Correspondence

Optimal Criteria for the Diagnosis of *Legionella* Coinfection

SIR—We read with interest the article by Tan et al. [1], which is a retrospective review of 6 cases of legionnaires disease with bacteremic coinfection. Although coinfection may occur, the diagnosis should be established on firm grounds. In the 6 patients described by the authors, the diagnosis was based on antibody response (3 patients) or detection of *Legionella* antigen in urine specimens (3 patients). Both methods have shortcomings. The specificity of antibody tests is questionable because of cross-reactions with other organisms [2]. The results of *Legionella* antigen detection in the urine, assuming that it has 100% specificity (which is questionable), remain positive several months after infection occurs, suggesting possible false-positive reactions [3]. Although these criteria may be acceptable in patients with pneumonia who do not have other documented infection, their significance is questionable when a definite diagnosis has been made. At best, the criteria are presumptive and, therefore, inadequate for the diagnosis of coinfection. Of the 6 patients described by Tan et al. [1], 4 did not receive any antibiotics with anti-*Legionella* activity, yet patient outcomes were not adversely affected. Furthermore, the authors hypothesized that *Legionella* infection may have predisposed to bacteremia with other organisms. This statement is at best speculative. No data were provided to support this conclusion.

Although the authors raise some concerns about possible coinfection, their report may have a substantial impact on antibiotic use practices. Many of us are struggling to preserve the use of pathogen-directed therapy for pneumonia. In cases without a documented etiology, initial empirical therapy may include antibiotics with activity against typical and atypical pathogens, in compliance with current guidelines, especially in areas or populations with a high prevalence of atypical organisms. However, treatment should be modified once an etiology is established. The article by Tan et al. [1] indirectly encourages overuse of antibiotics, which may lead to increased antibiotic resistance and cost.

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Reply

SIR—We agree with Khatib and Fakih [1] that the diagnosis of *Legionella* coinfection should be made on firm grounds when infection is suspected to be due to multiple agents. We used the stricter criteria recommended by Marston et al. [2], such as a 4-fold increase in the serologic titer or positive results of urinary antigen tests for detection of *Legionella pneumophila* serogroup 1 (Lp1). In their letter, Khatib and Fakih [1] stated that they questioned the specificity of serologic tests because of cross-reactions with other organisms. They quoted a review article by Waterer et al. [3] that questioned the specificity of serologic tests for *Legionella* species because of false-positive test results for infections due to several bacteria. Four papers were referenced by Waterer et al. [3]: Tsai and Fraser [4], Boswell et al. [5], Musso and Raoult [6], and Johnson et al. [7].

The letter to the editor by Johnson et al. [7] discussed neither a serologic test nor a urinary antigen test but a study that used direct fluorescent antibody (DFA) testing of lung tissue specimens or respiratory tract secretions for detection of *Legionella* antigen. The authors found false-positive cross-reaction with *Haemophilus influenzae.* Johnson and colleagues [7] quoted articles that reported cross-reaction to numerous other bacteria with use of DFA for detection of *Legionella* antigen in respiratory tract secretions.

There were 3 other articles quoted by Waterer et al. [3] that discussed serological testing for *Legionella* species. Tsai and Fraser's editorial [4], which was published during the early days after the discovery of legionnaires disease, stated that plague, tularemia, and leptospirosis have been incorrectly diagnosed as legionnaires disease because of cross-reaction in serological tests, but no numbers were given. Boswell et al. [5] called attention to cross-reactivity with *Campylobacter* species that occurs with an indirect fluorescent antibody test. They reported that a large proportion of patients with positive but nondiagnostic results of serological tests (i.e., single or stationary titers or <4-fold change in titer) appeared to have false-positive results. Musso and Raoult [6] demonstrated that 34.5% of patients with Q fever (*Coxiella burnetii* infection) had a significant an-

tibody titer against *Legionella micdadei,* and they suspected that this cross-reactions were due to both protein and lipopolysaccharide antigens. In a study not quoted by Waterer et al. [3], Finidori et al. [8] tested 211 serum samples (154 with known seropositivity for *C. burnetti* and 57 with known seropositivity for *Legionella* species) and found that 4 serum samples had antibodies to both *C. burnetii* and *L. pneumophila* (2 samples obtained from patients with Q fever had moderate levels of antibody against *Legionella* species, and l sample obtained from a patient with legionnaires disease had *C. burnetii* antibody; 1 sample was obtained from a patient who was reported to have concurrent Q fever and legionellosis). We believe that concern about cross-reactivity is valid, but cross-reactivity occurs infrequently and is usually associated with low titers on serological testing. There was no history of active diarrhea suggestive of *Campylobacter* infection among our patients. *Coxiella* infection is not endemic in our area.

In their letter, Khatib and Fakih [1] also suggested that a positive urinary antigen test result for Lp1 is at best presumptive and inadequate for diagnosis, because some patients have been reported to have persistence of urinary antigen for long periods of time. Kashuba and Ballow [9] reported that the various urinary antigen detection methods appeared to have specificity of 100%. As for the duration of antigen excretion, Kohler et al. [10] showed that 15 of 100 patients with a urine antigen test result positive for *Legionella* species excreted the antigen for ⩾42 days. Of these 15 patients, 10 were receiving immunosuppressive agents (6 were renal transplant recipients, 2 were receiving corticosteroids, and data for 2 were not specified) and 5 were not immunosuppressed. It appeared that immunosuppression may prolong the period of antigen excretion. Three of our patients had positive urinary antigen test results, and 1 of the 3 was receiving chemotherapy.

In the Discussion section of our article [11], we pointed out the importance of considering a coinfection or a sequential infection in patients with community-acquired pneumonia who do not respond to conventional therapy. Khatib and Fakih [1] were concerned about our statement that coinfection may have substantial impact on antibiotic use practices. We agree that pathogen-directed therapy should continue to be used, and we encourage clinicians to follow the current guidelines of Infectious Diseases Society of America (IDSA) [12]. The therapy recommended in the IDSA guidelines for empirical therapy for patients admitted to general medical ward are a β-lactam agent in combination with a macrolide or a fluoroquinolone alone; for patients who are admitted to the intensive care unit, the IDSA guidelines recommend a β-lactam agent plus either a fluoroquinolone or a macrolide. Both macrolides and fluoroquinolones have anti-*Legionella* activity. We agree with the IDSA guidelines [12] on the rationale for establishing an etiologic diagnosis, and we continue to recommend microbiologic diagnostic evaluation for every patient who is hospitalized so that, hopefully, the etiologic agent can be identified.

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Human Herpesvirus 8 Variants in Venezuelan Patients with AIDS-Related Kaposi Sarcoma

Sir—Di Alberti et al. [1] analyzed genome human herpesvirus 8 (HHV-8) sequences in 10 biopsy specimens of the oral cavity of HIV-infected patients and in 10 biopsy specimens obtained from patients with Mediterranean cutaneous Kaposi sarcoma (KS). Analysis was done by amplifying a 220-bp segment corresponding to ORF26 of HHV-8. Di Alberti et al. [1] also compared these sequences with 36 other HHV-8 sequences previously reported in African and North American patients [2–5]. This analysis allowed for the detection of genetic variants for classification of HHV-8 into 4 main subtypes (subtypes A–D) and 1 miscellaneous subtype.

Caterino-de-Araujo [6] analyzed the