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Editorial

Tuberculosis today: Evolution of a disease

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Introduction

In the last ten years pulmonary tuberculosis has changed: from a fading disease of industrialized countries it has returned as a first line health emergency. Its etiology and pathogenesis are significantly dependent from relevant social and epidemiological factors such as HIV infection, AIDS, drug addiction, immigration of extra-communitary populations.

This disease has not only changed from an epidemiological point of view, but also the clinical and symptomatological pictures are assuming yet undescribed forms due to the different patient substrate on which they flourish: AIDS, immigrant immunodeficiency status or immunosuppression due to drug addiction.

This is the reason for the renewed interest in the disease, that is also evident by the number of international congresses and studies sponsored by the WHO, that aim at the definition of the new epidemiological risks and prevention of this often life-threatening condition. Our journal thus proposes an editorial review of this topic that up to fifteen years would have been considered obsolete.

Epidemiology

Epidemiological data on tuberculosis in Italy from 1887 (first year of statistical data) show a constant reduction of morbidity and mortality. The maximum peak incidence was registered in 1889 with the presence of 64.143 cases and the minimum in 1967 with 4981 cases, 1500 cases a year were registered in the 1980s, with a morbility rate of 9.4/100.000 persons in 1984 and a positive tuberculin test in less than 10% of the population in the same year[1]. This progressive reduction, parallel to that of other industrialized countries, lead to a reckless optimism, that conditioned the issuing in 1978 of a Reform Law No 833 of the National Sanitary System on the closure of the referral institutions for the treatment and prevention of tuberculosis. These Provincial Antitubercular Clinics (Consorzi Provinciali Antitubercolari) were shut down and their functions were divided and randomly assigned to other public health structures. The control of tubercular infection on the territory has thus become extremely uncoordinated. However, the annual infective risk, calculated on the tuberculin sensitivity index was 0.26% in 1985 with a gradual annual reduction of 11.2%, far removed from that 0.002% that consents to define a disease as practically eradicated from the territory. For every 1% of the tuberculin index (ARI) there is a corresponding percentual incidence of tuberculosis of 45-50 cases/100.000 persons, with a prevalence of about 217 cases on 100.000 people and a mortality of 43/100.000 people[2]. This optimism had been indirectly induced by the documented international effectiveness of the standard brief outpatient therapies[3-4]. In 1982 the following statement was made "at 100 years from the discovery of the Kock bacillus virtually all cases of tuberculosis can be today cured with only 100 doses of drugs, administered for a period of 4-5 months; the collateral effects can be treated; patients can continue work; the risk of recurrences is practically inexistent[5]". The inversion of disease manife-

station has taken place in the western world around 1985, starting from the most populated cities of the USA, with a 25% increment in prevalence and the selection of a growing number of epidemics due to drug resistent strains[6-8]. This has lead to the demonstration in the only city of New York, of a 28-33% resistance to a first choice drug, and a 14-19% resistance to more than one drug which is typical of the situation in developing countries[9].

Before AIDS epidemic less than 10% of tuberculosis cases was considered a consequence of an exogenous infection and most of them were considered a reactivation of a latent infection. However, new epidemiological investigative techniques that utilize molecular biology procedures have shown that exogenous infection is really the preferred transmission route, especially in case of drug resistent strains.

This has lead the CDC in USA to apply rigorous and effective control programms with the aim of reaching in the year 2010 an incidence of less than 1 case of tuberculosis for milion people[10]. The WHO on its part, after documenting a worrisome rise in morbility and mortality especially in developing countries (in the period ranging from 1990 to 2015 the extimate on new cases is 8.000.000 new cases a year, of whom 50% will have positive sputum tests, with more than 3.000.000 deaths per year, and a prevalence of more than 20.000.000 affected and over one third of the world population infected, with a morbility risk of 10%) stated in 1995 that TBC is a "world wide medical emergency" and asked for more than 20 bilion dollars of investments in 96-97. Contemporarily WHO has suggested that all countries start national antitubercular programs following international guidelines with the aim of obtaining at least an 85% cure of the diagnosed cases and the diagnosis of at least 70% of the cases present in the population (at the moment less than 50% of the affected patients are accurately diagnosed and treated)[11-15].

New Clinical Manifestations of Tuberculosis

In industrialized countries we distinguish between tubercular disease specific for the resident population from that of the immigrant population. The two forms however overlap because the people who have recently immigrated carry severe forms of tuberculosis typical of their original countries with low resistance to the mycobacterium of tuberculosis and soon represent a strong infectious risk for the resident population that has a stronger immunological resistance.

However in the resident population with high immunological resistance tuberculosis infection has the same clinical manifestations present twenty years ago. There is a prevalence of productive chronic infections that are typical of elevated immunological resistance compared to exudative forms that are typical of patients with a high receptivity; the age of first infection is higher; acute and subacute miliary forms are rare; pulmonary symptomatology is paucisymptomatic, hemoptysis is rare (once this symptom was a clear index of tubercular pulmonary infection, today it is suggestive of bronchial carcinoma). A consequence of this symptomatological latency is the relative frequency of unexpected tubercular manifestations. For example extrapulmonary tubercular forms diagnosed as single organ diseases may be sometimes identified only by histological examination during an orthopedic or urologic operation. Pulmonary manifestations as well may reveal a bacteriological positivity in patients that have silently progressed to a phase of cavitation without any previous diagnosis of tubercular infection.

A very different clinical scenario is that encountered in immunodepressed patients with HIV infection and in drug addicts. In these cases we may see miliary radiological forms, without cavitation. This radiological finding however does not correspond at all to a pathological miliary spread. This is understandable if we think of the pathomorphosis of the disease that distinguishes productive miliary forms that are expressions of high resistance of the host in comparison to the aggressiveness of the germ (with epitheliod and giant cells) and exudative highly excavated forms (with many bacilli, great caseosis and specific inflammatory tissue) in which the virulence of the germ prevails over the subject's resistance. In patients with AIDS this equation is not true. In other words in AIDS patients and in severely compromised patients with drug addiction we will see tubercular disease that appears as miliaric because it is hi-

ghly diffuse, but does not present tissues with specific reaction against Kock bacillus or caseosis expression of a specific coagulation necrosis. For this reason in these subjects such pulmonary forms prevail and there is little evidence of the "specific struggle" between the microrganism and the host. Radiologically these pulmonary pictures appear as miliaric, eventhough are not so from a pathological point of view. They affect especially the medial and basal part of the lungs, without cavitation while presenting great adenopathic pseudolymphomatose involvement.

Instead in immunoreceptive immigrants we see the severe forms of tuberculosis that were once were frequent in Italy in the pre-streptomycin era. These involve an entire pulmonary lobe, present thereselves as tubercular pneumonitis or bronchopneumonitis, with great cavitation or acute or subacute miliary forms, with a severe hematogenous, lymphogenous and bronchogenous diffusion. In these cases the disease presents a classical form, but anymore no one is prepared to recognize this presentation. The real new disease is the tuberculosis of immunodepressed subjects.

Management of Suspect Pulmonary Tuberculosis

The currently accepted guidelines summarize as follows the management of a suspect pulmonary tuberculosis infection:

1. In the adult patient the standard posteroanterior roentgenogram remains of great importance for the diagnosis, together with the direct bacteriological test and culture on the expectorate (that must be repeated on three days consecutively). It is still common practice to treat with wide spectrum antibiotic therapy all microbiological or radiologically suspect cases. However, if after 3-4 weeks of wide spectrum antimicrobial therapy it has not been possible to achieve a positive clue for diagnosis or the patient still presents severe clinical manifestations, an antitubercular therapy is generally started.

2. In the pediatric population it has been proposed[16] to introduce a score from 1 to 3 for all the parameters studied and to treat with anti-tubercular therapy only subjects that reach the score of 7.

The points are thus attributed. One point for a clinical picture that is globally suspected of being tuberculosis, lasting from 2 to 4 weeks, loss of 20-40% of theoric body weight, positive familiar anamnesis with an affected relative.

Two points are attributed for persistent unexplained nocturnal fever, that has not responded to anti-malarial treatment.

Three points are attributed for disease lasting more than one month, an over 40% reduction of body weight, a positive familiar anamnesis with an affected relative with a bacteriologically ascertained expectorate, positive tuberculin test, enlargement of lateral neck, axillary and inguinal lymphnodes, articular or bone swelling, presence of abdominal masses or ascites, or associated neurological symptoms.

Present Therapy of Tuberculosis

AIPO protocol can be summarized as follows[17]:

- In all BK positive patients the first therapeutic approach is intensive and must be with H (isoniazid), R (rifampin), Z (pyrizinamide) and E (ethambutol), successively followed by 4 months (that may be extended to 7 months in very severely affected patients) with H and R.
- In patients that have fallen out of therapeutic protocols, when starting again the first intensive phase of therapy may be reduced to one month.
- In recurrences and in therapeutical failures the suggestion is to add to the HRZE therapy S (streptomycin) for the intensive phase, and prolonging maintainement phase to 5 months with HR + E.
- Finally, in BK negative cases, the therapeutic protocol should be HRZ during the two months of intensive phase, followed by a four month therapy with HE.
- Chronically ill patients instead should be referred to highly specialized centers where new or different therapeutical protocols can be tried according to susceptibility tests (rifambutine, quinolones, minor antimycobacterial drugs).

Before starting therapy the following exams are useful: posteroanterior and lateral chest roentgenogram, direct microbiological cultural examination for three consecutive days, routine blood exams and the differentiation of the

Mycobacterium complex. After one month it is important to again perform routine exams (hemochrome, platelets, uric acid, renal and hepatic function exams) to control tolerance to treatment. After two months a routine posteroanterior and lateral chest roentgenogram should be performed accompanied by a direct bacterioscopic and cultural exam on three consecutive expectorates, while at the end of therapy it is necessary to perform again chest roentgenogram and three consecutive bacterioscopic and cultural expectorate exams.

The Situation in Italy

In Italy updated statistical national data are missing from 1978. However, taking into account the activity of the Consorzio Antitubercolare of Milan, that assists over 4 milion persons, we can extimate a mean morbosity of 35/100.000 persons, of whom 15/100.000 in 1985 and 77/100.000 in 1990, well over the 9.1/100.000 reported from USA in 1988 in the national population.

Consequently the Associazione Italiana Pneumologi Ospedalieri (AIPO) through the formation of the Tuberculosis Study Group (Gruppo Studio Tubercolosi) that is constantly in contact with the WHO and the IUATLD after the two Consensus Conferences (Livigno, June 1982; Castrocaro Terme, October 1993; Palermo-Mondello, October 1994) activated[17] a national operative protocol for the control and the standardization of tuberculosis therapy on the guidelines of the international indications[18-26].

Preliminary investigations have revealed not only severe insufficiency of the health control system (insufficient communication of the diagnosed cases; inaccurate and non uniform system of communications; scarse accuracy and incomplete referral of data; insufficient laboratory data; retarded communication)[27], but also the fact that therapy of first diagnosed tuberculosis infection in Italy, also in the hospital setting, is particulary obsolete, with a bias toward the use of streptomycin and a very little use of pyrazinamide, with therapeutic protocols that are not standardized in which the "brief therapy" of ATS/WHO is employed in less than 30% of cases, both in the initial and maintanence phase, with a complexively and uselessly long length, wasting of resources, implementation of risks and reduced compliance and major index of collateral effects.

The same investigative researches demonstrate that new drugs such as Rifambutin and quinolones are beeing used without controlled indication. The percentual use of these drugs is not insignificant (10 and 3.3% respectively)[28].

The preliminary analysis on 2.230 patients from 39 centers (population distribution of 16.5 milion people) referring to the AIPO, presented at Vieste in the October of 97, to the XXXIV National Congress of the Italian Pneumological Association (AIPO) consented to obtain the following data, that are partial but significative: patients who are free of the disease (22.6%); completed treatment 60.4%; dead 3.2%, therapeutic failures (1%), lost to follow up 9.6%, transferred 3.2%. The clinical picture of the cases was the following: pulmonary forms with presence of BK in excreate (34.9%), pulmonary forms without demonstrated presence of BK (36.9%), and extrapulmonary forms (28.2%).

In 88% of cases standardized WHO therapy was administered and these showed a decisively superior resolution rate in comparison to the administration of non standardized treatments (88 vs 47%). The cases that presented resistance to one drug were 7.7% in 1995, and 1% in 1996, of whom 18.6% resistant to ryfampin (r), 24.8% to troniazide (H) and 29.6% to HR[29].

The same AIPO investigation on admission rate for TBC revealed that on 203 italian pneumological centers:

a) only in 46% of cases it is deamed important to admit all cases, while in hospital centers 63% of patients are admitted, in outpatient clinics in 80% of cases the only patients that are admitted to hospitals are the particularly severe cases;
b) in 61% of hospital centers the negativization of expectorate is considered important for dismissal;
c) mean hospital stay is 39.6 ± 23 days for excreate positive cases and 26.9 ± 19.6 days for excreate negative cases; 28.7 ± 20.9 days for extrapulmonary forms; mean ho-

spital stay is only minimally dependent from time required for diagnosis of the disease (4.7 ± 3.3 days)[29].

This is significantly different from international and national guidelines according to which hospital admission is required only for complicated cases, especially after the first two weeks of therapy, and with the economical criteria (from 1995 costs for every case of TBC is calculated on a mean hospital stay of 12,5 days, DRG 79-80).

Case Finding

Pertaining to microepidemics, local experiences consented us to understand that the when there is an increment of cases among younger subjects we must suspect the presence of unindividuated bacilliferous causes and epidemiological research must not stop at passive case finding procedures according to WHO guidelines[30] but adopt as well active investigation procedures such as a widespread tuberculine test and successive accurate research among relatives of tuberculin positive individuals[31-32].

In situations of high incidence and prevalence (immigrates, jails, schools, geriatric hospitals, psychiatric asylums, religious communities, drug abuse istitutions etc...)[33], active case finding has been demostrated cost-effective[34-35]. The costs of an active screening extended to a population at risk corresponds at least to a third of the costs that must be paid for the complete treatment of the cases that have not been evidentiated because of a missed diagnosis and treatment in contacts (3 to 10% of which will have the disease, half in one year of contact).

This is the reason for the importance of active research in communities at risk and for the necessity to extend the obligatory tuberculin test also to second degree school.

The control that must be carried out on the teaching staff and the non teaching staff operating in schools, must not be limited to routine chest roentgenogram every two years. It is much better to perform a tuberculin Mantoux test, leaving the chest roentgenogram only for the cases that result positive with a larger than 5 mm diameter infiltrate. Patients who show an infiltrate between 10 and 15 mm in presence of risk factors or bigger than 15 mm without signs of disease must, according to the recommendations of the CDC of USA, be submitted to chemioprophylaxis. WHO stated that routine chest roentgenogram is not indicated for active research of the disease, since even when chest rx screening is performed every six months, it is often very difficult to diagnose the disease at its onset. Sometimes in the most severe contagious forms 6 weeks are sufficient for a rapid evolution with cavitated pulmonary lesions. A recent letter from the Ministry of Health (1989) has stated that positivity to PPD is a preliminary condition to the performance of chest X ray that should be carried out only in case of evident positivity[36-37].

Educational Programs

Prevention in exposed operators is regulated by an internationally recognized protocol, that has been clearly defined by guidelines published in march 1995 by the National Commission for AIDS[38]. However it is very important to educate these workers on the updated problem of TBC and on the preventive measures to adopt at an individual and community level. This has proven to improve the scarse patient compliance even when there is the facility of a sanitary presidium on working place[39].

A recent investigation conducted at Forlanini Hospital of Rome on a purely local basis, has revealed that 30% of the cases of tuberculosis affect extra-communitary citizens, the double infection TBC-AIDS is exclusively limited to cathegories at risk and to immigrants coming from areas with endemic TBC. A high percentage of extracommunitary patients with bacilliferous infections prematurely leave the hospital[40].

These data, together with the good results reported in the USA by Direct Observation Therapy (DOT) in world tubercular therapy (as enforced by WHO)[41-42], suggest for Italy to start a control program similar to that proposed by AIPO. This program is centered on the following criteria:

a) national and local enforcement of the program;
b) national and local health education programs;

c) systematic research to individuate excreate positive individuals with passive tests and to perform active examination only in patients with elevated prevalence risk;
d) standard treatment prevalently on an out patient basis but with intensive supervision;
e) reinsertion of patients that have fallen out of the treament protocols;
f) BCG vaccination of neonatal population;
g) guidelines for surveillance of drug-resistance;
h) guidelines for management of contagious forms in families and health operators;
i) guidelines for prevention on work place;
l) guidelines for the treament of suspected cases;
m) guidelines for treament in particular conditions (pediatric population, pregnancy, puerperium etc).

Reorganization of Anti-tubercular Action

Consequently, it is necessary to organize a new antitubercular services in the context of health systems according to the following indications[43]:

1. Physical distinction of antitubercular services and departments from other health care organizations and registration of patients in order to save patients "lost to follow up and treatment".

2. Outpatient controlled treatment, utilizing for the control paramedical operators with adeguate training.

3. Productivity and result analysis (negativization rate, cure rate, completion of therapy rate, etc) rather than number of consultations or number of examined patients.

4. Territorial mobility of trained operators that must carry out analysis on groups at risk of infection and analysis of microepidemics.

5. Continuous patient assistance by the same operators and facility of access to the health structures so as to boost patient confidence and guarantee success of treatment.

6. Adeguate preparation of operators that must be exclusively devoluted to antitubercular activity. Without DOT many patients can be missed or can fall out of therapeutical regimens and cause epidemics.

7. Free and direct access with controlled administration of the drugs to extracommunitary, poor and homeless patients.

8. Identification of an adeguately prepared provincial referral laboratory that can carry out an early diagnosis (through application of rapid systems BACTEK/SEPTI-CHECK/ PCR TEST) of particular importance in cases with radiolografically atypical patterns with difficult differential diagnostic and expecially patients severely affected and with predisposition to a rapid progression of the disease (as those affected by AIDS). In these patients there is the possibility to use right from the beginning specific anti-tubercular therapy. PCR TEST makes possibile to identify in 6 hours the germ present in the expectorate[44-45] be it M. tuberculosis or its genotype rpoB which is Ryfampin-sensitive. This last evenience may be life-saving.

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