Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario
Regione Lombardia

Dipartimento delle Units multispecialistiche e dei Trapianti – Area Cardiopolmonare

U.O.C. Broncopneumologia - Direttore: Prof Francesco Blasi

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STUDY PROTOCOL

The Italian REgistry of pulmonary Non-tuberculous mycobactEria – IRENE

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BACKGROUND

Pulmonary disease due to non-tuberculous mycobacteria (NTM) has always been a tangible clinical entity [1]. An increase in NTM pulmonary and extra-pulmonary morbidity and mortality has been documented in Italy and worldwide, especially among patients suffering from chronic respiratory diseases, including bronchiectasis, chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF), as well as among HIV-positive and other immunocompromised patients [2-11]. Several determinants of the increasing epidemiological trend have been identified: the aging of the population with high prevalence of chronic and debilitating diseases; an intensified use of immunosuppressive therapies; a broader use of chest CT; a high diagnostic yield of microbiological conventional and molecular techniques; an increasing environmental exposure to NTM; an increase use of antibiotics which can favor the occurrence of niches for NTM; declining rates of *M. tuberculosis* infection; and a potential impact of person-to-person transmission as recently suggested among CF patients [12,13].

The epidemiology of patients suffering from a pulmonary disease due to NTM (NTM-PD), which is characterized by symptomatic, progressive inflammatory lung damage and defined in 2007 in the ATS/IDSA guidelines, still remains unclear [14,15]. Epidemiological and clinical uncertainties on NTM-PD cause significant confusion for clinicians in daily clinical practice when asked to diagnose

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NTM-PD. The clinical relevance of NTM respiratory infections significantly varies from patient to patient, and the interplay between exposure- and host-related factors is poorly understood [15]. NTM-PD shows a wide spectrum of clinical manifestations and frequently is diagnosed in the context of concomitant respiratory diseases (e.g., bronchiectasis or CF) [3]. Geographical diversity is another important factor in the epidemiology of NTM. A large inter- and intra-country heterogeneity in distribution of NTM species has been recently shown [16,17]. Finally, an Italian experience described NTM-PD risk factors whose qualitative and quantitative ascertainment could help clinicians to discriminate between colonization and disease [18].

Reporting of NTM-PD to health authorities is often not mandated in several countries and the current estimates have been obtained from sentinel surveillance or laboratory-based studies, retrospective cohort studies, or audits of administrative databases. Only a few European countries (*i.e.*, UK, Greece, Germany, and the Netherlands) have provided epidemiological data, showing an incidence rate of NTM isolation ranging from 2.9 to 7.0 per 100,000 population and a NTM-PD prevalence of 0.7-1.7 per 100,000 population [19-21]. Until now no data have been published on the epidemiology of respiratory NTM infections in Italy.

On this basis, robust national longitudinal data are needed. This manuscript describes the protocol of the first Italian registry of adult patients with respiratory infections caused by NTM.

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METHODOLOGY OF THE IRENE REGISTRY

Study design

The Italian registry of pulmonary NTM (IRENE) is an observational, multicenter, prospective, cohort study enrolling consecutive adult patients with either a NTM respiratory infection or NTM-PD. The coordinating center is located at the Pulmonary Department of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (hereby referred to as Policlinico Hospital), Milan, Italy, where the central approval from the Ethical Committee (EC) for this study was obtained on March 6th, 2017, and the first patient was enrolled on April 21st, 2017. A total of 35 centers, including mainly pulmonary and infectious disease (ID) departments, requested to join the registry, see Figure 1. All the centers are required to obtain local EC approval before entering the registry. Additionally, other EC approvals will be required by IRENE centers prior to commencement of the study at each site. All patients must provide written informed consent to participate in the registry. The study is sponsored by the Policlinico Hospital in Milan.

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Study subjects

Adult (≥18 years) patients with all of the following will be included in the registry: 1) at least one positive culture for any NTM species from any respiratory sample; 2) at least one positive culture for NTM isolated in the year prior the enrolment and/or prescribed NTM treatment in the year prior the enrolment; 3) Given consent to inclusion in the study. No exclusion criteria are applied to the study in order to increase the generalizability of the results. The inclusion criteria of the registry clearly identify a population of patients characterized by a recent/ongoing history of either a NTM infection or NTM-PD. The IRENE Steering Committee decided not to limit the enrolment to patients with NTM-PD, but to follow up also patients with a recent NTM infection not fulfilling the 2007 ATS/IDSA criteria for NTM-PD [15].

Patients included in the registry are mainly recruited among pulmonary and ID out- and in-patient services. Adult CF, lung transplant, and tuberculosis clinics represent other recruitment centers. A heterogeneous population of patients with NTM infection/NTM-PD sharing different clinical

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phenotypes is expected to be enrolled in the registry. IRENE has a special focus on four patients' categories: 1) immunocompetent/bronchiectatic, 2) HIV-positive, 3) CF and 4) lung transplanted patients. 500 patients are expected to be enrolled in the registry by the end of 2020. The registry has been developed to accept an unlimited number of patients and no deadlines have been decided.

Data Collection, definitions and quality control

Patients are managed according to standard operating procedures (SOPs) implemented in each IRENE clinical center without any interference from the study team. A baseline case report form (CRF) is collected at patient's enrolment including demographics, comorbidities, microbiological, laboratory, functional, radiological, clinical, and treatment data. Then, study investigators will enter follow-up data on an annual basis, see online supplement. Furthermore, a "start treatment" and a "stop treatment" CRF will also be collected. The database incorporates automated logic checks put in place to avoid the collection of out-of-range values. Once the case is entered into the registry, two members of the study team (SA and MS) manually verified its consistency and data queries will be solved with the local study investigator. In case of unresolved queries or incomplete cases, they will be rejected to have high quality data. To assure the high quality of the data, random audit will also be conducted at study sites.

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IRENE Biobank

An IRENE biobank has also been developed within the network and linked to the clinical data of the registry. IRENE sites can collect samples, including blood, serum, plasma, respiratory specimens (e.g., sputum, induced sputum, tracheal aspirate, or bronchoalveolar lavage), urine, and NTM isolates at the first visit and during follow up on a voluntary basis. The same SOPs for biological collection, processing, and storage (first locally and then centralized at the Policlinico Hospital in Milan for analysis) will be adopted by all IRENE sites.

The registry governance and the IRENE network

The registry is held securely at the Health Informatics Centre (HIC) of the Policlinico Hospital in Milan, Italy, and de-identified data will be accessible to the study investigators; however, they can have unrestricted access to their own data. Analysis of the entire IRENE database will be allowed after the submission of a specific research question, along with a complete study protocol, to the IRENE Executive Committee. The database will be run in accordance with the principles of Good Clinical Practice. Study results will be disseminated in the form of annual reports, conference

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abstracts, and peer reviewed publications. The IRENE network will follow the International Committee of Medical Journal Editors recommendations regarding authorship.

IRENE is the official Italian network within the EMBARC European NTM registry [22]. All Italian patients included in the European NTM registry will be enrolled through IRENE and IRENE data will be incorporated into the European NTM registry.

IRENE also promotes multi-disciplinary education and patient-professional collaboration in the field of NTM through its relationship with national scientific societies. So far, IRENE received the endorsement by the Italian Respiratory Society (IRS/SIP), the Italian Society of Cystic fibrosis and STOP TB Italia, with pending endorsement from other national scientific societies. There is a lack of a platform for communication between patients with NTM infection/NTM-PD and physicians in Italy and some patients within the IRENE network already expressed their will to develop a patient advisory group.

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Figure 1. IRENE centers

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- IRCSS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan
- ASST Grande Ospedale Metropolitano Niguarda, Milan
- L. Sacco Hospital, Milan
- San Gerardo Hospital, Monza
- Fondazione IRCCS Policlinico San Matteo, Pavia
- Brescia Spedali Civili Hospital, University of Brescia
- University of Turin
- Amedeo di Savoia Hospital, ASL of Turin
- AOU Città della Salute e della Scienza (Molinette), Turin
- Arzignano Hospital, Vicenza
- University Hospital of Padua
- Vittorio Veneto Hospital, Treviso
- Cattinara University Hospital, Trieste
- University Hospital of Parma
- Alma Master Studiorum University of Bolgna
- Ospedale Policlinico of Modena
- University Hospital of Ferrara
- Azienda USL of Ferrara
- IRCCS AOU San Martino, Genova
- University Hospital of Pisa
- Careggi University Hospital, Florence
- San Jacopo Hospital, Pistoia
- IRCCS Lazzaro Spallanzani, Rome
- Policlinico Umbero I, Rome
- Cotugno Hospital, Naples
- San Giuseppe Moscati Hospital, Avellino
- Hospital of Cosenza
- Fallacara di Triggiano Hospital, Bari
- University Hospital Paolo Giaccone, Palermo
- University Hospital G. Martino, Messina