SCIENTIFIC ASSEMBLY UPDATE

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

M. Miravittles^{*,##}, G. Ferrara^{#,##}, C. Lange[†], G. Dimopoulos⁺, G. Rohde[§],
F. Blasi[‡] and G.B. Migliori^{**}

ABSTRACT: Lower respiratory tract infections and tuberculosis represent some of the top health priorities in Europe. In the present report, the most recent advances in the field of disease control, clinical research and basic science of lower respiratory tract infections and tuberculosis are presented through analysis of some of the best abstracts presented at the 19th European Respiratory Society Congress in Vienna (Austria).

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 and extensively drug-resistant tuberculosis cases is presented and its impact analysed.

KEYWORDS: European Respiratory Society Congress, respiratory infections, tuberculosis

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

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

The European Respiratory Society (ERS) Respiratory Infection Assembly (Assembly 10) actively supports several activities in the field of research, disease control and education, also being involved in projects funded by the European Union (e.g. the network of excellence Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) [5] and the Pan-European network for study and clinical management of drug resistant tuberculosis (TB PAN-NET) [6], belonging to the 6th and 7th Framework Programmes, respectively) and in the European

Centre for Disease Prevention and Control (ECDC) through the involvement of the Tuberculosis Network (European Trials Group) (TBNET), which is an ERS clinical research collaboration [7].

The aim of the present article 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 (Austria) by members of the Assembly.

RESPIRATORY INFECTIONS

The number of abstracts submitted to, and accepted by, the Respiratory Infections Group has been growing during recent years, from 171 abstracts accepted and presented in 2007 to 204 abstracts accepted in 2009, representing 75% of those submitted, and fairly similar to the 77% general acceptance rate. These abstracts have been distributed among three oral, three E-poster and six thematic poster 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

AFFILIATIONS

*Fundació Clínic, Institut D'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, Barcelona, Spain,

#Section of Respiratory Diseases, Dept of Internal Medicine, Santa Maria Hospital, University of Perugia, Terni,

‡Respiratory Medicine Section, Dipartimento Toraco-Polmonare e Cardiocircolatorio, University of Milan, Istituto Di Ricovero e Cura a Carattere Scientifico Fondazione Ospedale Maggiore Policlinico Ca' Granda, Milan,

**World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy,

†Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Borstel, Germany,

+2nd Dept of Critical Care, Medical School, University of Athens, University Hospital Attikon, Athens, Greece, and

§Maastricht University Medical Center, Dept of Respiratory Medicine, Maastricht, the Netherlands,

##Both authors contributed equally to this article.

CORRESPONDENCE

G.B. Migliori, World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, via Roncaccio 16, 21049, Tradate, Italy
E-mail: giovannibattista.migliori@fsm.it

Received:

April 08 2010

Accepted after revision:

April 22 2010

First published online:

June 04 2010

European Respiratory Journal

Print ISSN 0903-1936

Online ISSN 1399-3003

compared to the treatments directed against common microorganisms, and the progression of the patients can be worse if antipseudomonal antibiotics are not given early enough [8]. JIANG and LI [9] analysed the relationship between the formation of the biofilm and production of various β -lactamases and observed that the biofilm may exert different effects on the production of β -lactamases by *P. aeruginosa* depending upon the different genotypes. Various studies in the literature have identified some of the risk factors associated with *P. aeruginosa* infection in chronic obstructive pulmonary disease (COPD) [10–13]. Impairment of lung function is the main risk factor for infection with this microorganism [10, 11]. Overall, the rate of *P. aeruginosa* infection is ~10–15% in series of patients with COPD exacerbations with a forced expiratory volume in 1 s of <50% requiring hospitalisation, and this proportion is increased in patients admitted to the intensive care unit 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 *P. aeruginosa* carriage patterns in patients with COPD, and that mucoid strains are uncommon but persistent [15]. Regarding treatment of *P. aeruginosa* infection, O'DONNELL *et al.* [16] reported the design of a phase-II randomised study of liposomal amikacin for inhalation nebulised once daily in patients with bronchiectasis and chronic *P. aeruginosa* infection. At the time of submission, only results regarding safety were available, and no efficacy data were provided. In contrast, BILTON *et al.* [17] reported the 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 *P. aeruginosa* colony-forming units over the 28-day treatment period of 3.5 log ($p<0.001$) and 4.0 log units ($p<0.001$), and the treatment was well tolerated. Treatment of bronchial infection with the newly formulated antibiotics by inhalation opens a new perspective that may be useful in a broad range of patients, from cystic fibrosis to bronchiectasis, severe COPD with bronchiectasis and frequent infective exacerbations. New studies in well-defined populations are required.

The second oral session included abstracts dealing with the impact of biomarkers in the management of community-acquired pneumonia (CAP). Biomarkers have received increasing attention in the management of LRTIs [18]. They may help in identifying bacterial aetiology in exacerbations of COPD [19] and in adequately staging severity and prognosis in CAP [18]. KRUEGER *et al.* [20] presented a communication investigating the predictive value of pro-atrial natriuretic peptide (pro-ANP) and pro-vasopressin (pro-AVP) on short- and long-term survival in 1,740 patients with CAP. In multivariate Cox's proportional hazards regression analyses adjusted for comorbidity and pneumonia severity, pro-ANP and pro-AVP were independent and the strongest predictors of 28- and 180-day survival [20]. In a second communication from the same group, the value of copeptin in the evaluation of the severity and prognosis of CAP was investigated using patients from the German Competence Network for Community-Acquired Pneumonia (CAPNETZ). Their results showed that copeptin levels were higher in patients with more severe CAP, but were also higher in patients without antibiotic pretreatment than in

those with antibiotic pretreatment, and, therefore, antibiotic pretreatment 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 marker studied as a prognostic marker in CAP by KRUEGER *et al.* [20], was also evaluated as a prognostic factor in patients hospitalised for exacerbation of COPD by BERNASCONI *et al.* [22]. They followed-up a group of 167 patients for 2 yrs following discharge for an exacerbation episode, and measured pro-ANP at admission and after 14 days and 6 months. The results showed that pro-ANP levels were higher on admission compared with during recovery and the stable state; additionally, pro-ANP and arterial carbon dioxide tension were independent predictors of mortality on 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, and the development of exacerbations are still under investigation [23]. DESAI *et al.* [24] evaluated the mechanisms explaining the persistence of *Streptococcus pneumoniae* in relation to specific antibiotics used during exacerbations in a group of 526 patients with isolation of this microorganism. In 94 of these patients, *S. pneumoniae* was also isolated from sputum at the end of treatment, 77 (82%) of the persistent strains being the same as the initial strain. Moreover, there was a trend for treatment with a β -lactam to be associated more often with strain replacement than that 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 (35%) patients, 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 with poorer health status as 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-negative or false-positive results due to oropharyngeal contamination [26]. In order to avoid these problems, the sampling of lower airways using bronchoscopic techniques may provide a clearer picture regarding 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 bronchial brush biopsy sampling. They isolated an infective agent in 36 (78%) cases, 26 with a single pathogen and 10 with mixed infections. Interestingly, their results demonstrated that the bronchial epithelium structure changed according to the type of causative agent, in terms of both cytology and the investigated inflammatory markers. The different inflammatory pattern associated with bacterial and viral aetiology 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 following treatment of an acute episode.

LUNG TUBERCULOSIS

During the period 2007–2009, the activities of the Tuberculosis Group within the ERS Respiratory Infections Assembly have been largely influenced by the activities of TBNET, a network of clinical and allied scientists who have joined together in Europe to run multicentric collaborative research projects. The collaboration of TBNET with the ERS as a clinical research collaboration has been very productive, permitting TBNET to operate under the umbrella of the largest respiratory diseases society at the global level, and offering the opportunity to the ERS to be on the front line in the fight against TB, with the publication of original works and reviews on hot topics, such as drug-resistant TB and new diagnostics for TB infection and disease. Furthermore, ongoing multicentric studies are now presented in the scientific sessions on TB during the congress, also increasing the interest and participation of colleagues from overseas. The congress in Vienna was characterised by the high quality of the presentations and posters selected for the scientific sessions; compared to the previous congresses in Berlin (Germany) and Stockholm (Sweden), more stringent and careful selection from the abstracts submitted led to a reduced number of scientific sessions, compensated for by the relevance of the studies presented. Indeed, the acceptance rate decreased from 85.4% (336 out of 397) in 2007 to 78.8% (360 out of 457) in 2008 and 63.6% (255 out of 401) in 2009. In Vienna, the 14 sessions (two oral, eight poster and four 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 aspects were the topics covered by the first oral session, where the selected abstracts focused on the new perspectives opened by IGRAs in the diagnosis of TB infection, especially recent *versus* latent, and the diagnosis of active TB disease. Interesting data were presented on the possibility of differentiating between recent and remote/treated latent TB infection based on the expression of interleukin-2 coupled with interferon- 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 subjects with remote latent TB infection present a significantly higher interferon- γ response to the antigen Rv2628 than do subjects with recent or active infection. Regarding the use of IGRAs for the diagnosis of active TB, the results of a TBNET multicentric European study presented by RUHWALD *et al.* [32] reported that an interferon- γ -inducible protein 10-based whole-blood assay showed improved accuracy compared to the respective IGRA. JAFARI *et al.* [33] also presented the final results of a large collaborative multicentric study on the diagnosis of active TB with an enzyme-linked immunospot technique performed on bronchoalveolar lavage fluid cells from sputum-smear-negative pulmonary TB suspects, reporting an extraordinarily 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 TMC207, 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 showed that homeless status and HIV infection are strong independent risk factors for the disease, highlighting the need for interventions in these particular groups [37].

Reports from India [38], Turkey [39] and Philippines [40] described how treatment outcomes of MDR-TB patients show 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 described the poor treatment outcomes achieved in XDR-TB cases (regardless of HIV status) [41], 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 numbers of reports regarding 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 noninvasive method may offer a real alternative to surgical resection or pneumothorax.

Eight thematic poster sessions addressed various important topics. The first session was dedicated to extrapulmonary TB, diseases caused by nontuberculous mycobacteria (NTM) and other emerging pathogens. Eight abstracts were dedicated to NTM, in both 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 isolation of *M. xenopi* (hazard ratio 1.34; 95% confidence interval 0.87–2.06, compared with *M. avium*), the presence of comorbid conditions (3.1; 2.3–4.1) and age of >65 yrs (9.2; 5.0–16.9). The difficulties in managing 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, which 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 also often neglected in high-prevalence countries. A report from Tehran (Iran) stressed very clearly the fact that the diagnosis of TB in paediatric subjects is hampered by the reduced sensitivity of the diagnostic tests used in adults [49]. A consistent proportion of patients gave negative chest radiography results, all of them having signs of disease on high-resolution computed tomography. It is noteworthy that the same study reported a slightly higher prevalence of the disease among females aged <15 yrs.

The difficulties in the management of paediatric cases with unusual presentations were highlighted in two case reports; a group from Germany discussed the opportunity and timing of surgical drainage of abscesses caused by MDR-TB [50], whereas a group from Romania described a case of meningitis with unusual cerebrospinal fluid features [51].

The need to increase the sensitivity of TB diagnosis among children was stressed by a Croatian study reporting a decrease in the number of paediatric cases in a major hospital [52]. The authors highlighted the facts that: 1) most of them were family contacts (in ~80% of cases the index case was one of the parents); and 2) an increasing number of them were diagnosed through implementation of quality contact-tracing procedures.

Another session reflected the increasing importance of another risk group, *i.e.* patients with immunosuppression induced by anti-tumour necrosis factor- α drugs. Seven out of 20 abstracts in the "Clinical immunology of tuberculosis" session were focused on this issue and on the need to improve pretreatment screening procedures.

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

A total of 80 abstracts were presented in four electronic sessions organised 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 sessions, interesting cases caused by emerging pathogens, such as *M. tuberculosis* [53] and *M. abscessus* [54], were reported and discussed, as well as the novelty and limits of new diagnostic techniques, such as 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, such as healthcare workers [57]. Preliminary results showed a high negative predictive value for serum procalcitonin levels 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 Congress.

Similarly, the contribution of the studies presented in Vienna permitted a clearer understanding to be obtained regarding the use of IGRAs in the diagnosis of latent and active TB, and shedding of further light on MDR- and XDR-TB diagnosis, clinical management and control.

Owing to the active involvement of several members of the Respiratory Infection Assembly in various high-profile projects [5–7], quality answers to the questions pending relating to the management of community-acquired LRTI and TB are expected in the near future.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors wish to thank R. Centis (World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, S. Maugeri Foundation, Care and Research Institute, Tradate, Italy) for support through the editorial process of this manuscript.

REFERENCES

- 1 Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–1180.
- 2 World Health Organization, Global Tuberculosis Control 2009: Epidemiology. Strategy. Financing: WHO Report 2009. Geneva, World Health Organization, 2009.
- 3 World Health Organization, Multidrug and Extensively Drug-Resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. Geneva, World Health Organization, 2010.
- 4 Sotgiu G, Ferrara G, Matteelli A, *et al.* Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J* 2009; 33: 871–881.
- 5 Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe. Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe. www.grace-lrti.org Date last updated: April 8, 2010. Date last accessed: April 8, 2010.
- 6 TB PAN-NET. European Network for Study and Clinical Management of TB Drug Resistance. www.tbpannet.eu Date last updated: April 8, 2010. Date last accessed: April 8, 2010.
- 7 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Development of a standardised tool to survey MDR-/XDR-TB case management in Europe. *Eur Respir J* 2010; 36: 208–211.
- 8 Ewig S, Soler N, Gonzalez J, *et al.* Evaluation of antimicrobial treatment in mechanically ventilated patients with severe chronic obstructive pulmonary disease exacerbations. *Crit Care Med* 2000; 28: 692–697.
- 9 Jiang H, Li Z. Effect of biofilm on induced β -lactamase production in *Pseudomonas aeruginosa* with different genotype. *Eur Respir J* 2009; 34: Suppl. 53, 231s.
- 10 Eller J, Ede A, Schaberg T, *et al.* Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. *Chest* 1998; 113: 1542–1548.
- 11 Miravittles M, Espinosa C, Fernandez-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999; 116: 40–46.
- 12 Lode H, Allewelt M, Balk S, *et al.* A prediction model for bacterial etiology in acute exacerbations of COPD. *Infection* 2007; 35: 143–149.
- 13 Monsó E, García-Aymerich J, Soler N, *et al.* Bacterial infection in exacerbated COPD with changes in sputum characteristics. *Epidemiol Infect* 2003; 131: 799–804.
- 14 Soler N, Torres A, Ewig S, *et al.* Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157: 1498–1505.
- 15 Murphy TF, Brauer AL, Eschberger K, *et al.* *Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 853–860.
- 16 O'Donnell A, Swarnakar R, Yashina L, *et al.* A placebo-controlled study of liposomal amikacin for inhalation nebulized once daily in the treatment of bronchiectasis patients with chronic *Pseudomonas aeruginosa* lung infection. *Eur Respir J* 2009; 34: Suppl. 53, 231s.

- 17 Bilton D, DeSoyza A, Haworth C, *et al.* Inhaled liposomal ciprofloxacin hydrochloride significantly reduces sputum *Pseudomonas aeruginosa* density in non-CF bronchiectasis. *Eur Respir J* 2009; 34: Suppl. 53, 231s.
- 18 Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J* 2007; 30: 556–573.
- 19 Stolz D, Christ-Crain M, Bingisser R. Antibiotic treatment of exacerbations of COPD: a randomised, controlled trial comparing procainin-guidance with standard therapy. *Chest* 2007; 131: 9–19.
- 20 Krueger S, Ewig S, Kunde J, *et al.* Pro-atrial natriuretic peptide and pro-vasopressin to predict short- and long-term survival in community-acquired pneumonia. *Eur Respir J* 2009; 34: Suppl. 53, 296s.
- 21 Krueger S, Ewig S, Kunde J, *et al.* Pro-vasopressin (copeptin) in patients with community-acquired pneumonia – influence of antibiotic pre-treatment; results from the German competence network CAPNETZ. *Eur Respir J* 2009; 34: Suppl. 53, 296s.
- 22 Bernasconi M, Christ-Crain M, Müller C, *et al.* MR-proANP predicts 2-year survival in patients admitted for acute exacerbation of COPD. *Eur Respir J* 2009; 34: Suppl. 53, 748s–749s.
- 23 Sethi S, Evans N, Grant BJ, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
- 24 Desai H, Johnson A, Murphy T, *et al.* Mechanisms of persistence of *Streptococcus pneumoniae* following treatment of acute exacerbation of chronic bronchitis. *Eur Respir J* 2009; 34: Suppl. 53, 749s.
- 25 Marín-Tapia A, García-Aymerich J, Monsó E, *et al.* Effects of colonisation by *Haemophilus influenzae* in COPD stable patients. *Eur Respir J* 2009; 34: Suppl. 53, 749s–750s.
- 26 Murphy TF, Brauer AL, Schiffmacher T, *et al.* Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 266–272.
- 27 Soler N, Agustí C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 62: 29–35.
- 28 Nesterovich S, Bukreeva E. Peculiarities of brush-biopsies of bronchial mucosa at different aetiology of COPD exacerbations. *Eur Respir J* 2009; 34: Suppl. 53, 412s.
- 29 Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
- 30 Biselli R, Mariotti S, Sargentini V, *et al.* Detection of IL-2 in addition to IFN- γ discriminates active tuberculosis patients, latently infected individuals and controls. *Clin Microbiol Infect* 2009; [Epub ahead of print PMID: 19886902].
- 31 Goletti D, Butera O, Vanini V, *et al.* Response to Rv2628 latency antigen associates with cured tuberculosis and remote infection. *Eur Respir J* 2010; 36: 135–142.
- 32 Ruhwald M, Bodmer T, Maier C, *et al.* Evaluating the potential of IP-10 and MCP-2 as biomarkers for the diagnosis of tuberculosis. *Eur Respir J* 2008; 32: 1607–1615.
- 33 Jafari C, Thijsen S, Sotgiu G, *et al.* Bronchoalveolar lavage enzyme-linked immunospot for a rapid diagnosis of tuberculosis. A Tuberculosis Network European Trialsgroup study. *Am J Respir Crit Care Med* 2009; 180: 666–673.
- 34 Dorman SE, Johnson JL, Goldberg S, *et al.* Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med* 2009; 180: 273–280.
- 35 Conde MB, Efron A, Loredó C, *et al.* Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet* 2009; 373: 1183–1189.
- 36 Diacon AH, Pym A, Grobusch M, *et al.* The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; 360: 2397–2405.
- 37 Sotgiu G, Sorete-Arbore A, Kliemann K, *et al.* Social determinants of MDR-TB in Europe: a multi-centre TBNET study. *Eur Respir J* 2009; 34: Suppl. 53, 786s.
- 38 Prasad BNB, Rai SP, Falleiro JJ, *et al.* Prevalence and treatment outcome of drug resistant pulmonary tuberculosis in HIV negative cases – experience from a tuberculosis treatment center in India. *Eur Respir J* 2009; 34: Suppl. 53, 786s–787s.
- 39 Saygi A, Sungun F, Ekinici T, *et al.* Treatment outcome in multidrug resistant tuberculosis cases at our clinic between 1996–2008. *Eur Respir J* 2009; 34: Suppl. 53, 787s.
- 40 Legaspi MV. A two-year post-treatment follow-up of multi-drug resistant tuberculosis cases who completed a programmatic MDR-TB management at the lung center of the Philippines: a preliminary report. *Eur Respir J* 2009; 34: Suppl. 53, 787s.
- 41 Dheda K, Shean K, Badri M. Extensively drug-resistant tuberculosis. *N Engl J Med* 2008; 359: 2390.
- 42 Mitnick CD, Shin SS, Seung KJ, *et al.* Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med* 2008; 359: 563–574.
- 43 Lovacheva O, Sivokozov I, Bagdasaryan T, *et al.* Local artificial atelectasis in treatment of end-stage XDR cavitary tuberculosis. *Eur Respir J* 2009; 34: Suppl. 53, 787s.
- 44 Andrejak C, Thomsen V, Johansen I, *et al.* The prognosis of patients colonized and infected with pulmonary nontuberculous mycobacteria in Denmark, 1997–2007: a nationwide population-based study. *Eur Respir J* 2009; 34: Suppl. 53, 435s.
- 45 Kobashi Y, Mouri K, Obase Y, *et al.* Long-term observation of pulmonary *Mycobacterium avium* complex disease treated with chemotherapy following the guidelines for treatment. *Eur Respir J* 2009; 34: Suppl. 53, 435s.
- 46 Sim YS, Park HY, Kwon OJ, *et al.* Treatment outcome and prognostic factor in patients with *Mycobacterium avium* complex pulmonary disease. *Eur Respir J* 2009; 34: Suppl. 53, 436s.
- 47 Greinert H, Hörster R, Hoffmann C, *et al.* Successful treatment of rhodococcal pneumonia in advanced HIV-infection. *Eur Respir J* 2009; 34: Suppl. 53, 436s.
- 48 Shah A, Strickland N, Thomas C, *et al.* Characterisation of patients with multiple isolates of different species of non-tuberculous mycobacteria: a new phenomenon? *Eur Respir J* 2009; 34: Suppl. 53, 435s.
- 49 Khalilzadeh S, Baghaie N, Bloorsaz MR, *et al.* Bacteriological evaluation for diagnosis of tuberculosis in children. *Eur Respir J* 2009; 34: Suppl. 53, 438s.
- 50 Brinkmann F, Schwerk N, Gappa M, *et al.* Psoas abscesses in a child with multidrug resistant tuberculosis: is surgical drainage indicated? *Eur Respir J* 2009; 34: Suppl. 53, 440s.
- 51 Dobrota L, Neamtu M-L, Neamtu B, *et al.* P2492 chronic meningitis: a rare form of onset of tuberculosis infection in infants. *Eur Respir J* 2009; 34: Suppl. 53, 440s.
- 52 Pavlov N, Dragisic-Ivulic S, Pavlov V. Epidemiologic trends in children with tuberculosis (1999–2009). *Eur Respir J* 2009; 34: Suppl. 53, 439s–440s.
- 53 Eker B, Welling J, Greinert U, *et al.* *Mycobacterium tuberculosis* infection in an HIV-seropositive host. *Eur Respir J* 2009; 34: Suppl. 53, 575s.
- 54 Guenther G, Uhrig A, Lange C, *et al.* High-frequency oscillatory ventilation (HFOV) effectively removed CO₂ in AIDS related severe *Mycobacterium tuberculosis* infection with acute respiratory distress syndrome (ARDS). *Eur Respir J* 2009; 34: Suppl. 53, 575s.
- 55 Leidl L, Mayanja-Kizza H, Sotgiu G, *et al.* Relationship of interferon-gamma release assay results and tuberculin skin test results to numbers of circulating CD4 T-cells in HIV infection. *Eur Respir J* 2009; 34: Suppl. 53, 573s.
- 56 Diez N, Latorre I, Giner E, *et al.* IFN- γ T cell response in the diagnosis of latent tuberculosis infection in children with a positive tuberculin skin test. *Eur Respir J* 2009; 34: Suppl. 53, 65s.

- 57** Losi M, Corona GL, Del Giovane C, *et al.* Using QuantiFERON-TB gold in-tube in contact tracing procedures. *Eur Respir J* 2009; 34: Suppl. 53, 66s.
- 58** Strassburg A, Guenther G, Sahly H, *et al.* Negative predictive value of serum-procalcitonin (PCT) for active pulmonary tuberculosis (pTB). *Eur Respir J* 2009; 34: Suppl. 53, 284s.