



ERS International Congress, Madrid, 2019: highlights from the Respiratory Infections Assembly

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ABSTRACT The European Respiratory Society (ERS) International Congress organised in Madrid, Spain, in 2019 welcomed >22000 participants from 134 countries. For each ERS assembly, an impressive number of abstracts were submitted. The topics covered by Assembly 10 (Respiratory Infections and Tuberculosis) were included this year in the top five research areas with the most submitted abstracts, with a total of 424 abstracts accepted for presentation. As it would be difficult for any delegate to stay up to date with all the scientific advances in the field, we wanted to highlight three of the Congress sessions that included presentations on respiratory infections and tuberculosis that we deemed as important and we hope the readers will consider this material of great interest.



@ERSpublications

The areas covered by @EuroRespSoc Assembly 10 were very well served at #ERSCongress 2019: 219 abstracts that focused on respiratory infections and 205 on tuberculosis <https://bit.ly/2XShcNs>

Cite this article as: Calarasu C, Chichirelo-Konstantynovych KD, Frent S. ERS International Congress, Madrid, 2019: highlights from the Respiratory Infections Assembly. *ERJ Open Res* 2020; 6: 00316-2019 [<https://doi.org/10.1183/23120541.00316-2019>].



Fighting antimicrobial resistance: from prevention to antimicrobial stewardship

The presentations included in this session focussed on the widespread clinical problem of antimicrobial resistance in respiratory diseases (community-acquired pneumonia (CAP) in particular) and on modern diagnostic approaches to overcome this sensitive issue.

Francesco Blasi discussed antimicrobial resistance in respiratory diseases and presented epidemiological data from the European Centre for Disease Prevention and Control [1]. Bacterial resistance was explained as a natural process caused by mutational alteration or incorporation of mobile genetic elements carrying resistance genes.

Clinical outcomes of CAP patients rely on the interaction between three main determinants: host, bacterium and drug [2]. Prof. Blasi argued that risk scores able to identify multidrug resistant (MDR) pneumonia upon hospital admission could inform patient treatment and prevent antibiotic misuse and complications. ALIBERTI *et al.* [3] developed a score to evaluate the presence of MDR pathogens in patients with pneumonia coming from the community in two independent European cohorts of consecutive patients hospitalised with pneumonia in Barcelona, Spain, and Edinburgh, UK. The Aliberti score was better than the healthcare-associated pneumonia classification in predicting MDR pneumonia, especially when used in the intensive care unit setting [4]. Pneumonia caused by an MDR pathogen acquired in the community depends on patients' previous health status/comorbidities and previous contact with the healthcare system. Hospitalisation in the previous 90 days and residency in a nursing home or extended-care facility were found to be independent risk factors for pneumonia with a resistant pathogen and increased in-hospital mortality. These results support an individual evaluation of each patient in order to develop a targeted approach when selecting empiric antibiotic therapy [3].

Immunodepression state as a risk factor for MDR pneumonia was present in 18% of the population from an international, multicentre study enrolling adult patients with CAP requiring hospitalisation. The most common single risk factors for immunodeficiency were chronic steroid use (45%), haematological malignancy (25%) and chemotherapy (22%). The authors of this study performed a multivariable regression analysis and found a strong association between *Pseudomonas aeruginosa* aetiology of pneumonia and a history of prior infection with *Pseudomonas* (OR 19.20, 95% CI 11.71–31.50) or tracheostomy (OR 6.95, 95% CI 2.87–16.85), and between *Mycobacterium tuberculosis* infection and malnutrition (OR 5.14, 95% CI 2.21–11.93) [5]. Broad-spectrum antibiotic use was associated with increased mortality risk (OR 3.8, 95% CI 2.5–5.9), a significant increase in length of hospital stay, greater cost and *Clostridium difficile* infection in another study recently published in the *European Respiratory Journal* [6].

Prof. Blasi concluded that improved infection control, widespread implementation of vaccination and reduction of antimicrobial consumption are efficient strategies to avoid development of antibiotic resistance.

Murat Akova, in his review "How to link antimicrobial and diagnostic stewardship", highlighted N. Fishman's data from the Hospital of the University of Pennsylvania (Philadelphia, PA, USA) suggesting that antimicrobial stewardship (AMS) is a key component of a multifaceted approach to prevent emergence of antimicrobial resistance [7]. This is a result of patients' and healthcare workers' proper education, rapid diagnosis and infection control, use of vaccines, and development of strategies to minimise antimicrobial resistance.

Various authors recommend using antibiotics 1) in a timely fashion (delay in antimicrobial therapy increases mortality), 2) appropriately (inappropriate therapy leads to higher mortality) and 3) per pharmacokinetic/pharmacodynamic parameters, and 4) to de-escalate at the earliest opportunity and 5) to discontinue as soon as possible [8–16]. Several studies showed a strong positive correlation between antibiotic use and resistance [17]. Using microbiological rapid diagnostic tests, such as multiplex immunoassays, would optimise treatment and reduce unnecessary prescription of antibiotics by as much as 30–50% in Europe and the USA [18–20].

The report by KLEIN *et al.* [21] on antibiotic use in 76 countries over 16 years showed that the antibiotic consumption rate in low- and middle-income countries has been growing, and in some countries exceeded levels typically observed in high-income countries. Dr Akova underlined several necessary actions in the global fight against antimicrobial resistance: improved sanitation, increased access to clean water, good governance with increased public healthcare funds and a regulated private health sector [22].

Obtaining necessary and reliable rapid diagnostic tests is problematic due the impossibility of bacterial specific detection in 62% cases [23], bacterial–viral mixed infection in 7–10% cases [24] and prescription of antibiotics in viral CAP (41% cases) [25] prior to specific diagnostics [26]. Several studies have demonstrated the important role of procalcitonin [27–30] and C-reactive protein [27] as biomarkers to

guide antibiotic therapy. WITTMANS [31] reports a positive association between the extent of microbiological testing and antibiotic alteration, defined as a narrowing of the antibiotic spectrum, switching to a different class of antibiotics or from dual to monotherapy and discontinuation of antibiotic treatment. Thus, improved targeted diagnostic tests in terms of accessibility and convenient use may lead to antibiotic avoidance [32].

Herman Goossens, in his presentation “The new era of diagnostics: will it ever start?”, emphasised that diagnostic tests affect around 60–70% of all clinical decisions [33] and account only for 0.8% of total healthcare expenditure in Europe [34]. Nowadays, medical activities require modern mobile multifunctional outpatient devices, which are easy to use and may provide an accurate, reliable diagnosis. Rapid diagnostic tests are more frequently used in clinical trials; however, their use faces many problems: unclear function and performance characteristics, a schism between pharmaceutical and diagnostic companies, unclear exploitation, regulatory blind spots, and demand of pharmaceutical companies to perform tests outside of microbiology labs. Performance characteristics of rapid diagnostic tests to guide narrow-spectrum antibiotics depend on the disease and targeted organism, on the prevalence of the disease, and on how the test and results will be used. New rapid tests are still being confronted with detection limits that are higher than standard amplification-based tests. The current diagnostic business model, focussed on technology used, laboratory activity measures and complexity indicators, is antiquated. Psychological, social, economic, ethical and organisational barriers prevent the uptake and development of diagnostics for AMS [35–38].

Prof. Goossens concluded that in order to reach the desired “golden age” of diagnostic testing, a consensus is necessary regarding a set of needs and the technologies required to satisfy those needs.

In the final presentation of this session, Keertan Dheda gave the definition of AMS as minimising the use of antibiotics through organised programmes, thus improving safety and quality of patient care by reducing the emergence and spread of MDR [39]. The evidence of AMS effectiveness was demonstrated in several studies on reduction in use of antibiotics. Pooled percentage change of total antimicrobial consumption after the implementation of AMS programmes was -19.1% (95% CI -30.1 – -7.5%), there was a decrease of disease burden in terms of colonisation and infection with MDR pathogens, and reduced mortality [40–43].

An expert consensus approach was used to develop a set of core elements for global hospital AMS: 1) hospital management leadership (leadership commitment), 2) accountability and responsibilities (single leader and defined roles), 3) expertise in infection management, 4) education and practical training, 5) actions driving responsible antimicrobial usage, 6) monitoring and surveillance, and 7) reporting and feedback. The experts recommend a combination of front- and back-end strategies using an AMS team. Front-end strategy makes antibiotics available through an approval process and back-end strategy reviews antibiotics after they are prescribed.

In conclusion, bacterial resistance is an international emergency and implementing AMS is a necessity; the scientific evidence is there and the time for action is now [44].

Recent developments and future perspectives in the diagnosis and treatment of tuberculosis

The aim of this session was to identify new therapeutic approaches for two categories of tuberculosis (TB) patients at increased risk: those with HIV co-infection and those with MDR/extensively drug-resistant (XDR)-TB.

François-Xavier Blanc reviewed some of the models of integrative care for patients with TB and HIV/AIDS. He discussed the three models of TB and HIV/AIDS services: standalone services with TB and HIV linked by referral, partially integrated services, and fully integrated services.

The most important identified areas requiring TB-HIV integration were 1) testing and counselling for HIV in all patients with TB, 2) intensified case finding for TB in HIV infected patients, 3) isoniazid preventive therapy for HIV-positive patients that screen TB negative, 4) the moment of antiretroviral therapy (ART) initiation for all TB-HIV co-infected patients, 5) cotrimoxazole therapy for TB-HIV co-infected patients, 6) enhanced retention strategies including the post-test counselling and use of community-based outreach workers, and 7) enhanced ART and TB treatment adherence strategies including the use of community care workers for adherence support and community-based management of selected patients [45].

The objectives of TB/HIV integrative departments are 1) to decrease TB and HIV transmission, 2) to decrease morbidity and mortality from HIV and TB or from other HIV-related illnesses, 3) to improve the efficiency of healthcare services, and 4) to create a patient-centred approach for management of co-infected patients. Since 2011, integrative care models have focussed on screening for TB symptoms,

with an emphasis on cough. Screening for cough is carried out whenever a patient enters a medical unit, in the reception area [46]. HIV diagnosis, staging and other services are also offered in every clinic service delivery area.

ART supply is offered in other dedicated TB/ART service areas with the exception of prevention treatment for mother to child transmission included in ante-natal services. TB diagnosis and treatment are given in the TB/HIV service area.

Dr Blanc underlined the necessity of a fully integrated data management system, adopting the approach of “one patient, one appointment, one file and one data management system”.

People living with HIV in resource-constrained settings should be screened with a clinical algorithm in order to quickly identify those at high risk for TB. Patients reporting symptoms such as current cough, fever, weight loss or night sweats should be further evaluated for TB and other diseases. Persons living with HIV who screen positive for TB should undergo a specific Xpert MTB/RIF test as a primary diagnostic test. Xpert MTB/RIF assay is the only World Health Organization (WHO)-recommended diagnostic test that simultaneously detects mycobacterial infection and rifampicin resistance and is suitable for use at lower levels of the health system [47]. People who are unlikely to have active TB should be offered treatment for presumed latent TB infection [47].

ART initiation for those with a concomitant HIV-TB diagnosis is recommended to be offered as soon as possible and within 8–12 weeks of the TB diagnosis. The evidence reviewed for guidelines [48] suggests that individuals with a CD4⁺ cell count <50 cells per mm³ should be offered ART as soon as possible, within 2 weeks after TB treatment was started. This recommendation can be extended to those with a CD4⁺ cell count <200 cells per mm³ as this has been proven to reduce mortality. Evidence does not support early initiation of ART in individuals with central nervous system TB [49, 50].

Integrated TB/HIV care remains challenging. Further investments must be made to minimise the danger of nosocomial transmission of TB in HIV-infected patients. TB/HIV centres should have a patient-centred orientation with focus on treatment adherence in order to avoid treatment failure and relapse. All efforts must be done to maintain confidentiality for all data. Electronic tools, like electronic directly observed treatment, can be an alternative to face-to-face contacts in instances where geographical distance is an important factor. and should be used [48].

The next speaker, Carole Mitnick, presented the clinical trial landscape for MDR/XDR-TB, reviewing the current evidence and future perspectives. The cardiac safety of concomitant use of bedaquiline and delamanid was demonstrated in several trials focussing on the effect of these drugs on the QT interval. The results of the trials showed no additive effect of the two drugs on the corrected QT interval by Fredericia [51]. Another phase III clinical trial (Nix-TB) that enrolled patients with XDR-TB who had failed or were intolerant to MDR-TB regimens, evaluated the safety and efficacy of pretomanid, bedaquiline and linezolid [52]. The rate of favourable outcomes was 40 (88.9%) out of 45, with a 95% confidence interval of 75.9–96.3%. Most of the treatment-emergent adverse events were due to linezolid, and included peripheral neuropathy, anaemia, nausea, vomiting and headache [53].

A study by O'DONNELL *et al.* [54] reviewed the effects of switching from antiretroviral efavirenz-containing regimens to twice-daily nevirapine in association with bedaquiline in patients with drug-resistant TB and HIV co-infection, highlighting a signal of low adherence to the new ART regimen leading to HIV viral failure, which could compromise the TB-specific benefits of bedaquiline in these patients. The need to establish whether kanamycin can safely and effectively be replaced by amikacin in new shortened regimens (without bedaquiline or delamanid) was emphasised in other studies reviewed in this session. Additional trials are also needed to compare shortened oral regimens with bedaquiline regimen.

Dr Mitnick's conclusions underlined the substantial progress with the three new drugs approved in the last 7 years but stressed the need to improve trial quality and to include vulnerable subgroups (*e.g.* pregnant women, substance users and homeless people). Reporting serious adverse events is critical for all drugs, not just for the “new” ones.

Cathy Hewison reviewed several observational studies on the efficacy and safety of new drugs for MDR/XDR-TB. The endTB cohort is an observational trial focussing on prospective data collection and having the advantage of including patients not enrolled in randomised clinical trials (RCTs). This was the largest multicentric prospective study, which included 2727 patients from 17 countries (heterogenous population) with the purpose of determining the safety and efficacy of bedaquiline- or delamanid-containing regimens for MDR-TB, according to WHO recommendations. Patients received a regimen containing bedaquiline and/or delamanid between 1 April 2015 and 31 March 2018. Overall, there is no evidence of any major safety issue with either delamanid or bedaquiline. Of the 1109 patients included in the final analysis, 943

(85%) achieved sputum culture conversion within 6 months. Sputum culture conversion was defined as two consecutive negative cultures for TB, collected ≥ 30 days apart. Comparable sputum culture conversion rates were reported in other studies with bedaquiline (78%) [55], delamanid (88%) [56] or both (74%) [57].

Managing drug-resistant tuberculosis: from new guidelines to clinical practice

Giovanni Battista Migliori presented the new recommendations of the American Thoracic Society, the Centers for Disease Control and Prevention, the ERS and the Infectious Diseases Society of America guidelines for MDR-TB. These guidelines were developed in the last 3 years by a team of experts including specialists in pulmonary medicine, infectious disease, pharmacokinetics, paediatrics, primary care and public health after multiple face-to-face meetings and weekly telephone calls. Strength of recommendations was formulated after reviewing all evidence, using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. For each recommendation, the guideline panel considered and agreed on the quality of the evidence, balance of desirable and undesirable effects of compared alternative management options, and possible extent of resources. “Strong” and “weak” recommendations were defined for patients, clinicians and policy makers.

According to the guidelines, an effective MDR-TB treatment regimen should combine at least five drugs in the intensive phase and four drugs in the continuation phase of treatment. The recommended duration of intensive phase of treatment is 5–7 months after culture conversion. The recommended total treatment duration is 15–21 months after culture conversion for MDR-TB, and 15–24 months for XDR-TB and pre-XDR-TB.

Available oral drugs for MDR-TB treatment, in the order of strength of recommendations, are a later generation of fluoroquinolone (levofloxacin or moxifloxacin), bedaquiline, linezolid, clofazimine, cycloserine, ethambutol (when other more effective drugs cannot be added to achieve a total of five drugs in the regimen) and pyrazinamide (in regimens for patients with isoniazid-resistant TB). However, delamanid has a conditional recommendation according to the 2019 WHO Consolidated Guidelines of Drug-Resistant Tuberculosis Treatment for patients aged ≥ 3 years on longer regimens. Injectables were also reviewed in the guidelines.

Other discussions referred to the necessity of consultation with a TB expert, a clinical service also active within the Global TB Network. Focus on rapid diagnosis and precision treatment includes newer genomic approaches such as the use of an automated Xpert drug resistant cartridge and the use of point-of-care portable battery-operated genomic tools (e.g. Xpert Edge and Xpert Omni) [58].

Therapeutic dose monitoring in the treatment of MDR-TB is used to identify patients with drug absorption problems, thereby needing dose adjustments in order to prevent poor response to TB treatment despite adherence.

Hospital admission requirements in Europe include clinical expertise on TB and MDR/XDR-TB management, quality-controlled laboratories, respiratory isolation capacity, infection control capability, and a patient-centred approach that includes psychological support and social services after discharge when needed [59, 60].

The guidelines support good management practices, recommending a TB consilium approach, prompt use of rapid diagnostic methods and drug sensitivity test-based regimens, management of adverse events, and adequate infection control [61–63].

Therapeutic breakthrough Year in review

The aim of this session was to highlight the key therapeutic developments that are likely to influence care and improve outcomes for adults and children with respiratory diseases. These therapies also have impact on long-term evolution of the underlying diseases, and on the number of future exacerbations and future respiratory infections.

The use of triple therapy *versus* dual bronchodilation and long-acting β -agonists (LABA)/inhaled corticosteroids (ICS) in COPD [64, 65] was reviewed by Mario Cazzola in the light of newly accumulating evidence from a couple of recently published network meta-analyses. Prof. Cazzola emphasised the importance of effectiveness data collected in real-life studies for the positioning of new therapies [66] and discussed the use of meta-analysis as a means of synthesising evidence across RCTs [67]. Compared to dual therapies, such as a LABA/long-acting muscarinic antagonists (LAMA) or LABA/ICS, triple therapy (ICS/LABA/LAMA) reduced the rates of moderate to severe exacerbations, and improved lung function and quality of life [68–72]; however, due to the increased risk of pneumonia for ICS-containing regimens [68] and to the fact that blood eosinophil count was found to be a significant effect modifier of triple

therapy in the prevention of exacerbations [69, 71], the patients that are likely to benefit most from triple therapy are those with blood eosinophils counts ≥ 300 cells per μL [69, 73].

Keith Grimwood reviewed the therapeutic breakthrough of the year in the field of cystic fibrosis (CF) by presenting the results of the OPTIMIZE clinical trial [74]. The aim of this study was to assess whether the addition of azithromycin to tobramycin inhalation solution in children with CF and new-onset *P. aeruginosa* infection will reduce the risk of exacerbation, thus delaying *P. aeruginosa* recurrence. This was a multicentre, randomised, double-blind, placebo-controlled trial of 18 months duration, which included clinically stable children with CF, aged 6 months to 18 years, with new positive cultures of *P. aeruginosa* within the previous 40 days. The risk of pulmonary exacerbation was reduced by 44% (hazard ratio 0.56, 95% CI 0.37–0.83; $p=0.004$) and weight increased by 1.27 kg (95% CI 0.01–2.52 kg; $p=0.046$) in the azithromycin group as compared with the placebo group. No significant differences were seen in microbiological or other clinical or safety endpoints. These data support the use of azithromycin as a therapeutic option for children with CF and early *P. aeruginosa* infection, with no major safety concerns over the long-term use of azithromycin.

The therapeutic breakthrough of the year in pulmonary rehabilitation was presented by Elena Gimeno-Santos. A number of interventional studies on physical activity in patients with COPD published in the last 4 years [75–78] were reviewed. Physical activity is a complex and multifactorial behaviour [79], the evidence on its nonphysiological determinants being scarce. Urban Training is a multicomponent behavioural intervention that consists of physical training using walkable trails, located and adapted to the social environment of the patient, and other optional components for feedback, motivation, information and support. Dr Gimeno-Santos presented the results of a study aiming to assess the long-term efficacy and effectiveness of the Urban Training intervention to increase physical activity in COPD patients [80]. This was a RCT allocating COPD patients from primary and hospital settings 1:1 to usual care or Urban Training. Efficacy analysis (patients classified as adherent to the assigned intervention) showed an improvement in physical activity (steps per day) in the Urban Training group. Effectiveness analysis (patients completing the study at 12 months, including unwilling and self-reported nonadherent patients) showed no differences between groups. Leg muscle pain during walks was more frequently reported in Urban Training than usual care, without differences in any of the other adverse events. Dr Gimeno-Santos concluded her talk by briefly presenting other recently published studies on the duration, implementation and determinants of physical activity in COPD [81–84].

Paul Corris gave an overview on the role of extracorporeal assistance as a bridge and as support during lung transplantation. In the context of a constant increase in the number of organ donors and lung transplants, and improved pre-transplant treatment and noninvasive support for advanced disease, extracorporeal life support (ECLS) has become extremely relevant for patients referred for lung transplant procedure. Prof. Corris highlighted that ECLS has an established indication as a bridge to transplant in patients who have been evaluated and accepted for this procedure, and has potential indications in highly selected cases: 1) bridge to transplant decision in potentially eligible patients who have not yet been evaluated, and 2) bridge to recovery in patients with untreated or undertreated pulmonary hypertension or with a treatable cause of right ventricle failure [85, 86]. ECLS has also become an established strategy for the support of patients with grade 3 primary graft dysfunction after lung transplantation. ECLS is contraindicated in patients with end-stage disease without a realistic chance for recovery [85].

Concluding remarks

The authors of this article wanted to highlight the importance of new therapeutic interventions in respiratory infections and TB. We also hope that this summarised information will be a useful tool for the readers to inform their daily practice clinical decisions.

Conflict of interest: None declared.

Author contributions: C. Chichirelo-Konstantynovych reported on the session “Fighting antimicrobial resistance: from prevention to antimicrobial stewardship”, C. Calarasu reported on the sessions “Recent developments and future perspectives in the diagnosis and treatment of tuberculosis” and “Managing drug-resistant tuberculosis: from new guidelines to clinical practice”, and S. Frent reported on the session “Therapeutic breakthrough Year in review”. All authors reviewed and agreed on the content of the article.

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