Eur Respir J 2003; 21: 741–742
DOI: 10.1183/09031936.03.00023003
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European Respiratory Journal
ISSN 0903-1936

EDITORIAL

Is *Chlamydia pneumoniae* an important pathogen in patients with community-acquired pneumonia?

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Chlamydia pneumoniae has been established as a respiratory pathogen since 1986, when the association of this pathogen with respiratory infections was demonstrated by culture in a study of seroconverting patients in Seattle, USA, in 1984 [1]. Since then, the majority of studies evaluating the aetiology of community-acquired pneumonia (CAP) have reported the occurrence of *C. pneumoniae* in ~10–20% of patients [2–8]. Current guidelines published by the American Thoracic Society (ATS) [9], the Infectious Diseases Society of America (IDSA) [10], the Canadian Infectious Diseases Society, the Canadian Thoracic Society [11], the European Respiratory Society [12] and the British Thoracic Society (BTS) [13] all agree that *C. pneumoniae* is an important pathogen that should be covered when targeting empirical initial antimicrobial treatment.

Obviously, the variation of incidence rates across these studies is not only due to differences in the populations and geographical areas studied but also to inconsistencies in the methodologies used to establish acute *C. pneumoniae* infections. Whereas most studies applied serological methods, the criteria of seropositivity differed and only a minority of studies also included culture and/or molecular methods. To make things even more complicated, there is no generally accepted technique to firmly diagnose acute *C. pneumoniae* infection. Whereas complement fixation is only genus- and not species-specific, microimmunofluorescence is difficult to perform, has an important subjective element with regard to reading and remains open to diverse interpretations of seropositivity [14]. Moreover, seropositivity is not irrefutably diagnostic of acute infection as positive serological tests were also found to occur in asymptomatic individuals in up to 20% of cases [15]. In addition, culture and polymerase-chain reaction (PCR) techniques also have inherent limitations in terms of specificity. In general, it remains difficult, if not impossible, to interpret the significance of diverse results of serology and culture or PCR.

Another area of much debate is the significance of *C. pneumoniae* as a co-pathogen. *C. pneumoniae* has been identified as forming part of mixed infections in several studies. Again, the exact rate varies considerably, ranging between 25–60% and more [16]. In fact, since this pathogen induces ciliostasis in human bronchial epithelial cells [17], it may promote subsequent superinfection with other pathogens, particularly *Streptococcus pneumoniae*. However, the question remains whether the role of *C. pneumoniae* is limited to such promotion of infection or whether it acts as a true independent pathogen. This has important clinical implications in terms of targeting empirical antimicrobial treatment regimen.

In this issue of the *European Respiratory Journal*, MARRIE *et al.* [18] present important new insights into the role of *C. pneumoniae* as a cause of CAP. In a prospective cohort observational study conducted at 15 teaching centres in eight Canadian provinces during a 22-month period, they studied 539 acute and 272 convalescent serum samples, examining *C. pneumoniae* by the microimmunofluorescence test. With regard to seropositivity, the data presented correspond well with previous results in that seropositivity is high (75% in this study) and increases with age. Tobacco smoking, non-White race and higher body mass index were identified as risk factors for seropositivity. The results are truely intriguing in terms of acute infection. First, only 12 of the 539 patients (2.2%), including 12 of 272 (4.4%) studied by paired serology, had acute *C. pneumoniae* infection as judged by a four-fold increase in antibody titres or an immunoglobulin (Ig)M antibody titre of $\geqslant$1:16. An additional 32 cases (5.9%) had possible acute infection as defined by an IgG titre of $\geqslant$512. Secondly, patients with acute infection were not different from those with possible infection. Thirdly, of the 44 patients, only 16 (38%) had no other pathogen identified, whereas the remaining 26 had one (n=26 patients) or two or more pathogens (n=10 patients) identified. *S. pneumoniae* and respiratory viruses accounted for most of these infections.

What is the meaning of these results? Although the authors conclude that *C. pneumoniae* is an important pathogen, the exact opposite could also be concluded. Applying strict criteria, the rate of 2.2% (or 4.4% if only patients with paired serology are taken into account) is not high, and certainly three to 10 times lower than previously reported. For example, in the authors' study, where only seroconversion was judged as acute *C. pneumoniae* infection, the incidence was 15 of 204 (7.4%) [7]. Given that overall seropositivity rates were very high, there is only limited confidence in the significance of the remaining "possible acute infections". Therefore, prior to any preterm conclusion, it would be important to include culture and deoxyribonucleic acid amplification methods concurrently in order to get some idea of the meaning of these possible infections. However, currently available data have provided conflicting results in this regard. In a Spanish study including 184 patients with CAP, *C. pneumoniae* was detected in the PCR of throat-swab specimens in nine patients, but only one showed seroconversion [19]. Conversely, in a study originating from Germany, 46 patients with pneumonia who had experienced a treatment failure in the majority of cases and, therefore, were subject to bronchoscopy and bronchoalvolar lavage (BAL) were investigated. These authors found a positive PCR of BAL fluid in seven cases, resulting in a 15% incidence [20]. However, culture was positive in only one case and, unfortunately, serology was not performed. Without any doubt, the latter study highlights the relevance of this pathogen in this

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particular population with treatment failures. In fact, the subject of mixed infections including *C. pneumoniae* is difficult to settle, and, therefore, different approaches must be applied to improve the understanding of the particular role of this pathogen.

The present study confirms the observation of previous studies that *C. pneumoniae* may frequently be involved in mixed infections. Unfortunately, the authors do not report the frequency of mixed infections in the 12 patients with definite acute infection, leaving their study open to the conclusion that mixed infections may be caused by a large amount of artefacts due to the single antibody titre criteria applied. Another concern when considering mixed infections established mainly by serological methods is the possible cross-reactivity of serological measurements. However, interesting clinical differences between patients with *C. pneumoniae* as the only pathogen and the mixed-infection group appeared. Duration of symptoms prior to hospitalisation was considerably shorter in the prior group and this group was more likely to have asthma, nausea and vomiting. These observations resemble the clinical presentation of viral lower respiratory tract infections and this may be the true clinical picture of pure *C. pneumoniae* infection.

Another shortcoming of this study is that the authors do not report the mortality of definite acute *C. pneumoniae* infection separately. The reported mortality of the whole group (4.9%) is low and lower than the 9.4% of the remainder of the cohort. To the best of the authors′ knowledge, there are no data in the literature analysing the impact of Chlamydial infection on pneumonia mortality.

Should *Chlamydia pneumoniae* be regularly included in the initial antimicrobial treatment of patients hospitalised with community-acquired pneumonia? Are mixed infections including Chlamydia pneumoniae important? Obviously, the exact answers are unknown. In addition to the concerns expressed here, there is some anecdotal data suggesting that treatment may not be effective or even necessary in all patients. For example, patients may have persisting positive culture results despite adequate treatment and clinical recovery [21]. Moreover, patients may recover despite having received appropriate antimicrobial treatment [22, 23]. The present study is important in that it shows how the unanswered questions should be addressed in future studies. First, large populations have to be recruited. Secondly, serological and deoxyribonucleic acid amplification methods should be applied concurrently. Thirdly, analysis should strictly divide patients with definite and possible infections, particularly when analysing mixed infections. Finally, the independent impact of *Chlamydia pneumoniae* infection on morbidity and mortality must be addressed. Only data from such studies will firmly establish the role these pathogens have in patients with community-acquired pneumonia.

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