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EDITORIAL

Legionella spp. in acute exacerbations of chronic obstructive pulmonary disease: what is the evidence?

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Acute exacerbations are a frequent complication during the clinical course of chronic obstructive pulmonary disease (COPD). A recent monograph dealing with COPD exacerbations demonstrated that virtually all issues related to the management of acute exacerbations remain unsettled and controversial, including the definition, aetiology, microbial patterns, and antimicrobial treatment of this condition [1]. This is of particular concern in view of the high burden of this complication on public health resources.

With regards to microbial patterns and their possible involvement in the aetiology of acute exacerbations, it is a common view that *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the leading pathogens. Viruses have also been shown to cause acute exacerbations, frequently working as copathogens together with bacterial pathogens [2–4]. Only recently, important extensions of this concept have been provided. Firstly, evidence has grown that microbial patterns may move towards an increasing incidence of Gram-negative enterobacteriaceae and *Pseudomonas aeruginosa* in more advanced stages of COPD [5]. Similar observations were made in severe exacerbations requiring ventilatory support [6, 7]. Secondly, several studies found evidence of *Chlamydia pneumoniae* playing a role as a pathogen or copathogen in acute exacerbations [7–10]. Finally, new challenges emerge from drug-resistant micro-organisms [11]. Overall, bacterial pathogens were found to be present in approximately 50%, and atypical bacterial and viral pathogens in an additional 25% of cases. The presumptive aetiology in the remaining 25% of cases remained unclear [12].

In this issue of the *European Respiratory Journal*, LIEBERMAN *et al.* [13] present data on a large population, hospitalized with acute exacerbations of COPD, which provides evidence for the first time for *Legionella* spp. infection as a potential underlying pathogen in as many as 16.7% of cases [13]. These pathogens were detected serologically by an indirect immunofluorescence method using an in-house kit and applying strict criteria of seroconversion in paired samples. What is the meaning of these findings: should *Legionella* spp. be included in the list of potential pathogens of acute exacerbations of COPD and should antimicrobial treatment regimens, targeted against these pathogens be designed?

Up to now, *Legionella* spp. have not been reported to form part of the microbial patterns of acute exacerbations. This may simply reflect the principal methodological problems of diagnosing such infections. *Legionella* spp. can only rarely be cultured from sputum, and bronchoalveolar lavage fluid is usually not suitable in COPD patients with acute exacerbations. In fact, performing bronchoalveolar may prove harmful in these patients. Antigen detection, although highly specific and sensitive, exclusively covers infections by *Legionella pneumophila* serogroup 1. A paired serum for serology is only rarely obtained, mainly because hospitalization is not usually required for >2 weeks. Moreover, usual serology only covers *Legionella pneumophila* serogroup 1. Using this approach, LIEBERMANN *et al.* [13] would only have detected Legionella infections in 4% of cases. Thus, the study confirmed that a vigorous search usually results in unexpected findings. In fact, they provided much indirect evidence that these findings are truely valid.

Legionellosis is known to cause not only pneumonia but also an acute illness, that of Pontiac fever. Fever and chills associated with myalgia, malaise, and headache are the leading symptoms. The symptoms develop progressively. A dry cough may occur as well as minor respiratory symptoms such as sore throat, coryza, and sore eyes. In addition, neurological symptoms have been reported [14]. These clinical features of Pontiac fever are compatible with those described in the report here. No patient had an abrupt onset of exacerbation, and all systemic symptoms were more prevalent in patients with evidence of Legionella infections, however due to the limited number of patients studied the difference was only significant for myalgia/arthralgia. Thus, there is considerable evidence that the group seroconverted for *Legionella* spp. truely forms a clinically distinguishable group of its own.

Conversely, serology as an indirect diagnostic tool does not provide irrefutable evidence for the involvement of a microbial pathogen. This is particularly true for an in-house kit which is not externally validated. Nevertheless, there are several hints which point at the validity of the serological kits as explained by LIEBERMAN *et al.* [13] in the discussion. One of the most important is the low rate of false-positive results

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in the control group. The rate of 3% compares favourably to serological studies of *Chlaymdia pneumoniae* in COPD and asthma [15, 16].

The rate of 16.7% of infections with *Legionella* spp. seems to be excessive. In fact, LIEBERMAN *et al.* [13] cannot exclude the presence of possible epidemic outbreaks during the study period. However, the diversity of *Legionella* spp. identified argues against the presence of such a confounder. Again, the documented figure is comparable to those figures reported for *Chlamydia pneumoniae* [7–10].

Overall 65% of patients with seroconversion for *Legionella* spp. had evidence for an additional pathogen, including seroconversion for viruses, bacterial isolates in culture, and, *Mycoplasma pneumoniae*. Dual infections of viruses and bacteria in acute exacerbations have been repeatedly documented, although the subject of the interrelationship of viral and bacterial pathogens has not been clarified satisfactorily [17–19]. "Atypical" pathogens may act as independent pathogens but may also simply favour bacterial superinfection and overgrowth. In any case, the demonstration of multiple pathogens must not be interpreted against a causal role of any "atypical" pathogen, including *Legionella* spp.

In general, there was some evidence for Legionella infections causing a more severe exacerbation than the other pathogens. Whereas the severity of COPD as assessed by forced expiratory volume in one second, the type of exacerbations according to ANTHONISEN *et al.* [20], and the rate of patients requiring admission into intensive care were similar, oxygenation was worse in the Legionella group and there was a trend for a higher rate of patients requiring ventilatory support (15% *versus* 9%) and a higher mortality (5% *versus* 2%). These preliminary observations would fit with the experience that Legionella infections tend to cause more severe illness than the majority of other respiratory pathogens [21].

The need for designing an antimicrobial regimen which covers *Legionella* spp. would impose a significant challenge to clinicans. Macrolides and probably also the new ketolides are not an ideal choice because of the limited activity against *Haemophilus influenzae*. In the era of a worldwide spread of microbial resistance, the use of fluoroquinolones should be confined to patients with defined risk factors [22]. At present, however, there is no such need. Firstly, the effect of antimicrobial treatment in acute exacerbations is probably confined to the subgroup of patients with ANTHONISEN *et al.* [20] type-1 exacerbations and those with defined risk factors according to BALL *et al.* [23] and other studies (cardiopulmonary comorbidity and frequent hospitalizations) [12, 20, 24, 25]. Even then, the cure rate using placebo is high. Secondly, the study was not designed to examine the effect of antimicrobial treatment directed against *Legionella* spp., and certainly does not even allow for preliminary conclusions. Thus, only controlled studies can provide a valid estimate about antimicrobial treatment effects in patients with acute exacerbations and evidence of Legionella infections.

To conclude, the present study provides considerable evidence for *Legionella* spp. as pathogens involved in the aetiology of acute exacerbations of chronic obstructive pulmonary disease. However, the study awaits confirmation from future studies. The true impact of these pathogens in terms of incidence and outcome still remains uncertain. It must be assessed with priority, including diverse populations at risk. In the meantime, unless there is evidence of a local epidemic outbreak of Legionellosis, there is no reason to include *Legionella* spp. as an additional target in any empirical antimicrobial strategy.

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