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TB or not TB: update from the ERS Respiratory Infection Assembly 10.

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Abstract

Lower respiratory tract infections (LRTIs) and tuberculosis represent some of top health priorities in Europe. In this report the most recent advances in the field of disease control, clinical research and basic science of LRTIs and tuberculosis are presented through the analysis of some of the best abstracts presented at the 19th ERS Congress in Vienna.

Pathogenesis, diagnosis, treatment, prognostic factors, and novel diagnostic techniques relevant for bacterial and viral infections as well as new tools for the diagnosis of latent and active tuberculosis in different sub-groups of patients are discussed. The growing epidemiological threat represented by multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) tuberculosis cases is presented and its impact analysed.

Introduction

Lower respiratory tract infections (LRTIs) are common and associated with major morbidity, mortality and financial burden [1]. On the other hand, tuberculosis (TB) confirmed to be a global emergency in terms of morbidity and mortality [2,3]. The "cursed duet" of TB/HIV continues to have a dramatic epidemiologic impact in settings with high HIV prevalence (e.g. in Sub-Saharan Africa, India, Russia and Latin America), with potentials for further worsening when multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) TB are present [4] (e.g. in several countries of the Former Soviet Union, representing the borders of Europe).

Apart from the critical issue of political commitment and funding available in the southern part of the world, several key research questions are still open in the field of infection and disease control, clinical research and basic science.

The ERS (European Respiratory Society) Respiratory Infection Assembly (Assembly 10) actively supports several activities in the field of research, disease control and education, being also involved in EU funded projects (e.g. the network of excellence Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) [5] and the European network for study and clinical management of TB drug resistance (TB PAN-NET) [6] belonging to the 6th and 7th Frameworks Programmes, respectively) and in ECDC (European Centre for Disease Prevention and Control) through the involvement of TBNET (Tuberculosis Network European Trialsgroup), which is a ERS CRC (Clinical Research Collaboration) [7].

Aim of the manuscript is to describe the main activities performed by the two groups (10.1 and 10.2) composing Assembly 10 through the analysis of some of the best abstracts presented to the 19th ERS Congress in Vienna by members of the Assembly.

Respiratory Infections

The number of abstracts submitted to, and accepted by the Respiratory Infections group has been growing during the last years, from 171 abstracts accepted and presented in 2007 to 204 abstracts accepted in 2009, representing 75% of those submitted, fairly similar to the 77% general acceptance rate. These abstracts have been distributed into 3 oral, 3 E-posters and 6 thematic posters sessions. These sessions covered the most important aspects of respiratory infections, from pathogenesis to diagnosis, treatment, prognostic factors, and the description of novel diagnostic techniques that may represent an advance in the care of patients in the future.

The first oral session was dedicated to the respiratory infections caused by *Pseudomonas aeruginosa*. The definition of risk factors for *P.aeruginosa* infection is a potentially important issue. The antibiotic treatment is totally different compared to the treatments directed to common

microorganisms and the evolution of the patients can be worse if antipseudomonal antibiotics are not given early enough [8]. Jiang et al [9] have analysed the relationship between the formation of biofilm and the production of different beta-lactamases and observed that bio-film may exert different effects on the production of beta-lactamases by *Pseudomonas* according to the different genotypes. Different studies in the literature have identified some of the risk factors associated with *P.aeruginosa* infection in COPD [10-13]. Impairment of lung function is the main risk factor for infection with this microorganism [10,11]. Overall, the percentage of *Pseudomonas* infection is around 10-15% in series of patients with COPD exacerbations with a FEV1 lower than 50% requiring hospitalisation, and this proportion is increased in patients admitted to ICU needing mechanical ventilation [8,14]. However the issue of *P.aeruginosa* in COPD exacerbations is far from being clear. A recent study has demonstrated that there are different *Pseudomonas* carriage patterns in patients with COPD and that mucoid strains are uncommon but persistent [15]. Regarding treatment of *Pseudomonas* infection, O'Donnell et al [16] reported the design of a phase 2 randomised study of liposomal amikacin for inhalation nebulised once daily in patients with bronchiectasis and chronic *Pseudomonas* infection. At the time of submission, only results regarding safety were available, but no efficacy data were provided. In contrast, Bilton et al [17] reported results of their trial of inhaled liposomal ciprofloxacin hydrochloride in patients with non-cystic fibrosis bronchiectasis. They reported that both, the 3 mL (150 mg) and 6 mL (300 mg) doses of the drug demonstrated significant mean decreases against baseline in *Pseudomonas* colony-forming units (CFU) over the 28-day treatment period of 3.5 log ($p<0.001$) and 4.0 log ($p<0.001$) units and the treatment was well tolerated. Treatment of bronchial infection with the new formulated antibiotics by inhalation opens a new perspective that may be useful in a wide range of patients, from cystic fibrosis to bronchiectasis and severe COPD with bronchiectasis and frequent infective exacerbations. New studies in well defined populations are required.

The second oral session included abstracts dealing with impact of biomarkers in the management of community-acquired pneumonia (CAP). Biomarkers have received increasing attention in the management of lower respiratory tract infections [18]. They may help in identifying bacterial etiology in exacerbations of COPD [19] and in adequately staging the severity and prognosis in CAP [18]. Krueger et al [20] presented a communication investigating the predictive value of pro-atrial natriuretic peptide (proANP) and pro-vasopressin (proAVP) on short- and long-term survival in 1740 patients with CAP. In multivariate Cox proportional hazards regression analyses adjusted for co-morbidity and pneumonia severity, proANP and proAVP were independent and the strongest predictors of 28 and 180 days survival [20]. In a second communication by the same group, they investigated the value of copeptin in the evaluation of severity and prognosis of CAP using patients

from the German CAPNETZ (competence network community acquired pneumonia) network. Their results showed that copeptin levels were higher in patients with more severe CAP, but were also higher in patients without antibiotic pre-treatment compared to those with antibiotic pre-treatment, and, therefore, antibiotic pre-treatment has to be taken into account for the correct interpretation of copeptin levels in CAP [21].

The third oral session was dedicated to new findings in exacerbations of COPD. Interestingly, pro-ANP, the same maker studied in CAP as prognostic marker by Krueger et al [20] was evaluated as prognostic factor in patients hospitalised for exacerbation of COPD by Bernasconi et al [22]. They followed up a group of 167 patients for 2 years after discharge for an exacerbation episode, and measured proANP at admission, after 14 days and 6 months. The results showed that proANP levels were higher on admission compared with recovery and stable state; additionally, proANP and pCO2 were independent predictors of mortality in multivariate analysis. The relationship between the pathogen and the host in the bronchial mucosa of COPD is complex and the mechanisms explaining persistence and colonisation, or the development of exacerbations are still under investigation [23]. Desai et al [24] evaluated the mechanisms explaining the persistence of *Streptococcus pneumoniae* (Sp) in relation to specific antibiotics used during exacerbations in a group of 526 patients with isolation of this microorganism. In 94 of these patients, Sp was also isolated from sputum at the end of treatment, of which 77 (82%) of the persistent strains were the same as the initial strain. Moreover, there was a trend for treatment with a beta-lactam to be associated more often with strain replacement than with a ketolide or macrolide. The impact of colonisation by *Haemophilus influenzae* in patients with COPD was analysed in an abstract presented by Marin-Tapia et al [25]. They investigated 175 stable COPD patients and were able to isolate 71 potentially pathogenic microorganisms (PPMs) from 62 patients (35%), with *H.influenzae* being the most prevalent PPM identified. Besides the association of tobacco smoking with a higher prevalence of colonisation, patients carrying PPMs in bronchial secretions also presented poorer health status measured by the St. George's Respiratory Questionnaire, indicating the relevance of bronchial colonisation in the general well being of patients. Although sputum is the most readily available sample for microbiological testing, it is subject to the possibility of false negatives or false positives results due to oro-pharyngeal contamination [26]. To avoid these problems, the sampling of lower airways using bronchoscopic techniques may provide a clearer picture of the presence of PPMs and associated inflammation in this setting [27]. Nesterovich and Bukreeva [28] presented a study on 46 exacerbated COPD patients undergoing bronchoscopy and sampling of bronchial brush biopsies. They isolated an infective agent in 36 cases (78%), in 26 cases with a single pathogen and 10 mixed infections. Interestingly, their results demonstrated that the bronchial epithelium structure changed

according to the type of causative agent, both in terms of cytology and inflammatory markers investigated. The different inflammatory pattern associated with bacterial and viral etiology has been observed in severe patients admitted for an exacerbation [29], but the differences in patterns of bronchial damage between intracellular and extracellular pathogens is an interesting finding that may have therapeutic implications or may explain bacterial persistence and residual colonisation after treatment of an acute episode.

Lung Tuberculosis

In the 2007-9 period, the activities of the TB group within the ERS Respiratory Assembly have been largely influenced by the activities of TBNET, a network of clinical and allied scientists joined together in Europe to run multicentre collaborative research projects. The collaboration of TBNET with ERS as a CRC has been very productive, allowing TBNET to operate under the umbrella of the largest respiratory diseases society at the global level, and offering the opportunity to ERS to be in the front-line on the fight against TB, with the publication of original works and reviews on hot topics like drug resistant TB and new diagnostics for the TB infection and disease. Furthermore, ongoing multicentre studies are now presented in the scientific sessions on TB during the congress, increasing the interest and participation of colleagues from overseas as well. The congress in Vienna was characterised by high quality of the presentations and posters selected for the scientific sessions: compared to the previous congresses in Berlin and Stockholm, a more stringent and careful selection of the abstracts submitted lead to a reduced number of scientific sessions, compensated, on the other hand, by the relevance of the studies presented. The acceptance rate, in fact, decreased from 85.4% (336/397) in 2007, to 78.8% (360/457) in 2008, to 63.6% (255/401) in 2009. In Vienna, the 14 sessions (2 oral, 8 poster and 4 E-poster sessions) addressed the most important topics in the field of epidemiology, control, clinical aspects and basic research of TB, with a special focus on the threat represented by MDR- and XDR-TB and on the use of interferon-γ release assays (IGRAs). These latter were the topics covered by the first oral session, where the selected abstracts were focused on the new perspectives opened by IGRAs in the diagnosis of TB infection, especially recent vs. latent, and in the diagnosis of active TB disease. Interesting data were presented on the possibility to differentiate between recent and remote/treated latent TB infection (LTBI) based on the expression of IL-2 coupled with IFN-γ [30]. Addressing this question, Goletti et al. [31] presented a modified whole-blood assay based on T-cell stimulation with antigens selectively expressed by *Mycobacterium tuberculosis* in the latency phase. The results of this study show that the subjects with remote LTBI present significantly higher IFN-γ response to the antigen Rv2628 compared to subjects with recent or active infection. On the use of IGRAs for

the diagnosis of active TB, the results of a TBNET multicentre European study presented by Ruhwald et al. [32] reported that an Interferon-γ inducible protein (IP)-10 based whole blood assay showed an improved accuracy compared to the respective IGRA. Jafari et al. [33], as well, presented the final results of a large collaborative multicentre study on the diagnosis of active TB with an ELISpot technique performed on bronchoalveolar lavage (BAL) fluid cells from sputum smear negative pulmonary TB suspects, reporting extraordinary high sensitivity and specificity of the method and offering a powerful, fast, and relatively simple tool for this challenging diagnosis of the disease.

The second oral session was focused on drug-resistant TB, and especially on MDR- and XDR-TB. In the last year important studies were published, defining the potential role for moxifloxacin in the standard treatment of TB, to replace ethambutol [34,35], as well as that of the diarylquinoline TMC 207, a very promising new compound tested in phase II studies [36].

An analysis on determinants of MDR-TB in Germany, Italy, Estonia, Russia and Romania [37] showed that homeless status and HIV infection are strong independent risk factors for the disease, highlighting the need of interventions in these particular groups.

Reports from India [38], Turkey [39] and Philippines [40] described how treatment outcomes of MDR-TB patients have a relevant inter-country variation, being improved by the rational use of second-line drugs. These studies confirm once more that MDR-TB can be treated successfully when appropriate control programmes and adequate resources are put in place. Conversely, a study from South Africa [41] described the poor treatment outcomes achieved in XDR-TB cases (regardless HIV status), a result quite different from that recently reported in Peru [42].

The need for alternative strategies in the treatment of MDR/XDR-TB was also reflected by the increasing number of reports about surgical and endoscopic treatment of the disease. In this context, particularly interesting was an abstract reporting the use of endobronchial valves determining atelectasis of cavities caused by XDR-TB [43]. Despite the limited number of observations available, this relatively non-invasive method may offer a real alternative to surgical resections or pneumothorax.

Eight thematic poster sessions addressed various important topics: the first session was dedicated to extrapulmonary TB, diseases caused by Non-tuberculous Mycobacteria (NTM) and other emerging pathogens. Eight abstracts were dedicated to NTM, both in immunocompromised and competent hosts, reflecting the increasing number of cases recorded in Europe, and the improved sensitivity of chest physicians to the problem. An interesting nation-based study from Denmark [44] showed that worse prognosis of the disease was associated with isolate of *M. xenopi* (HR 1.34, 95%CI 0.87-2.06, compared with *M. avium*), presence of comorbidities (HR 3.1, 95%CI 2.3-4.1) and age >65

years (HR 9.2, 95%CI 5.0-16.9) . The difficulties to manage these patients and very high rate of treatment failure/relapse were also highlighted by the follow-up results in two cohorts of patients from Japan [45] and South Korea [46]. A case report of rhodococcal pneumonia [47] and other case reports about NTM diseases [48] highlighted the severity of these events, that are being reported with increased frequency.

The second session was dedicated to TB in different age-groups, and most of the abstracts reported data from paediatric cohorts, reflecting the increasing attention and sensitivity of doctors to a problem that is often neglected also in high prevalence countries. A report from Tehran [49] stressed very clearly the fact that the diagnosis of TB in paediatrics is hampered by the reduced sensitivity of the diagnostic tests used in adults. A consistent proportion of patients had a negative chest radiography, all of them having signs of disease at the high resolution Computerised Tomography (HR CT). Noteworthy, the same study reported a slightly higher prevalence of the disease among females under 15 years of age. The difficulties in the management of paediatric cases with unusual presentations were highlighted in two case reports: a group from Germany [50] discussed the opportunity and timing of surgical drainage of abscesses caused by MDR-TB, while a group from Romania [51] described a case of meningitis with unusual cerebrospinal fluids features.

The need to increase the sensitivity of TB diagnosis among children was stressed by a Croatian study [52] reporting a decrease in the number of paediatric cases in a major hospital: the Authors highlighted the fact that i) most of them were family contacts (in about 80% of cases the index case was one of the parents) and ii) an increasing number of them were diagnosed through implementation of quality contact tracing procedures.

Another session reflected the increasing importance of another risk group, e.g. the patients with immunosuppression induced by anti-TNFα drugs. Seven out of 20 abstracts in the session “Clinical immunology of Tuberculosis” were focused on this issue and on the need to improve pre-treatment screening procedures.

As in Berlin, also in Vienna participants had the chance to present and discuss original research studies through electronic sessions, a new methodology ERS is still evaluating with particular interest.

Eighty abstracts were presented in 4 electronic sessions organized to discuss TB and HIV co-infection, contact tracing procedures, proof of concepts for new diagnostics and treatment of MDR- and XDR-TB. During these session, interesting cases caused by emerging pathogens, like *M. tilburgii* [53] and *M. sherisii* [54] were reported and discussed, as well as the novelty and limit of new diagnostic techniques like IGRAs in patients with advanced HIV co-infection [55].

The session dedicated to contact tracing procedures reported data from different settings and targeted populations, highlighting the improvements and operational advantages related to the use of new blood tests, especially among children [56] and subjects with confounding factors like health-care workers [57]. Preliminary results showed a high negative predictive value for serum-procalcitonin in the differential diagnosis between pulmonary TB and other pulmonary infections [58].

Conclusions

Interesting contributions towards a better understanding of pathogenesis, diagnosis, treatment, prognostic factors, and new diagnostic techniques for bacterial and viral infections were presented at the Vienna Conference.

Similarly, the contribution of the studies presented in Vienna allowed to obtain a clearer understanding on the use of IGRAs in the diagnosis of latent and active TB, and to shed further light on MDR- and XDR-TB diagnosis, clinical management and control.

Due to the active involvement of several members of the Respiratory Infection Assembly in different high profile projects [5-7], quality answers to the pending questions related to the management of community-acquired LRTI and tuberculosis are expected in the near future.

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