/5 (40)

Data are expressed as number positive/number tested (%). ADA = adenosine deaminase, PCR = polymerase chain reaction.
[*] For the definition of diagnostic cut-off values of ADA in different fluids refer to text.

(2%). Being foreign born was associated with a higher risk of primary isoniazid resistance (OR 2.27, 95% CI 1.2–4.25) and MDR-TB (OR 4.9, 95% CI 2.4–9.9), whereas HIV infection was associated with XDR (OR 5.7 95% CI 2.2–14.74).

Although not statistically significant, primary isoniazid resistance has increased over the periods of the study (from 3.8% to 8%, $P=.39$) while MDR-TB has decreased (from 4.5% to 2.2%, $P=.6$). XDR was found only in the 1st period of the study (1995–1999).

3.5. Outcomes

Among all the patients with TB, 1239 (96.5%) received anti-TB treatment. Forty-four patients (3.4%) did not receive treatment due to death or loss to follow-up; in 1 patient no information regarding treatment could be collected. Median duration of treatment was 6 (range, 6–9) months in patients with solely pulmonary involvement and 6 (range 6–12) months in those with extrapulmonary locations. The duration of treatment was longer in some particular forms of extrapulmonary TB. It was 12 months in the case of meningitis and osteo-articular TB, and 9 months for other forms (miliary, multifocal, renal, and abdominal).

Adverse events were reported by 138 patients (11%). The most frequent adverse events were hepatotoxicity in 65 cases (5.2%) followed by skin manifestations (mainly rash) in 37 cases (3%). There was a patient published elsewhere[6] with fulminant hepatotoxicity who required an urgent liver transplant. Univariate analysis showed HIV-infection and chronic hepatitis C, Hispanic ethnicity, active intravenous drug use, chronic liver failure, and ongoing prophylaxis with isoniazid to be associated with a higher risk of adverse events. Multivariate analysis identified HIV infection as the single independent factor associated with the occurrence of adverse events (OR 2.9 CI 95% 1.99–4.2). During the study period, the percentages of adverse events were barely changed, ranging from 13% to 7% of the total sample ($P=.15$).

Regarding anti-TB treatment, a 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol was the therapy most frequently used (47.8%). The 4-drug regimen was increasingly prescribed toward the end of the study period (75.8% in 2010–2013 vs 46.5% in 1995–1999, $P<.001$), in contrast with a 3-drug regimen (isoniazid, rifampin, and pyrazinamide) (16.9% in 2010–2013 vs 42.8% in 1995–1999, $P<.001$).

Adjunctive steroids treatment was given to 81 patients (6.3%), manly in extrapulmonary forms, especially in meningeal TB

(20 patients) and pericardial TB (12 patients). A trend to a higher all cause-mortality was observed in patients not receiving steroids in both meningitis (75% vs 42%, $P = .08$) and pericarditis (28.6% vs 16.7%, $P = .6$).

Therapy was discontinued in 224 patients (17.4%). A microbiological cure was documented in 832 (64.8%) patients and therapeutic failure in 56 cases (4.8%). A total of 117 (9.1%) patients died, and death could be attributed to TB in 83 cases (6.5%). The majority of deaths occurred in the 1st period 1995 to 1999 (11%) with a decrease observed during the following periods (from 11% to 2%, $P < .001$).

A multiple logistic regression analysis was performed to identify independent risk factors contributing to mortality associated to TB. In this analysis, age (OR 1.03 CI 95% 1.01–1.05), native origin (OR 5 CI 95% 14.28–1.03), HIV infection (OR 9.28 CI 95% 4.37–19–74), previous use of steroids (OR 4.78 CI 95% 2.35–9–71), miliary TB (OR 2.11 CI 95% 1.13–3.93), meningeal TB (OR 3.04 CI 95% 1.26–7.28), and abdominal TB (OR 2.85 CI 95% 1.28–6.3) were independently associated with a higher risk of mortality attributable to TB.

4. Discussion

Nowadays, the epidemiology and outcome of TB in western countries has changed considerably due to the less important role of HIV infection and the emergence of other factors such as ageing, the presence of comorbidities, immigration, and the spread of resistance to anti-TB drugs. This study, performed over a 19 years period, confirms a stepwise decrease in the annual incidence of TB from 115 patients in 1995 to 31 in 2013, despite the increasing percentage of TB diagnosis among the immigrant population. This finding has been well documented in other southern European countries like Italy,[5] Portugal,[7] and Greece.[8] HIV infection as the principal risk factor for TB has been replaced by immigration from TB-endemic areas. This change has conditioned a different profile of TB in many aspects.

Immigration has increased in our country, which has been considered a very frequent destination for foreign-born from Latin America. At the beginning of 2000, there has been a continuous rise in the flow of immigrants in Spain. In our influenced are the number of immigrants accounted for 11.6% of overall population in 2003.[9]

Indeed, HIV infection was the single most important risk factor for the development of TB in the 1st period of the study (1995–2000), even when combination antiretroviral therapy was being used. However, the progressively extensive use of effective antiretroviral therapy together with the implementation of preventive measures for the control of the disease led to the observed significant reduction in the incidence. It is well known the deleterious role of HIV in the pathogenesis of TB.[10,11] In addition, TB also hastens the progression of HIV infection, making complications about its treatment[12] and increasing the risk of other opportunistic infections.[13] In fact, in our study HIV infection has been identified as an independent risk factor for the development of adverse events and mortality attributed to TB. The incidence of a higher rate of adverse events has been widely reported in the literature,[14,15] as well as the association of mortality with HIV infection.[16,17]

Another classical factor associated with a higher incidence of TB, that has remained constant during the years of our study, is ageing.[18] Furthermore, TB in the older population is complicated by other comorbidities, the coadministration of other drugs, and a higher rate of treatment discontinuation which leads to increased rates of therapeutic failure and retreatment. In the aged population, most cases of TB are due to reactivation of a latent infection,[19] although anecdotal cases of primary infection have been reported.[20] In our cohort, a progressive increase in the age of patients with TB has been observed, although a significant number of cases developed in people 30 to 40 year-old, mostly related to HIV infection and immigration.

The increasing rate of extrapulmonary TB deserves some comments. This is a well described phenomenon for which several theories have been proposed. The proportional rise in extrapulmonary TB cases has been associated with the HIV infection epidemic at the end of the 1980s,[21] with a clear relation with the degree of immunosuppression.[22] However, the persistence of higher rates of extrapulmonary forms over the different periods of the study, including those in which HIV-infection clearly decreased as a risk factor, points to other factors which may play a role in this finding. Worthy of note is the key role of immunosuppressive agents, such as glucocorticoids, which could facilitate more cases of extrapulmonary forms[23,24] including miliary TB. The role of glucocorticoids and immunosuppressive therapy including biotherapies using TNF antagonists must be underlined. Again, the immigrant population has a higher risk of developing extrapulmonary TB in possible relation with a delay in medical care that could account for a greater progression of the disease. Thus, a possible factor contributing to the higher rate of extrapulmonary TB cases in Western countries is the higher over-all proportion of foreign-born patients.[25]

Microbiological methods for the diagnosis of TB have also been modified during the last decades. Traditionally, rapid diagnosis of TB has relied on the detection of AFB by microscopy and less frequently by culture. The low sensitivity of these methods, together with the frequent challenge in diagnosing extrapulmonary TB, prompted the search of new diagnostic methods. Nucleic acid amplification tests, which provide results within hours, have been developed to address these issues.[26] Our results show the increasing use and yield of PCR in very distinct specimens. PCR-based tests have been used successfully in patients with genitourinary TB,[27] bronchoscopy specimens,[28] problematic lymphatic TB,[29] and a more limited use in peritoneal TB.[30] Our results show the effectiveness in lymph nodes, genitourinary specimens including urine, tissue biopsy specimens such as bone tissue, peritoneal, and meningeal fluid. We have previously published the importance of detection of DNA in urine in patients with disseminated TB,[31] and the results have been confirmed in this study. Overall, AMTD has high specificity (95%–100%) and sensitivity (91%–100%) in smear-positive respiratory samples, although sensitivity is lower in smear-negative samples (65%–93%).[32,33]

Drug resistance has been an important limitation to control TB worldwide. In Europe, the highest rates of MDR-TB were reported in the former Soviet Union and the Republic of Moldova.[34] In Spain, a multicenter study carried out in 2011 showed a high rate of isoniazid-resistance (6.7%) and a rate of MDR-TB of 1.9%.[35] In the present series, rates of isoniazid resistance have increased during the period of study, while MDR-TB has slightly decreased. Being an immigrant was the principal risk factor associated with primary resistance to isoniazid and MDR-TB. Other studies have identified different clinical risk factors including previous TB treatment, younger age groups, and foreign-born.[36,37] In the past, HIV infection was also associated with isoniazid-resistance,[38] although this association does not appear to persist nowadays.

González-García et al. Medicine (2017) 96:26

Medicine

The outcome of TB has improved during the years of the study, despite the fact that no significant changes have been introduced in therapy. Improved prognosis appears to be more related to the underlying risk factors and comorbidities. We have found that HIV infection, elderly age, and steroidal treatment were all associated with a higher mortality. These factors have been identified in previous studies, including the use of glucocorticoids in different clinical situations in which TB developed (associated to hematological malignancies,[39] transplant recipients).[40] Some forms of extrapulmonary involvement also associated a significantly higher mortality, reaching 24% in patients with miliary TB and 28% in patients with central nervous system involvement. We could not demonstrate an association between mortality and resistant TB, despite the high mortality rates shown in XDR-TB outbreaks in the last 90s.[41] The small number of patients with resistant TB explains this lack of association.

Our findings may be limited by a number of factors. This is a retrospective study, and information was not complete for all the variables analyzed in all the patients. During the long period of the study heterogeneous clinical resources and medical strategies have been in practice that may have influenced some of the results. However, the interest of our study was to describe the changes over time that might have drawn a different reality for TB. In addition, our study has been performed in a single center in Spain, and this may limit the generalization of our findings to other countries. We feel that, with particular aspects in different contexts, this information could be extrapolated to other western countries of similar characteristics. The strengths of the current study include the long period of study (the last 2 decades), the large number of patients analyzed, and the homogeneity in the management of patients by the same team which minimizes variability associated to human factors.

In conclusion, we have confirmed a steady declined of TB during the last 2 decades in a hospital of a Western European country with a traditional high incidence. Changing trends on HIV infection and immigration have modified other epidemiological and clinical aspects of the disease including the clinical presentation, treatment response, and mortality. The use of molecular tests has provided an improvement in the diagnosis of pulmonary and extrapulmonary TB.

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González-García et al. Medicine (2017) 96:26

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