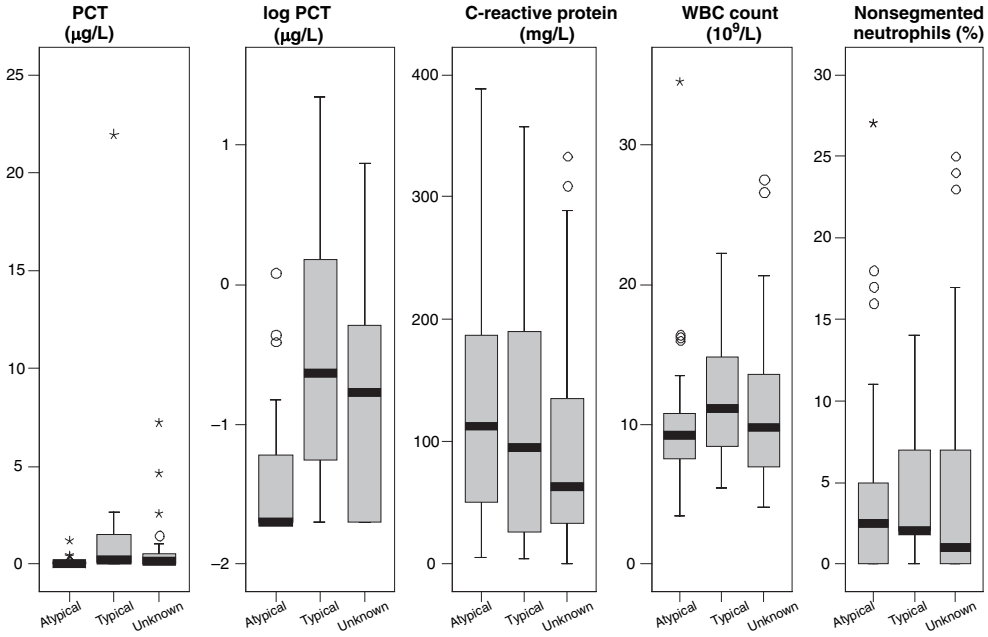

Fig. 1. Serum procalcitonin (PCT), log PCT, C-reactive protein, white blood cell (WBC) counts and non-segmented neutrophils (median, interquartile range, outliers, and extreme cases of individual variables) in patients with typical, atypical and unknown aetiology of pneumonia.

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Elevated serum transaminases in patients with *Mycoplasma pneumoniae* pneumonia

The recent report in *CMI* by Daxboeck *et al.* [1] described a study in which serologically diagnosed patients with *Mycoplasma pneumoniae* community-acquired pneumonia (CAP) were compared with 38 patients with *Streptococcus pneumoniae* CAP. Increased *M. pneumoniae* IgM titres suggest current or recent respiratory tract infection, but the authors based their diagnosis of *Mycoplasma* CAP on 'highly elevated complement fixation antibody titres' which, if unspecified, usually indicate IgG immunoglobulins [2]. Elevated IgG titres indicate past exposure/infection, and are not diagnostic of acute infection, although a >4-fold increase in IgG titres also suggests recent infection. The authors reported that serum alanine transaminase (ALT) levels were increased in 36% of patients with elevated complement fixation IgG *Mycoplasma* titres [1].

Serological diagnosis is fraught with interpretational difficulties without clinical correlations. The report does not provide any description of extra-pulmonary findings characteristic of

M. pneumoniae CAP, e.g., bullous myringitis/otitis, non-exudative pharyngitis, erythema multiforme, or watery diarrhoea. [3,4]. The data are difficult to interpret because there is insufficient clinical/laboratory information regarding other possible causes of elevated ALT levels in the patients studied. Increased serum ALT levels are a common finding in CAP caused by atypical *Legionella*, psittacosis, Q fever and adenoviruses. It is likely that some/many of the patients with elevated serum ALT levels had CAP caused by *Legionella*, psittacosis, Q fever or adenovirus. Without specific testing for these aetiologies of CAP, it is difficult to draw firm conclusions regarding increased ALT levels from the data [5–12].

Increased ALT levels may also be caused by a variety of medications that affect the liver, as well as by hepatically eliminated antibiotics. Ten of the 12 patients received macrolides, which may have been responsible for some/many elevated ALT levels [13]. Besides macrolides, there are also many medications that are used commonly and cause drug fevers in hospitalised patients, and that cause mild increases in serum ALT levels [14,15].

In addition to the laboratory information provided, epidemiological data would be helpful in suggesting or eliminating Q fever or psittacosis. Clinical descriptions would have been helpful; for example, how many patients had the prolonged non-productive dry cough typical of *M. pneumoniae* CAP? How many had non-exudative pharyngitis, ear findings (bullous myringitis/otitis) or erythema multiforme often associated with *Mycoplasma*? How many patients in the study had relative bradycardia suggestive of *Legionella*, Q fever, or psittacosis (but not *Mycoplasma*)? These clinical features would help to clarify whether the patients had CAP caused by *M. pneumoniae* or were infected with another atypical pathogen associated with increased serum ALT levels. Similarly, non-serological laboratory tests would be helpful. How many of these patients had highly elevated cold agglutinin titres (> 1:64) suggesting acute *M. pneumoniae* respiratory infection rather than past exposure? How many had microscopic haematuria or mild renal insufficiency suggestive of *Legionella*, but not *Mycoplasma*, CAP? How many had the watery diarrhoea that is commonly present in cases of *M. pneumoniae* or *Legionella* CAP [5,6]?

Until there is a definitive study with histologically proven liver involvement in *M. pneumoniae* CAP, clinicians should view increased serum ALT levels in a patient with CAP as being associated with *Legionella*, psittacosis, Q fever or adenovirus until proven otherwise. Elevated *M. pneumoniae* IgM titres, highly elevated cold agglutinin titres (≥ 1:64), or the recovery of the organism from respiratory secretions in a patient with typical clinical manifestations of *Mycoplasma* CAP, confirm the diagnosis.

Although anything is possible in medicine, hepatic involvement manifested by increased ALT levels in *M. pneumoniae* CAP should still be regarded as rare [5,16]. In patients with CAP, increased ALT levels, even with increased *M. pneumoniae* IgG titres, should suggest an alternative diagnosis until there is proof to the contrary.

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REPLY FROM DR DAXBOECK

We thank Dr Cunha for his interesting comments concerning our study [1] and would like to address the specific points raised.

The first comment of Dr Cunha refers to the diagnosis of *Mycoplasma pneumoniae* infection by highly elevated antibody titres. We stated specifically in our report that patients with titres ≥ 1:256 by complement fixation test or ≥ 1:1280 by microparticle agglutination assay were included in the study. These titres are diagnostic for acute *M. pneumoniae* infection [2]. The comment that the complement fixation test (and the same objection may be made concerning the microparticle agglutination assay) 'usually indicates IgG immunoglobulins' should be subject to further debate. It is, of course, correct that these tests are not designed to distinguish between IgG and IgM antibodies. Specific IgGs are produced in larger quantities than IgM during infection, and persist for a longer time after infection. Therefore, low positive titres may be caused by specific IgG antibodies. However, importantly, both tests are very sensitive for specific IgM, and specific IgM formation results in a significant rise in both

complement fixation and microparticle agglutination titres [17,18]. The obvious shortcoming of these tests is that low positive titres are difficult to interpret, because they may be caused by either a past infection or the beginning of a new infection. This poses significant problems in individual patients. In contrast, high titres are mostly caused by the presence of specific IgM, and are diagnostic of acute *M. pneumoniae* infection. The problem of low positive titres being difficult to interpret is easily overcome in a retrospective format by choosing a high cut-off value, as was done in our own study. In this context, it should be mentioned that the real shortcoming of the study was that the results were derived from patients with very high antibody titres, and thus may not necessarily apply to patients with lower titres, i.e., with a less pronounced immune response. Cold agglutinins are the first antibodies to appear in the course of *M. pneumoniae* infection, and the first antibodies to decrease after acute infection. In some situations, particularly if more advanced tools for *Mycoplasma* diagnosis are unavailable, cold agglutinins may be helpful. However, if assays for detection of specific antibodies are available and patients are selected for retrospective analysis, testing cold agglutinins would mean going one step back with regard to specificity [19].

Dr Cunha states that serological diagnosis is problematic without clinical correlations, which is unquestionably true. However, in our study, all patients had community-acquired pneumonia (CAP) diagnosed by the responsible physicians, followed by, as part of the study, re-review of the chest X-ray results. CAP is a consistent clinical correlation with regard to *Mycoplasma* infection. We believe that additional clinical data would not have improved the study significantly, as it has been shown that *Mycoplasma* pneumonia cannot be distinguished from CAP caused by other pathogens on the basis of clinical findings in individual patients [20].

All non-respiratory manifestations of *M. pneumoniae* infection mentioned by Dr Cunha, including watery diarrhoea, ear symptoms and erythema multiforme, occur in a minority of patients, and are not specific for *Mycoplasma* infection [21]. Therefore, the presence of these manifestations should not be used to either confirm or rule out a *Mycoplasma* aetiology for pneumonia. They may, however, be used as additional inclusion criteria to define a study population, but such a study population could hardly be claimed to be representative of patients with *M. pneumoniae* pneumonia in general [7].

Another comment by Dr Cunha referred to other possible explanations for the elevated alanine aminotransferase (ALT) levels in our patients. Particularly in a purely retrospective study, a failure to consider confounding factors may weaken the interpretation of the results. However, specifically for this reason, a control group was included, consisting of patients with CAP caused by *Streptococcus pneumoniae*. To the best of our knowledge, none of the other potential explanations for elevated ALT levels mentioned by Dr Cunha (i.e., medication or other infectious diseases) had a greater association with the *Mycoplasma* group than with the *S. pneumoniae* group. No infection with *Legionella*, *Coxiella burnetii*, *Chlamydia psittaci* or adenovirus was documented for the patients studied, although the possibility of co-infections being overlooked in the course of routine diagnosis cannot be ruled out entirely. However, the probability of such co-infections would be identical in the *M. pneumoniae* group and the control group. As highlighted by Dr Cunha, macrolides may cause elevated ALT levels. However, as stated in our report, the ALT levels decreased during macrolide therapy for most patients.

While welcoming Dr Cunha's comments, we still conclude from the data obtained that ignoring the possibility of elevated ALT levels in patients with *Mycoplasma* pneumonia may lead to an incorrect differential diagnosis for patients with CAP.

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