Tuberculosis and immigrants: a SIMIT (Italian Society of Infectious Diseases) Clinical, Epidemiological Multicentric Research Investigation

Gaetano Scotto[1,2], Chiara Fornabaio[1], Rosa Prato[3], Annalisa Saracino[1,2], Alessandra Tartaglia[1], Rocco Di Tullio[1], Sergio Carbonara[4], Gioacchino Angarano[1], Italian Study Group for Infectious Diseases in Immigrants

[1]Clinic of Infectious Diseases, University of Foggia, Italy;
[2]Committee on Migration of the Italian Society of Infectious and Tropical Diseases (SIMIT);
[3]Department of Public Health, University of Foggia, Italy;
[4]Clinic of Infectious Diseases, University of Bari, Italy

---- SUMMARY ----

The aim of the study was to evaluate the epidemiology and the diagnostic, clinical and therapeutic aspects of immigrants affected by tuberculosis, hospitalized in 35 Italian Infectious Diseases Clinics during 2003. The data obtained showed that 300/2392 (12.5%) patients had active tuberculosis, 10.3% of whom had concomitant HIV infection. 53% of the patients were legal residents and were assisted by the National Health Service; 48.3% came from African regions. The mean length of residency in Italy at the time of hospitalization was 4 years. The main clinical forms were pulmonary (66%), lymph nodal (15.3%) and bone TB (5.3%). Drug resistance was demonstrated in 16% of cases with 9% cases of resistance to isoniazid, 8.2% to streptomycin, 5.1% to pyrazinamide, 2.6% to ethambutol, 2.6% to rifampicin; in 5.3% of cases a multiple resistance was demonstrated. A complete adherence to treatment was achieved in 213 patients. Statistical analysis disclosed a significant correlation between compliance with treatment and legal citizenship status. In conclusion, TB still represents an important disease among immigrants. Improved living conditions, both in countries of origin and in Italy, especially in the first few years, would certainly decrease the incidence of TB.

KEY WORDS: Immigration, Tuberculosis, Drug resistance, Mycobacterium

INTRODUCTION

TB currently represents one of the main causes of mortality and morbidity among the infectious diseases and a significant reappearance was observed in the early 1990s due to various factors: the spread of HIV infection, the migratory phenomenon, the increase in poor living conditions and drug addiction, and immunosuppression (Raviglione *et al.*,1995; Dolin *et al.*, 1994; Dye *et al.*, 1999). At present, the health situation is serious in developing areas in which historically the infection arrived later and its gravity is now evident with an annual mortality of 3.9% and 290/100.000 new cases each year (WHO, 2001). After a long time of oblivion, in 1994 the situation led the World Health Organization to declare: "TB represents an health emergency worldwide", triggering new health policies based on screening among the population and preventive and

Corresponding author
Gaetano Scotto, MD
Clinic of Infectious Diseases,
University of Foggia
Luigi Pinto Street, 1
71100 Foggia (Italy)
E-mail: g.scotto@medicina.unifg.it

therapeutic approaches (Dolin *et al.*, 1994; Dye *et al.*, 1999). Nevertheless, these policies seem inadequate in decreasing the incidence of TB in the southern areas of the world, though they had some results.

According to the United Nations High Commissioner for Refugees, in 2003 refugees requiring housing and healthcare were about 20 million people, mostly coming from high-incidence TB areas. Because of malnutrition and poor hygienic conditions, these populations are especially exposed to TB reactivation or to a new infection. These conditions, together with the migratory phenomenon in industrialized countries, are responsible for the TB epidemiological trend (Roberts and Kemp, 2002). Immigration from the aforementioned countries now represents a normal component of our society and the presence of immigrants from highly endemic areas is considered by many authors the most important co-factor, together with HIV infection, of the recent TB renewal reported in Italy (Matteelli *et al.*, 2003; Scotto, 1999; El-Hamad *et al.*, 2001).

In the previous multicentric study performed by our group in 2002, TB was demonstrated to be the second most common cause of hospitalization in Italian Infectious Diseases Clinics after HIV infection, with a prevalence of 13.4% (Scotto *et al.*, 2004). During the year 2003, the Committee on Migration of the Italian Society of Infectious and Tropical Diseases *(SIMIT, Società Italiana di Malattie Infettive e Tropicali)* carried out a new multicentric study, described in this paper, with the aim to evaluate not only the epidemiological factors but also the diagnostic, clinical and therapeutic aspects of immigrant TB patients hospitalized in Italian Infectious Diseases Clinics.

PATIENTS AND METHODS

A total of 35 Italian Infectious Diseases Clinics participating in the study were invited to complete a questionnaire to collect data for each immigrant patient at the time of hospitalization, either as an ordinary admission or as an out-patient, including sex, age, country of origin, length of stay in Italy, resident status (legal/illegal), sanitary assistance, previous BCG vaccination, and HIV infection. After patient's discharge,

the clinics were asked to complete the questionnaire with the diagnosis, focusing on TB localization, microbiological findings, radiology, tuberculin skin test, possible histology, therapy (multi-drug regimens, changes, duration, compliance) and the final outcome.

As concerns the diagnostic criteria, it was asked to specify if acid-fast bacilli (AFB) were found in sputum or in other biologic samples, if a polymerase chain reaction (PCR) was performed and its result, and if a cultural data was available, with the identification of the Mycobacterium involved and the drug-susceptibility pattern. Other information about the tuberculin skin test, the radiological and histological findings was requested, particularly when microbiological data were missing.

If the patient was hospitalized more than once but the diagnosis at discharge was the same, the form was completed only once.

A written informed consent containing information on the trial and the goal of the study was obtained from each subject. The study complies with the Declaration of Helsinki.

Once collected, the questionnaires were evaluated by our team and data analysed for statistics.

Statistical analysis

In order to evaluate the statistical association among the variables considered in the questionnaire, contingency double-entry tables were used and Odds Ratio and relative 95% Confidence Intervals and X^2 value were calculated. A p value of <0.05 was considered statistically significant. Data were analyzed by Statview 5.0 for MacOs and Epi Info 6.05 software.

RESULTS

A total of 2392 immigrant patients, both ordinary hospital admissions (65.5%) and out-patients (34.5%) in 35 Italian Infectious Diseases Units (12 Northern, 13 Central, 10 Southern) were enrolled. Active TB was found in 300 patients (12.5%), 31 (10.3%) of whom had concomitant HIV infection. The mean age was 34 years (range 1-75) with no significant difference between males and females (34.7 vs 32.7 years); most of the patients were males (193, 64.3%). Regional distribution was as follows: 153 patients (51%) in Northern regions,

particularly Emilia Romagna (64 pts, 41.8%); 117 patients (39%) in Central Italy (Tuscany 66 pts, 56.4%) and 30 patients (10%) in the Southern regions (Sicily 10 pts, 33.3%).

Half of the patients (159/300, 53%) were legal residents and were assisted by the National Health Service, while 82/300 (27.3%) were illegal residents and no data were available for 59/300 (19.7%) subjects. As for the country of origin, almost half of the patients came from African regions (145, 48.3%), 60 (20%) were Asiatic while 61 (20.3%) came from Eastern Europe and 34 (11.3%) from South America. The mean length of residency in Italy at the time of hospitalization was 4 years (range 4 months - 17 years); only 7.3% had been in Italy for less than 1 year, 30% for 1-2 years, 19% for 3-5 years, and 14% for more than 5 years; in 29.6% of cases no data were available (Table 1).

A previous vaccination with BCG was reported in only nine patients (3%), while in half of the cases this datum was unknown (159, 52.5%); the remaining 135 subjects (44.6%) were not vaccinated.

The clinical TB forms were distributed as follows: lung tuberculosis in 198 cases (66%), 21 of whom were HIV-infected, lymph node tuberculosis in 46 cases (15.3%), four of whom were HIV-infected, bone TB in 16 cases (5.3%) including 1 HIV-infected patient, urinary TB in 9 cases (3%), pleural TB in three cases (1%), central nervous system (CNS) and muscular TB in two cases respectively, and one case each for intestinal, peritoneal, dermal and disseminated TB. In 20 patients a multiple localization of TB was found, three of whom were HIV-infected (Table 2).

The distribution of TB prevalence according to age is described in Table 3.

When analyzing the country of origin, together with the different TB forms we noticed the following distribution: among African patients, 95 lung forms and 50 extra-pulmonary forms; Asiatic patients showed 26 pulmonary cases, 34 extra-pulmonary forms; among East European patients, 48 had pulmonary and 13 extra-pulmonary forms, while among South Americans 29 had pulmonary forms and 5 had extra-pulmonary TB (Table 4).

No significant correlation was found between any TB form and African patients; on the contrary, a statistically significant correlation was found

TABLE 1 - *Demographic data of patients with TB.*

Number of patients	300
Mean age	34 years (range 1-75)
Sex (M/F)	193/107
Status (%)	Legal resident 159 (53%) Illegal resident 82 (27.3%) Unknown 59 (19.7%)

Countries of origin	Africa 145 (48.3%)
	  Senegal(35.2%), Morocco(23.4%),
	  Nigeria(8.3%)
	Asia 60 (20%)
	  Pakistan (40%), India (18.3%),
	  Philippines(16.7%)
	East-Europe 61 (20.3%)
	  Rumania (44.3%),
	  Albania (19.7%), Ukraine(11.5%)
	South-America 34 (11.3%)
	  Peru (44.1%), Brazil (26.5%),
	  Ecuador (17.6%).

Mean length of residence	4 years (range 4 months-17 years)
Prophylactic (%) vaccination	Yes 9 pt (3%) No 135 pts (44.6%) Unknown 159 pts (52.5%)

between extra-pulmonary TB and Asian origin (35% vs 10,4%; OR: 4,63 95%CI: 2,24-9,58; chi-square=22,27; p<0,001), while the lung forms were less represented in this population (43,3% vs 71.6%; OR: 0.30 IC95%: 0.16-0.56; chi-square=17.11; p<0.001). A significant correlation was also found between lung TB and East-Europeans (78.7% vs 62.8%; OR: 2.19 95%CI: 1.08-4.52; chi-square=5,48; p=0,019) and South Americans (85.3% vs 63.5%; OR: 3.33 95%CI: 1.18-10.15 chi-square=6.34; p=0.011). People from East-Europe were also at higher risk for developing urinary TB (8.2% vs 1.7%; OR: 5.25; 95% IC: 1.17-24.19; chi-square=7.08; p=0.007).

A significant difference was noticed between lung forms and residency in Italy for more than 5 years (OR: 2.94 95% IC: 2.9-6.39; chi-square= 9.29; p=0.002). No significant difference was noticed between other TB localization and length of residency in Italy (≤5 years; >5 years).

When considering the methods for TB diagnosis, we found different results for the most common

TABLE 2 - *Main clinical TB forms localization.*

TB localization	HIV		Total
	Negative	Positive	
Pulmonary	177	21	198
Lymph Node	42	4	46
Multiple sites	17	3	20
Lung+Lymph Node	6	2	8
Lung+Peritoneal	3	0	3
Lung+CNS	3	0	3
Lymph Node+Bone	2	0	2
Mediastinal+Peritoneal	1	0	1
Lung+Thyroid	1	0	1
Lung+Urinary+Bone+Dermal	1	0	1
Lung+Urinary	0	1	1
Bone	15	1	16
Urinary	9	0	9
Pleural	3	0	3
Central Nervous System	1	1	2
Muscular	2	0	2
Disseminated	1	0	1
Intestinal	0	1	1
Peritoneal	1	0	1
Dermal	1	0	1
Total	269	31	300

tests (tuberculin skin test, acid-fast bacilli smear and culture examination, PCR), and different methods according to the site of disease.

The tuberculin skin test (TST) was not performed in 54 subjects (9 HIV positive), positive in 203 cases (12 HIV positive) and negative in 43 (10 HIV-infected). TST was positive in a total of 70.4% (143/203) of lung forms (133/203, 65.5% lung only), 19.7% (40/203) of lymph node TB (34/203,16.75% lymph node only), 3.9% (8/203) of urinary form (7/203, 3.4% urinary only), 6.9% of bone forms (11/203, 5.4% bone only), and 14.28% of other extra-pulmonary forms (6.4% multiple sites).

Chest X-Ray was positive in almost all lung forms (99.5%), 87.5% of mixed lung forms, in all pleu-ral forms, 61.5% of bone forms, 50% of CNS forms, 30.8% of lymph node forms, 20% of uri-nary forms. CT was positive in 2.2% of lymph node forms and 1% of lung forms. MRN was pos-itive in 6.3% of bone forms.

Acid fast bacilli (AFB) smear showed different results according to the clinical localization with an overall 58.5% positivity: 89.9% for lung, 4.4% for mixed forms, 3.85% for lymph-nodal, 10.12% for other extra-pulmonary forms.

Culture examination showed different results according to the clinical localization with an over-all 79.5% positivity: 74.2% for lung forms, 5.9% for mixed forms, 4.52% for bone, 3.16% for uri-nary and 25.8% for other extra-pulmonary forms. PCR was not performed in 174 cases (58%), and

TABLE 3 - *Distribution of TB forms in relation to age.*

Age (years)	Number of patients (%)	Localization
0-14	4 (1.3)	3 pulmonary (1 HIV +) 1 extra-pulmonary: bone TB
15-30	114 (38)	80 pulmonary (6 HIV +) 34 extra-pulmonary: • 15 lymph node (1 HIV+) • 9 multiple site (1 HIV+) • 4 bone • 2 urinary • 2 pleural • 1 CNS (HIV+) • 1 cutaneous
31-50	165 (55)	104 pulmonary (14 HIV +) 61 extra-pulmonary: • 29 lymph node (3 HIV+) • 11 bone (1 HIV+) • 8 multiple site (2 HIV+) • 6 urinary • 2 muscular • 2 gastrointestinal(1HIV+) • 1 CNS • 1 disseminated • 1 pleural
>50	17 (5.6)	10 pulmonary 7 extra-pulmonary: • 4 multiple site • 2 lymph node • 1 urinary

TABLE 4 - *Distribution of TB forms in relation to country of origin.*

Origin	Localization
Africa	95 pulmonary (10 HIV +) 50 extra-pulmonary (8 HIV +): • 19 lymph node (4 HIV+) • 11 bone (1 HIV+) • 10 multiple sites (2 HIV+) • 3 urinary • 2 muscular • 2 CNS (1 HIV+) • 1 disseminated • 1 pleural • 1 peritoneal
Asia	26 pulmonary (2 HIV +) 34 extra-pulmonary: • 21 lymph node • 9 multiple site • 3 bone • 1 cutaneous
East-Europe	48 pulmonary (3 HIV +) 13 extra-pulmonary: • 5 lymph node • 5 urinary • 1 bone • 2 pleural
South-America	29 pulmonary (6 HIV +) 5 extra-pulmonary (2 HIV +): • 1 lymph node • 1 intestinal (1 HIV+) • 1 bone • 1 urinary • 1 multiple site (1 HIV+)

when performed, it was positive in 76,9% of lung forms, 40% of urinary forms, 42.8% of lymph node forms and 9.5% of all other extra-pulmonary forms.

Histological evaluation, when performed (51/300, 17%), provided a diagnosis confirmation (90.2%) in patients affected by the following forms: lymph-nodal (50%), lung (15.2%), lymph node and bone, disseminated and muscular forms (2.2% for each one), urinary (6.5%), bone (8.7%), mixed forms (15.2%).

In 226 cases (75.3%), *Mycobacterium tuberculosis* was the etiological agent, whereas three cases were due to *M. bovis* (1 pulmonary and 2 mixed forms - bone-lymph node); *M. goroonae* and *M. avium* were responsible for only one case each, a

TABLE 5 - *Compliance and response to treatment.*

Compliance	Patients (%)	Response
Complete	213 (71%)	Recovery 134 pts (63%) Improvement 68 pts (32%) Unchanged 5 pts (2.3%) Drop-Outs 3 pts (1.4%) Death 2 pts
Sub-optimal	51 (17%)	Recovery 9 pts (17.6%) Improvement 15 pts (29.4%) Unchanged 10 pts (19.6%) Drop-outs 16 pts (31.4%) Death 1 pt
Refusal	19 (6.3%)	Unchanged 11 pts (57.9%) Drop-outs 6 pts (31.6%) Death 2 pts (10.5%)
Unknown	17 (5.7%)	Unknown

lung form in an HIV-infected patient and a disseminated TB, respectively. In 69 cases, no etiological agent was identified.

A drug-sensitivity study was performed in 187/221 cases (84.6%) with a positive cultural test. Rifampin, isoniazid, and ethambutol were tested in 187 patients, pyrazinamide in 175 and streptomycin in 134. Thirty strains (16%) showed a resistance to at least one anti-tubercular drug: 20 strains showed one drug resistance (9 to INH, 5 to PZA, 5 to STP, 1 to ETB), in 10 cases (10/187, 5.34%) a multi-drug resistance was demonstrated, but only in 5 cases were INH and RIF involved.

For each molecule, a resistance panel was established as follows: 17 cases (9%) of resistance to isoniazid, 11 (8.2%) to streptomycin, 9 (5.1%) to pyrazinamide, 5 (2.6%) to ethambutol, 5 (2.6%) to rifampin. The pattern of multi-drug resistance was tested for statistical correlation with HIV-infection, the country of origin and TB localization. No relation was found between drug resistance and HIV-infection for any drug tested. Resistance to ethambutol was associated with origin from South America (12.5% vs 2.5%; OR: 5.68 95%CI: 0.93-33.13; chi square =5.83; p=0.015), whereas no relation was found between other drug resistances and country of origin.

A total of 257 patients (85.7%) received therapeutic regimens with more than three drugs and the most common association was isoniazid + rifampin + ethambutol + pyrazinamide (211/257; 82.1%). Therapy was reduced to two drugs (mainly INH and RIF) after 2 months of treatment in 70 cases (27.24%). A three-drug regimen was administered in 43 patients (14.3%) and isoniazid + rifampin + ethambutol was the most common association (25/43; 58.1%).

The choice of therapeutic regimen (≤3 or >3 drugs) was analyzed in relation to TB location, legal patient status and HIV-infection. A weak statistical correlation was found between ≤3 drugs regimens and lymph node TB (23.9% vs 12.2%; OR: 2.26 95%CI: 0.97-5.21; chi square=4.42; p=0.035), while a strong correlation existed with urinary forms (66.7% vs 12.3%; OR: 14.17 95%CI: 2.97-75.37; chi square=21.30; p<0.001).

Considering four or more drug regimens, a weak relation existed with the lung TB forms (88.9% vs 80.4%; OR: 1.95 95%CI: 0.96-3.97; chi square=4.02; p=0.044). No statistical association

was found between different therapeutic regimens and legal status or HIV-infection.

The length of treatment was as follows: 6 months in 153 cases (51%), 32 of whom were included in a Directly Observed Therapy (DOT) programme (personal communication), 9 months in 22 cases (7.3%), 12 months in 102 cases (34%), 20 of whom were HIV positive, >12 months in 14 cases (4.6%).

An evident statistical correlation was found between bone TB and a 12-month therapy (OR:4.52 95%CI 1.4-15.44; chi-square=8.63; p=0.003) and >12 month therapy (OR:5.6; 95%CI 1.09-25.79; chi-square =7.28; p=0.006).

The overall number of subjects following a complete or sub-optimal therapeutic advice were 264 (88%), 143 (54.2%) of whom healed, 84 (31.8%) improved, and 26 (9.8%) had no change (see Table 5).

Adherence to treatment was analyzed in relation to therapeutic regimen (≤3 or >3 drugs), legal status and HIV-infection. Statistical analysis evidenced a significant correlation between compliance to treatment and legal citizen status (16.7% vs 40.5%; OR: 3.41 95%CI: 1.73-6.74; chi square =15.18; p<0.001), whereas no significant association was found with HIV infection. When analyzing complete adherence versus refused therapy, a statistical association existed between adherence and HIV-negative status (93.6% vs 77.8%; OR: 4.22 95%CI: 1.27-13.6; chi square =7.97; p=0.004). The same occurred analyzing complete plus suboptimal adherence versus no administered therapy (94.9% vs 78.6%; OR: 5.08 CI 95%: 1.54-16.3; chi square =10.71; p=0.001).

The only side effects observed were hepatotoxicity in eight cases due to isoniazid and in one case due to rifampin.

DISCUSSION

In our group of patients a 12.5% prevalence of active TB was observed, representing the second main cause of hospitalization in Infectious Diseases Units in the immigrant population after HIV infection, thus confirming previous medical reports (Matteelli *et al.*,2003; El-Hamad *et al.*, 2001; Lopez-Velez *et al.*, 2003). The epidemiological trend and the demographic features of patients did not differ from the ones observed in

previously published studies regarding TB and immigrant patients characteristics: 50% African, male, age 20-40 years (Ramos *et al.*,2003; Lifson *et al.*, 2002; Watkins *et al.*, 2002). However, comparing our data with those of the previous multicentric study performed by our group in 2002 some differences can be noted (Scotto *et al.*, 2004). In 2002 the patients' mean age was lower (29.7 yrs vs 34 yrs) and the time spent in Italy shorter (2.4 yrs vs 4 yrs); almost 90% of the patients were legal residents and, for the country of origin, East-Europe was less represented (15.5% vs 20.3%). Comparing the clinical TB forms, central nervous system TB was more frequent (13.8% vs 0.7%), while bone and urinary TB were less represented (3.3% vs 5.3%, 0.6% vs 3%, respectively). Analyzing the distribution according to age, in 2002 the number of TB cases reported for children (0-14 yrs) was higher (45 vs 4 cases), while those reported for the 15-30 yrs patients were lower (53 vs 114 cases). Except for these differences, the main characteristics of patients and TB forms overlapped.

The TB spread in Italy is not homogeneous, but follows the migratory flow towards areas with better economic conditions, mostly in Northern and Central Italy, as confirmed by our study. Most immigrant patients (about 53%) were legal residents assisted by the National Health Service. Obviously, these data cannot offer indications on the incidence of TB among illegal residents, who live in poor conditions and are considered at higher risk, as they infrequently turn to the public heath services because of the access difficulty and the fear for identification and possible repatriation. About 56% of the studied patients had been living in Italy for less than 5 years and 37% for less than 2 years. This epidemiological trend is justified by the fact that immigrants in the early years after arrival live in worse conditions than in their countries of origin, and this may support latent infection reactivation.

The first diagnostic method used was the Tuberculin skin test, later confirmed by specific diagnostic techniques (radiology, AFB, cultural, PCR, histology), according to the different clinical TB forms. The pulmonary form was the most represented, but the high number of lymph node cases must be highlighted. Some studies show that in the majority of cases this form is the expression of a post-primary infection due to the reactivation of a latent lymph node TB and it is infrequent in native subjects and observed only in foreigners, and related to HIV infection (4 cases in our cohort) (Sepkowitz *et al.*, 1995; Hayase and Tobita, 1997). Unfortunately we are unable to confirm this aspect by numerical data, as the country of origin and disease site at the statistical analysis indicate that extra-pulmonary forms were mostly related to Asian patients; the pulmonary form was frequently found in East-Europeans and South-Americans, while no correlation was found between TB site and African origin.

In 231 subjects in whom the etiologic agent was found, *M. Tuberculosis* was identified in 226 cases. A 16% incidence of drug resistance was found, probably related to inadequate treatment of the first infection in the country of origin, length and compliance with prescribed therapy; this datum is lower than that found in previous reports (Ormerod, 2005; Coll *et al.*, 2005; Atkas *et al.*, 2005). As concerns the drug tested, no relation was found between drug resistance and HIV-positivity, while a statistically significant association was found between ethambutol resistance and South American origin, in contrast with a lower rate of ethambutol resistance found in previous studies on drug resistance in Peruvian and Brazilian populations (Escalante *et al.*, 1998; Höfling *et al.*, 2005). Pyrazinamide is considered a first-line drug for bone-TB treatment, therefore the drug resistance evidenced could be due to a punctiform mutation (pncA) determining a loss of pyrazinamidic activity. More than 90% strains with MIC (minimal inhibent concentration) >100 µg/ml and all *M. bovis* strains presented this mutation and were of course resistant to pyrazinamide (McCammon *et al.*, 2005; Scorpio *et al.*, 1997; Barouni *et al.*, 2004).

The classic use of three or four drugs was the therapeutic approach in the majority of cases and the choice was related to disease site but not influenced by HIV co-infection.

When considering treatment, it is noteworthy that 32 patients were treated with the DOT program, followed by the various centers. Directly observed therapy was suggested to ensure a regular supply of drugs until the end of the treatment, mostly in immigrant patients or those suffering social, physical or mental problems determining poor compliance and consequent therapy failure. This kind

of approach allows a better compliance and a regular follow-up, and is an aid in the detection of drop-outs and adverse events. The DOT strategy is rarely used in European countries with a low prevalence of tuberculosis, but when adopted, it has demonstrated increased healing because of its impact on the disease evolution. In our study we registered a 90.6% recovery rate (29/32 cases). As these subjects are often not controlled, it is important to consider adherence to therapy (complete, suboptimal compliance or refusal to therapy) when evaluating the progression of the TB infection. In fact, in patients with complete adherence, only 13.9% patients showed no change in clinical conditions, whereas about 50% patients with sub-optimal adherence did not show improved conditions. Adherence to therapy was related to legal status, with a significant difference between resident subjects and illegal subjects.

In conclusion, the presented data show that TB still represents an important disease among immigrants. Improved living conditions, both in countries of origin and in Italy, would certainly decrease the incidence of TB. The control programs should be based on: first-line screening studies using the Tuberculin skin test and chest X-rays in Hospitality Centers where subjects temporarily reside after arrival in Italy, to disclose either active or latent TB forms; the use of prophylactic and therapeutic resources available; the activation of out-patient clinics for immigrants; an easier access to public facilities. In addition to medical services, a cultural mediator should be provided in these out-patient clinics to establish both medical and human relationships. The DOT strategy should be adopted, since the optimal results reached both in less developed countries and in the rare European experiments, in order to complete the therapeutic design and support the patient favorable disease evolution.

REFERENCES

AKTAS E., DURMAZ R., YANG D., YANG Z. (2005). Molecular characterization of isoniazid and rifampin resistance of Mycobacterium tuberculosis clinical isolates from Malatya, Turkey. *Microb Drug Resist.* Summer; **11** (2), 94-99.

BAROUNI A.S., AUGUSTO C.J., LOPES M.T., ZANINI M.S., SALAS C.E. (2004). A pncA polymorphism to differentiate between Mycobacterium bovis and Mycobacterium tuberculosis. *Mol Cell Probes*. **18** (3), 167-170.

COLL P., ARAGON L.M., ALCAIDE F., ESPASA M., GARRIGÓ M., GONZÁLEZ J., MANTEROLA J.M., ORÚS P., SALVADÓ M. (2005). Molecular analysis of isoniazid and

rifampin resistance in Mycobacterium tuberculosis isolates recovered from Barcelona. *Microb Drug Resist*. **11** (2), 107-114.

DOLIN P.J., RAVIGLIONE M.C., KOCHI A. (1994). Global tuberculosis incidence and mortality during 1990-2000. *Bull World Health Organ*. **72**, 213-230.

DYE C., SCHEELE S., DOLIN P., PATHANIA V., RAVIGLIONE M.C. (1999). Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*. **282**, 677-686.

EL-HAMAD I., CANALINI C., MATTEELLI A., CASARI S., BUGIANI M., CAPUTO M., BOMBANA E., SCOLARI C., MOIOLI R., SCARCELLA C., CAROSI G. (2001). Screening for tuberculosis and latent tuberculosis infection among undocumented immigrants at an unspecialised health service unit. *Int J Tuberc Lung Dis*. **5** (8), 712-716.

ESCALANTE P., RAMASWAMY S., SANABRIA H., SOINI H., PAN X., VALIENTE-CASTILLO O., MUSSER J.M. (1998). Genotypic characterization of drug-resistant Mycobacterium tuberculosis isolates from Peru. *Tuber Lung Dis*. **79** (2), 111-118.

Global tuberculosis control: WHO report 2001, Geneva: World Health Organization, 2001 (WHO/CDS/TB/2001. 287).

HAYASE Y., TOBITA K. (1997). Cervical tuberculous lymphadenitis in a frequent traveller to endemic areas of tuberculosis. *Intern Med*. **36** (3), 211-213.

HÖFLING C.C., PAVAN E.M., GIAMPAGLIA C.M., FERRAZOLI L., AILY D.C., DE ALBUQUERQUE D.M., RAMOS M.C. (2005). Prevalence of katG Ser315 substitution and rpoB mutations in isoniazid-resistant Mycobacterium tuberculosis isolates from Brazil. *Int J Tuberc Lung Dis*. **9** (1), 87-93.

LIFSON A.R, THAI D., OFALLON A., MILLS W.A., HANG K. (2002). Prevalence of tuberculosis, hepatitis B virus, and intestinal parasitic infections among refugees to Minnesota. *Public Health Rep*. **117** (1), 69-77.

LOPEZ-VELEZ R., HUERGA H., TURRIENTES M.C. (2003). Infectious diseases in immigrants from the perspective of a tropical medicine referral unit. *AM. J. Trop. Med. Hyg*. **69**, 115-121.

MATTEELLI A., GORI A., PINSI G., EL-HAMAD I., BOMBANA E., MASTAGLIA F., DEGLI ESPOSTI A., BANDERA A., TEDOLDI S., CASALINI C., SCOLARI C., CARVALHO A.C., CAROSI G. (2003). Clustering of tuberculosis among

senegalese immigrants in Italy. *Int J Tuberc Lung Dis*. **7** (10), 967-972.

MCCAMMON M.T., GILLETTE J.S., THOMAS D.P., RAMASWAMY S.V., ROSAS I.I., GRAVISS E.A., VIJG J., QUITUGUA T.N. (2005). Detection by denaturing gradient gel electrophoresis of pncA mutations associated with pyrazinamide resistance in Mycobacterium tuberculosis isolates from the United States- Mexico border region. *Antimicrob Agents Chemother*. **49** (6), 2210-2217.

ORMEROD L.P. (2005). Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. *Br Med Bull*. **14** (73), 17-24.

RAMOS J.M., PASTOR C., MASIA M.M., CASCALES E., ROYO G., GUTIÉRREZ-RODERO F. (2003). Health in the immigrant population: prevalence of latent tuberculosis, hepatitis B, hepatitis C, human immunodeficiency virus and syphilis infection. *Enferm Infecc Microbiol Clin*. **21**, 540-542.

RAVIGLIONE M.C., SNIDER D.E.J., KOCHI A. (1995). Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic. *JAMA*. **273**, 220-226.

ROBERTS A., KEMP C. (2002). Infectious diseases of refugees and immigrants: hookworm. *J. Am. Acad. Nurse. Pract*. **14** (5), 194.

SCORPIO A., LINDHOLM-LEVY P., HEIFETS L., GILMAN R., SIDDIQI S., CYNAMON M., ZHANG Y. (1997). Characterization of pncA mutations in pyrazinamide-resistant Mycobacterium tuberculosis. *Antimicrob Agents Chemother*. **41** (3), 540-543.

SCOTTO G., SARACINO A., EL-HAMAD I., IANNECE M.D., GERACI S., PALOMBO I., CIBELLI D.C., ANGARANO G. (2004). Epidemiology of tuberculosis in immigrant patients hospitalised in Infectious Diseases Unit in Italy: multicentric study. *Infez. Med*. **12** (*Suppl* 4), 245-251.

SCOTTO G. (1999). Influenza del flusso immigratorio sui ricoveri nella U.O. di Malattie Infettive di Foggia negli anni 1994-1998. *Giorn Ital di Mal Inf*. **5**, 244-247.

SEPKOWITZ K.A., RAFFALLI J., RILEY L., KIEHN T.E., ARMSTRONG D. (1995). Tuberculosis in the AIDS era. *Clin Microbiol Rev*. **8** (2), 180-199.

WATKINS R.E., PLANT A.J., GUSHULAK B.D. (2002). Tuberculosis rates among migrants in Australia and Canada. *Int J Tuberc Lung Dis*. **6** (7), 641-644.