Editorial

Respiratory infection: insights from Assembly 10 of the European Respiratory Society 2017 Annual Congress

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Introduction

The European Respiratory Society Annual Congress featured exciting research studies in the topic of respiratory infections. In this article, we highlight four important studies featured at the congress and discuss their impact on the field of respiratory infections.

An imbalanced airway microbiota correlates with greater peak flow decline in virus-induced asthma exacerbations

Wong *et al.* (1) examined the airway microbiota during naturally-occurring colds and experimental rhinovirus (RV) infection in asthma and correlated microbiota community composition with clinical symptoms and peak flow decline. Two independent studies were performed. The first study included 46 asthmatic subjects who experienced naturally-occurring colds. Induced sputum samples were obtained before and during cold. The second study was conducted with 11 asthmatic and 12 healthy subjects, who were experimentally infected with RV-16. Bronchoalveolar lavage (BAL) was obtained at baseline and post-infection. Sputum and BAL samples subsequently underwent *16S rRNA* gene sequencing and microbiota community analysed. In both studies, increased *Neisseria sp*. relative abundance following cold/RV-16 infection was significantly associated with greater peak expiratory flow (PEF) decline (natural cold: R^2=0.13, P<0.05; RV-16: R^2=0.41, P<0.05. P values adjusted using false discovery rate). In contrast, increased *Prevotella spp*. relative abundance correlated with lower PEF decline (natural cold: R^2=0.14, P<0.05) and upper respiratory tract symptom score (RV-16: R^2=0.56, P<0.005) respectively.

The authors concluded that an imbalanced microbiota dominated by *Neisseria sp*. was associated with greater PEF decline both naturally-occurring cold and experimental RV-16 infection, whilst a predominantly 'commensals' (*Prevotella spp*.) community was associated with less PEF decline and symptoms.

These findings appear to support the hypothesis that dysregulation of the microbiota may result in greater degree of airway inflammation and clinical outcomes during virus-induced exacerbations. However, the key question remains whether if the airway microbiota actively contributes to the level of airway inflammation or simply reflects the local inflammatory state. *Prevotella spp*. have been shown *in vitro* to induce weaker TLR-4 dependent response than other 'potential' pathogens such as *Haemophilus influenzae* (2). In contrast, *Neisseria sp*. have not been classically associated with lower respiratory tract infections and further work is needed to accurately identify the *Neisseria sp*. detected in the current study and evaluate if it is capable of inducing airway inflammation.

Time to blood culture positivity as a predictor of clinical outcomes and severity in adults with bacteremic pneumococcal pneumonia

Previous evidence suggests that high bacterial load is associated with worse clinical outcomes in invasive pneumococcal pneumonia (3), suggesting that determination of pneumococcal load may have a clinical utility. Previous studies also suggest that time to positivity (TTP) of blood culture may provide early clues about microorganisms involved and the source of bacteremia. As TTP is inversely associated with blood bacterial load and it may represent a surrogate marker of more severe disease and a potential early predictor of mortality.

Cillóniz *et al.* (4) investigated the association between the TTP of blood culture with clinical outcome and severity of pneumococcal bacteremic pneumonia. They carried out a prospective observational study including all adults consecutively admitted between 2003 to 2015 with a diagnosis of community-acquired pneumococcal pneumonia to the Hospital Clinic of Barcelona, Spain, an 800-bed third-level hospital covering an urban population of 540,000 inhabitants. A total of 278 cases of bacteremic pneumococcal pneumonia were analyzed, median age 62 years (46–79 years). Fifty-one percent of the cases were severe with a pneumonia severity index (PSI) IV–V. Twenty-one (8%) died within 30-days of admission. The analysis of the TTP showed that the first quartile of the TTP (9.2 h) was the best cut-off for differentiating two groups of patients at risk, early (TTP <9.2 h) and late (TTP ≥9.2 h) detection groups (AUC 0.66, 95% CI: 0.53–0.79). Early TTP was associated with a statistically significant risk of invasive mechanical ventilation (18% *vs.* 6%, P=0.007), longer length of hospital-stay (12 *vs.* 8 days, P<0.001), higher in-hospital mortality (15% *vs.* 4%, P=0.010), and 30-day mortality (15% *vs.* 5%, P=0.018). After adjustment for potential confounders, regression analyses revealed early TTP as independently associated with high risk of invasive mechanical ventilation (OR 4.60, 95% CI: 1.63–13.03), longer length of hospital stay (β 5.20, 95% CI: 1.81–8.52), higher in-hospital mortality (OR 5.35, 95% CI: 1.55–18.53), and a trend to higher 30-day mortality (OR 2.47, 95% CI: 0.85–7.21) to be a contributing factor.

The authors concluded that a TTP of blood culture shorter than 9.2 h in patients with bacteremic pneumococcal pneumonia is independently associated with a more severe disease. TTP is an easy to obtain parameter available in all Microbiology laboratories that could provide useful prognostic information and may help clinicians to identify patients at risk of worse outcome that could benefit from more aggressive early management.

Exhaled breath metabolomics for the diagnosis of pneumonia in intubated and mechanically ventilated intensive care unit (ICU)-patients

The diagnosis of hospital-acquired pneumonia remains challenging. Clinical, radiological and microbiological criteria lack sensitivity and specificity (5-7), resulting in over-prescription of antibiotics. An ideal diagnostic test would be objective, non-invasive, and clinically available at the bedside, enabling rapid exclusion of the presence of pneumonia and, thus, withholding certain patients from receiving antimicrobial treatment unnecessarily. Exhaled breath contains metabolites in the gas phase called volatile organic compounds (VOCs) that are produced by the host and bacteria.

van Oort *et al.* (8) carried out a prospective, single centre, cross-sectional cohort study in the ICU of the Academic Medical Centre Amsterdam. Consecutive patients with an expected duration of mechanical ventilation of more than 24 hours were included. Exhaled air samples were collected within 24 hours after ICU admission, as well as clinical pneumonia scores (defined as *none*, *possible*, *probable* or *definite*) and endotracheal aspirates.

Of 93 patients, 12 patients were classified as probable pneumonia, 21 as possible pneumonia and 13 had colonized airways. Forty-seven patients did not have colonized airways or pneumonia and were regarded as controls. One hundred and forty-five VOCs were found in the breath of all patients. VOCs were selected for partial least square discriminant analysis (PLS-DA) by a P value <0.05 and an AUROC >0.7. Eleven (7.6%) VOCs were significantly lower in breath of cases *vs.* controls (P<0.05). 1-Propanol and hexafluoroisopropanol showed the highest AUROC of response 0.83 (95% CI: 0.72–0.93) and 0.82 (95% CI: 0.72–0.93).

PLS-DA classified patients with modest accuracy (AUROC: 0.73, 95% CI: 0.57–0.88) after leave-one-out cross-validation. Fifty-two VOCs (35.9%) were significantly lower in patients with colonized airways *vs.* patients without colonization (P<0.05); 7 of these showed a P value <0.001. The AUROC for this PLSDA model was 0.69 (95% CI: 0.57–0.82).

These data suggest that VOCs in exhaled breath could be used to discriminate between intubated and mechanically-

ventilated patients in ICU with CAP or HAP and ventilated patients without pneumonia with moderate to good accuracy. 1-Propanol was found to be consistently lower in patients with pneumonia and, independently, also in patients with colonized airways, and might be a marker for bacterial presence and growth.

Bedaquiline (BQ)-containing regimen at the programmatic level for multidrug-resistant tuberculosis (MDR-TB): preliminary results

MDR-TB has become a global threat for TB control. It has been estimated that in 2015 there were around 480,000 new MDR cases, 100,000 rifampicin resistant (RR-TB) cases (9). Of all MDR cases, around 10% are already cases of extensively drug-resistant tuberculosis (XDR-TB), which by definition, beyond being resistant to Isoniazid and rifampicin, are also resistant to at least one fluoroquinolone and at least one second-line injectable drug. Given that TB should be treated with at least four different antituberculosis drugs to avoid the selection of natural mutants, the therapeutic options for treating these patients are limited. In addition to being exposed to more toxic, expensive and lengthier regimens, treatment success for MDR-TB and XDR TB patients treated with available second line regimens are considerable lower than for susceptible TB: 52% for MDRTB (2013 cohort) and 28% for XDR-TB (2013 cohort) compared to 83% of drug susceptible TB (2014 cohort) (9). In 2013, two new anti-tuberculosis drugs, BQ and delamanid, were marketed, and soon after were introduced in many countries.

Borisov and colleagues presented a study aimed to evaluate the safety and effectiveness of bedaquiline-containing regimens in a large, retrospective, observational study conducted in 25 MDR-TB reference centres located in 15 different countries, covering five continents (10). They included patients who started treatment between January 1st, 2008 and August 30th, 2016 (11). BQ had to be administered within an individualized TB regimen which was administered following results of drug susceptibility testing. BQ was prescribed under programmatic conditions, expanded access and compassionate use following local guidelines.

A total of 428 culture-confirmed MDR-TB cases were included in the analysis (61.5% were male, and 22.1% HIV-positive). Of all patients, 45.6% fulfilled the definition of XDR-TB. MDR-TB cases were exposed to BQ for a median of 168 days [interquartile range (IQR): 86–180 days] (10). Treatment regimens included several other drugs, such as linezolid, moxifloxacin, clofazimine and carbapenems (82.0%, 58.4%, 52.6% and 15.3% of cases, respectively) (10). Sputum smear and culture conversion rates in MDR-TB cases were 63.6% and 30.1%, respectively at 30 days; 81.1% and 56.7%, respectively at 60 days; 85.5% and 80.5%, respectively at 90 days; and 88.7% and 91.2%, respectively at the end of treatment (10). The median (IQR) time to smear and culture conversion was 34 days (30–60 days) and 60 days (33–90 days) respectively (10). Out of 247 culture-confirmed MDR-TB cases completing treatment, 71.3% achieved success (62.4% cured; 8.9% completed treatment), 13.4% died, 7.3% were lost to follow up and 7.7% did not culture-convert (10). BQ was interrupted due to adverse events in 5.8% of cases. The most frequent adverse events in the study were nausea (31.5%), peripheral neuropathy (23.3%) and otovestibular toxicity (23.3%) (11). Ten percent of patients experienced QTcF prolongation >500 ms. A single case died, having electrocardiographic abnormalities that were probably non- BQ related (11).

The results of this retrospective evaluation show that bedaquiline-containing regimens achieved high culture conversion and treatment success rates (11). This study also shows that patients put under BQ containing regimens are well tolerated and safe, as can also be concluded from other available evidence (12). It is important to continue monitoring safety and effectiveness of new drugs under programmatic conditions. Larger phase IV pharmacological surveillance-based evaluations will allow to elucidate the magnitude of the concerning cardiotoxic adverse events which have been associated with the use of bedaquiline (13). Further research that can provide further evidence of its best use within second line drug combinations is also needed. Although the advent of new antituberculosis drugs has been a game changer for many patients with DR-TB, the quest for new drugs and the expansion of use of repurposed drugs (linezolid, carbapenems, among others) (14,15) continues to be a priority for TB control.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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