

## CORRESPONDENCE

# Serological evidence of *Legionella* species infection in acute exacerbation of COPD

To the Editor:

We are concerned about the alleged aetiological role of *Legionella* spp. in acute exacerbations of chronic obstructive pulmonary disease (AECOPD), as has been recently suggested by both LIEBERMAN *et al.* [1] in their study published in the *European Respiratory Journal*, and EWIG [2] in an editorial in the same issue [2]. To the best of our knowledge, the distinctive results of the study by LIEBERMAN *et al.* [1] have not been reported in any other aetiological survey of AECOPD. A recent, in-depth review of bacterial infection in chronic obstructive pulmonary disease, by a worldwide expert on this subject, does not even mention any role for *Legionella* spp. in AECOPD [3]. Although attachment to bronchial cells is the first step of *Legionella* spp. infection, it is well known that the primary pathogenic process takes place at the macrophage cell level. There are no consistent data that might favour a theoretical isolated infectious bronchitis without any pneumonic involvement [4]. In fact, *Legionella* spp. isolation remains the gold standard for diagnosing any form of Legionella infection [5]. An exhaustive review of AECOPD studies that have focused on the search of an aetiological agent by means of invasive procedures, such as bronchoscopic techniques, shows that *Legionella* spp. have never been identified until now. Moreover, the provided clinical data do not seem to correspond with the clinical syndrome of Pontiac fever.

Doubts about the validity of serological testing for a reliable diagnosis of Legionella infection can definitely be seen if the accumulated experience on these techniques during the last 25 yrs is reviewed. There are two well-known drawbacks of serology: low sensitivity, even for *Legionella pneumophila* serogroup 1 (<70%) [5], and a serious concern about specificity [6]. Specificity (~96–99%) has only been acceptably established for *L. pneumophila* serogroup 1. Cross-reactivity between *L. pneumophila* serogroup 1 and other serogroups and species has been consistently reported in the literature [7].

The risk of false-positive results should then not be neglected since the use of a completely nonspecific diagnostic method in a low prevalent disease, such as legionellosis, will, from a statistical point of view, undoubtedly increase the likelihood of false-positive reactions. This risk must be even higher when considering serology for non-*L. pneumophila* serogroup 1 infections and especially *Legionella* spp. other than *L. pneumophila* [8]. In fact, as EWIG [2] points out, if only *L. pneumophila* serogroup 1 had been evaluated, the incidence of alleged Legionella infection would have decreased to 4%. The concept of unreliable specificity

of immunofluorescent antibody (IFA) for diagnosing clinically relevant infections by Legionella is also supported by some studies. ANDERSEN *et al.* [9] found a clinically silent four-fold indirect IFA seroconversion in their prospective study on annual (3–5 yrs) serum specimens among 52 children, more than 20-yr old. More recently, a four-fold IFA asymptomatic seroconversion has also occasionally been observed in high-risk populations such as adult renal transplantation patients [10]. In a study by DOWLING *et al.* [11], 7% of their 89 receptors seroconverted during the 6 months after transplantation, without any clinical evidence of pneumonia. In a recent cohort study, after an outbreak of travel-associated Legionnaires disease and Pontiac fever, 3–6% of patients who were not ill showed immunoglobulin (Ig)G seroconversion or IgM seropositivity, respectively [12].

A variety of possible serological cross-reactions have been reported in the literature. Among them, some Gram-negative bacteria and anaerobic microorganisms, including *Pseudomonas*, *Proteus*, *Bordetella* and *Bacteroides fragilis*, may sometimes be incriminated in AECOPD [6]. Moreover, cross-reactions have also been reported with certain microorganisms that may be endemic or cause epidemic outbreaks in determined geographical areas, such as *Rickettsia conorii*, the agent of Mediterranean fever, *R. typhi*, the agent of murine typhus, *Coxiella burnetii*, and *Campylobacter* spp. [13–16]. Synchronous serological studies would perhaps have been appropriate. We could also speculate on a possible cross-reactivity of *Legionella* spp. with other less studied common human pathogens that share some similarities. For example, serological cross-reaction between *Capnocytophaga* spp. and *Legionella* spp. has been reported [17] and these periodontal bacteria seem to be frequently identified by polymerase chain reaction (PCR) assay in apparently periodontally healthy subjects [18]. In addition, *Helicobacter pylori* has shown cross-reactivity with *L. micdadei* [19]. This finding could be of interest if further studies confirm that preliminary report, since *H. pylori* seropositivity has been reported to be common both in chronic bronchitis [20] and bronchiectasis [21]. In fact, chronic bronchitis has been identified as a predictive factor of seropositivity for IgG antibodies to *H. pylori* [22].

In any case, if we accept that seroconversion means real infection, it is worth remembering that, in their outbreak case-control study, BOSUIZEN *et al.* [23] recently observed that control seroconverters did not show any statistically significant clinical difference when compared to nonseroconverters. Their results would suggest then that Legionella infection could

theoretically produce either pneumonia or just asymptomatic infection.

**J. Roig\***, **X. Soler<sup>#</sup>**, **C. Domingo<sup>†</sup>**, **G. de Celis<sup>+</sup>**

\*Pulmonary Division and <sup>†</sup>Dept of Internal Medicine, Hospital Nostra Senyora de Meritxell, Escaldes, Principality of Andorra. <sup>#</sup>Servei de Pneumologia, Hospital Germans Trias I Pujol, Badalona and <sup>+</sup>Servei de Pneumologia, Corporació Hospitalària Parc Taulí, Sabadell, Barcelona, Spain.

### References

- Lieberman D, Lieberman D, Shmarkov O, *et al*. Serological evidence of *Legionella* species infection in acute exacerbations of COPD. *Eur Respir J* 2002; 19: 392–397.
- Ewig S. *Legionella* spp. in acute exacerbations of chronic obstructive pulmonary disease: what is the evidence? *Eur Respir J* 2002; 19: 387–389.
- Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a State-of-the-Art review. *Clin Microbiol Rev* 2001; 14: 336–363.
- Andersen P. Pathogenesis of lower respiratory tract infections due to *Chlamydia*, *Mycoplasma*, *Legionella* and viruses. *Thorax* 1998; 53: 302–307.
- Roig J, Rello J, Yu VL. Legionnaires' disease: a guide to diagnosis and therapy. *J Respir Dis* 2002; 23: 229–234.
- Maiwald M, Helbig JH, Lück PC. Laboratory methods for the diagnosis of *Legionella* infections. *J Microbiol Methods* 1998; 33: 59–79.
- Wilkinson HW, Reingold AL, Brake BJ, McGiboney DL, Gorman GW, Broome CV. Reactivity of serum from patients with suspected legionellosis against 29 antigens of legionellaceae and *Legionella*-like organisms by indirect immunofluorescence assay. *J Infect Dis* 1983; 147: 23–31.
- Bornstein N, Janin N, Bourguignon G, Surgot M, Fleurette J. Prevalence of anti-*Legionella* antibodies in a healthy population and in patients with tuberculosis or pneumonia. *Pathol Biol (Paris)* 1987; 35: 353–356.
- Andersen RD, Lauer BA, Fraser DW, Hayes PS, McIntosh K. Infections with *Legionella pneumophila* in children. *J Infect Dis* 1981; 143: 386–390.
- Renoult E, Kessler M, Jonon B, Schmit JL. Significance of seroconversion against *Legionella* after renal transplantation: report of five cases. *Clin Nephrol* 1990; 33: 209.
- Dowling JN, Pasculle AW, Frola FN, Zaphyr MK, Yee RB. Infections caused by *Legionella micdadei* and *Legionella pneumophila* among renal transplant recipients. *J Infect Dis* 1984; 149: 703–713.
- Benin AL, Benson RF, Arnold KE, *et al*. An outbreak of travel-associated Legionnaires disease and Pontiac Fever: the need for enhanced surveillance of travel-associated legionellosis in the United States. *J Infect Dis* 2002; 185: 237–243.
- Raoult D, Dasch GA. Immunoblot cross-reactions among *Rickettsia*, *Proteus* spp. and *Legionella* spp. in patients with Mediterranean spotted fever. *FEMS Immunol Med Microbiol* 1995; 11: 13–18.
- Bernabeu-Wittel M, Pachón J, Alarcón A, *et al*. Murine typhus as a common cause of fever of intermediate duration. A 17-year study in the south of Spain. *Arch Intern Med* 1999; 159: 872–876.
- Musso D, Raoult D. Serological cross-reactions between *Coxiella burnetii* and *Legionella micdadei*. *Clin Diagn Lab Immunol* 1997; 4: 208–212.
- Boswell TC, Marshall LE, Kudesia G. False-positive *Legionella* titres in routine clinical serology testing detected by absorption with *Campylobacter*: implications for the serological diagnosis of legionnaires' disease. *J Infect* 1996; 32: 23–26.
- Chen S, Hicks L, Yuen M, Mitchell D, Gilbert GL. Serological cross-reaction between *Legionella* spp. and *Campylobacter* by using latex agglutination test. *J Clin Microbiol* 1994; 32: 3054–3055.
- Kimura S, Ooshima T, Takiguchi M, *et al*. Periodontopathic bacterial infection in childhood. *J Periodontol* 2002; 73: 20–26.
- Andersen LP, Espersen F. Immunoglobulin G antibodies to *Helicobacter pylori* in patients with dyspeptic symptoms investigated by the western immunoblot technique. *J Clin Microbiol* 1992; 30: 1743–1751.
- Caselli M, Zaffoni E, Ruina M, *et al*. *Helicobacter pylori* and chronic bronchitis. *Scand J Gastroenterol* 1999; 34: 828–830.
- Tsang KW, Lam SK, Lam WK, *et al*. High seroprevalence of *Helicobacter pylori* in active bronchiectasis. *Am J Respir Crit Care Med* 1998; 158: 1047–1051.
- Rosenstock SJ, Jorgesen T, Andersen LP, Bonnevie O. Association of *Helicobacter pylori* infection with lifestyle, chronic disease, body-indices, and age at menarche in Danish adults. *Scand J Public Health* 2000; 28: 32–40.
- Boshuizen HC, Neppelenbroek SE, van Vliet H, *et al*. Subclinical *Legionella* infection in workers near the source of a large outbreak of Legionnaires disease. *J Infect Dis* 2001; 184: 515–518.

### From the author:

There is no agreement on the answer to the question concerning the preferred method for the diagnostic aetiology of respiratory tract infections in general and of *Legionella* spp. in particular.

The opinion expressed in the letter by J. Roig and colleagues presents one side of the spectrum of opinions on this issue. Their explicit opinion that *Legionella* isolation remains the gold standard for diagnosing any form of *Legionella* infection is a minority position, so it is no coincidence that the reference quoted by them in support of this position is their own. This approach assumes an optimal and, in our opinion, unrealistic assumption that in all cases of *Legionella* infection it is feasible to isolate the pathogen. This approach completely ignores the difficulty involved in obtaining appropriate material for the isolation of the pathogen in some of the patients, as well as the technical complexity of the isolation. Defining this problematic laboratory test as a gold standard would turn the