the HbA1c assay using immunological and HPLC methods [7].

In addition, we note that recently, according to the American Diabetic Association [8], a preprandial plasma glucose level of 90–130 mg/dL has been recommended. These values are slightly lower than those found in our diabetic women. Furthermore, in our study [2], microalbuminuria and an increased plasma fibrinogen level (a well-known marker of inflammation) were not demonstrated as risk factors for ASB. Pyuria did occur at a similar rate in bacteriuric women with and without diabetes.

We confirm that, in our cohort of 176 women with type 2 diabetes, there was a significant association between an increase in the HbA1c level and the risk of developing ASB. We agree with Ribera Montés et al. [1] that it is difficult to compare the results of different reported studies, because patients included in the studies may be very heterogeneous. For this reason, studies are in progress in our laboratory to identify further risk factors for ASB, in addition to the role played by the degree of metabolic control of diabetes.

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References


Legionnaires Disease and the Updated IDSA Guidelines for Community-Acquired Pneumonia

SIR—Having read the updated Infectious Diseases Society of America (IDSA) practice guidelines for the management of community-acquired pneumonia (CAP) in immunocompetent adults by Mandell et al. [1], we agree that an update is appropriate, given the voluminous information that has accumulated during the past 3 years. The key point that the NCCLS cutoff points for resistance to penicillin and third-generation cephalosporins were not accurate in predicting outcome was appropriately emphasized [2, 3]. Unfortunately, the update on legionnaires disease is not of the same rigor and quality as other updates. In fact, the recommendations are not evidence-based, and data to support opposing conclusions are strong.

In recommendation 2, the IDSA guidelines recommend testing for Legionella species only for patients with “enigmatic” pneumonia, patients in the presence of an epidemic, or patients who do not respond to β-lactam therapy. This recommendation is inconsistent with numerous studies documenting that underdiagnosis of legionnaires disease is common and that the incidence of Legionella pneumonia increases in direct relationship to the intensity of application of Legionella testing [4–9]. Moreover, in many observational studies, Legionella is the third or fourth most common cause of CAP in immunocompetent hosts [10]. The large-scale pneumonia study conducted in Ohio by the Centers for Disease Control and Prevention (CDC) [5] suggested that, in the United States, only 3% of sporadic cases of community-acquired legionnaires disease are diagnosed. Thus, we recommend testing for Legionella species for all patients admitted to the hospital with CAP. Our recommendation is consistent with the basic infectious diseases principle of emphasizing laboratory diagnosis to allow targeted antibiotic therapy [11].

The IDSA guidelines recognize that “a delay in therapy is associated with an increased mortality rate” [1, p. 1419]. However, illogically, they do not endorse testing for all patients admitted to the hospital with CAP, but instead endorse testing for Legionella species if the patient does not respond to therapy with a β-lactam; obviously, this will lead to a significantly higher mortality, as has been documented in a number of studies [12, 13].

Surprisingly, the IDSA guidelines suggest that some clinical features are suggestive of legionnaires disease. It has been well established that the clinical syndrome of Legionella pneumonia is nonspecific and that accurate diagnosis requires laboratory testing that is specific for Legionella species. From 1982 through 2003, numerous studies demonstrating the lack of any pathognomonic symptoms or signs were published [14–20].

The IDSA guidelines cite an unpublished CDC abstract in which a multivariate model was used to identify parameters suggestive of legionnaires disease [21]. Although such an approach is interesting, it
is accepted that a validation study must be done before such recommendations can be taken seriously. The validation study by Fernandez-Sabe et al. [22], however, showed that the criteria used in the CDC abstract failed to differentiate legionnaires disease from pneumococcal pneumonia. Unlike the CDC study, the Winthrop University Hospital point-scale formulated by Cunha [23] has been published. Moreover, it has been validated by an independent investigator [24]. However, this study [23] was not cited in the IDSA guidelines. The fatal flaw of those studies that use various scoring systems to assess etiologies of CAP is that the gold standard, positive results of laboratory tests for Legionella species, was often skewed toward patients who had symptoms that were considered to be classic for legionnaires disease—an overwhelming bias, involving circular reasoning, that would confound the study results.

We point out that the Winthrop University Hospital point scale (and other scores) might be used to screen patients for application of testing for Legionella species, but with an emphasis diametrically opposite to that of the IDSA guidelines [25]. If the criteria are fulfilled, then the patient should immediately receive antibiotics active against Legionella species as empiric therapy without undergoing laboratory testing for Legionella species. But if the criteria were not fulfilled, testing for Legionella species could be performed for those patients who may have legionnaires disease without the classic syndrome. This would minimize the chance of overlooking a treatable pneumonia with a high mortality.

Two recent studies [26, 27] show that more than one-quarter of patients do not have the classic risk factors of cigarette smoking or chronic obstructive pulmonary disease, thus underscoring the fact that using a syndromic approach will overlook patients who already have a high established mortality. The IDSA guidelines incorrectly rated the supportive evidence for their recommendations as A III—good evidence based on consensus—when, in actuality, the evidence supporting our recommendation of performing Legionella diagnostic testing for all patients hospitalized with CAP is A II—good evidence with numerous supportive studies.

In recommendation 3, the IDSA guidelines indicate that treatment is appropriate when there is epidemiological evidence of disease despite negative test results. This is a safe recommendation, and we do not disagree with it. However, we point out that it is now recognized that “epidemic” is often not an appropriate term for legionnaires disease, because it connotes a cluster of infections from a single-point source over a short time period. Some cooling tower–associated “outbreaks” of large magnitude occur over a longer period of time (e.g., months) [28] and might be more accurately described as areas of endemicity in which a cluster of infections is fortuitously discovered. In these instances, attention should be focused on increasing the implementation of tests specific for Legionella species, especially urinary antigen tests, rather than on administering indiscriminate empiric antibiotic therapy to all individuals with CAP in a large geographic area. Because some of these cases may be caused by species of Legionella other than Legionella pneumophila serogroup 1 [29], culture of respiratory tract specimens on Legionella species–selective media may be useful both in identifying the pathogen and in allowing identification of the source by molecular subtyping of Legionella isolated from the patient and the putative source.

Recommendation 4, the 21-day recommendation for the duration of antibiotic therapy, is obsolete. Cure rates of 90%–100% have been reported for patients receiving antibiotics for 7–14 days, including those receiving azithromycin [4, 30], clarithromycin [31], dirithromycin [32], roxithromycin [33], levofloxacin [26, 34], ofloxacin [35, 36], sparfloxacin [37], and grepafloacin [38]. A 3–5 day course of therapy with oral azithromycin resulted in a 100% cure rate in 2 studies [39, 40], although we do not favor such a short duration of antibiotic therapy. We recommend prolonged therapy only if the patient has not responded (as defined by objective signs, such as defervescence) within 5 days after initiation of therapy.

It is important to keep in mind that the original experience that suggested that a longer duration of therapy was necessary involved hospitalized patients and occurred without the knowledge that Legionella species could be in the water supply [41]. We suspect that many of these patients, rather than experiencing relapses, were merely reinfected with contaminated water after treatment.

Although the IDSA recommendations for a preferred treatment include erythromycin, most authorities agree that this antimicrobial agent is no longer indicated. Clinical experience with erythromycin therapy was sufficiently poor that we recommended the addition of rifampin to regimens that include erythromycin. Given the advent of new macrolides, use of erythromycin (and routine use of rifampin) is now obsolete for treatment of Legionella pneumonia [42, 43].

The newer macrolides have more potent intracellular activity and superior penetration into lung tissue, alveolar macrophages, and WBCs. Moreover, they have pharmacoeconomic advantages over earlier drugs, including once- or twice-daily dosing. In comparative trials, azithromycin therapy was associated with a significantly lower incidence of adverse effects and was cheaper than erythromycin therapy [4, 44].

In summary, the updated IDSA guidelines are generally appropriate, with the exception of their comments on legionnaires disease. This portion of the guidelines is not only inaccurate, but could lead to unwarranted morbidity and mortality if clinicians heed these non–evidence-based recommendations.
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Reply to Yu et al.

Str—We appreciate the opportunity to respond to the letter of Yu et al. [1], but we were disappointed by its inflammatory tone and by the fact that many of their concerns resulted from incorrect interpretation or selective referencing of the Infectious Diseases Society of America (IDSA) guidelines on management of community-acquired pneumonia (CAP) [2]. Their criticism of our recommendations for Legionella testing suggests that Legionella species are the third or fourth most common cause of CAP in immunocompetent hosts. This is clearly incorrect; their own article [3] deals with cases of severe CAP, not all CAP cases.

They refer to the principle of emphasizing laboratory diagnosis to allow targeted antibiotic therapy. We in fact do exactly this. Recognizing the morbidity and mortality associated with CAP among hospitalized patients, we stressed initial empiric therapy aimed at the pneumococcus and Legionella species, which are the pathogens associated with the highest mortality in the subset of patients with severe CAP.

The reason for the specific wording that we chose is that the guidelines must be practical, and we must recognize that the guidelines become medical legal documents. The reality of clinical practice is that the majority of patients with CAP undergo no diagnostic studies for an etiological agent, other than blood cultures. The Medicare audit of 18,000 patients with CAP indicated that only 5% of those admitted to intensive care units had undergone testing for Legionella species (Peter Houck, personal communication). Our guidelines [2] attempted to reflect some of the realities of clinical practice and the need to establish good practice standards by stating that it is appropriate to test for Legionella species in any patient hospitalized with CAP, particularly if that patient is seriously ill. Perhaps even more importantly, we recommend rapid treatment with antibiotics that are always active against Legionella species.

Yu et al. [1] state that, although we acknowledge that a “delay in therapy is associated with an increased mortality rate,” we are illogical in not recommending that all patients hospitalized with CAP receive testing for Legionella species. They seem to be confusing diagnostic tests with treatment and have missed the point entirely. As stressed in the IDSA guidelines [2], rapid treatment aimed at the likeliest pathogen, including Legionella species, is entirely in keeping with our concern for the patient and our desire to minimize morbidity and mortality. The statement that “this will lead to a significantly higher mortality” [1] is a nonsequitur and is incorrect. The statement that tests for Legionella species should be used more frequently, rather than “administering indiscriminate empiric antibiotic therapy to all individuals with CAP,” [1] exemplifies the letter’s misinterpretation coupled with a propensity for inflammatory and misleading comments.

The IDSA guidelines, in agreement with the American Thoracic Society guidelines and the Canadian CAP guidelines, have stressed the rationale behind both initial empiric therapy and the specific regimens recommended. The guidelines have been repeatedly validated, and their use results in a statistically significant decrease in the cost, length of stay, and mortality associated with CAP.

Regarding duration of treatment, Yu et al. [1] reject our recommendation of 21 days of therapy as “obsolete,” but they refuse to accept the findings of 2 studies involving a short-course regimen of azithromycin [4, 5]. Actually, our exact recommendation was “10–21 days, but it should be less for azithromycin” [2, p. 1419]. Accuracy and attention to detail would strengthen their case considerably. Although 21 days was the outside limit of our recommendation, it was taken from an article by Dr. Yu. “A 21 day course has been recommended for immunosuppressed patients or those with extensive disease on chest radiographs” [6, p. 685]. We are not convinced that the differences here are particularly profound.

The communication by Yu et al. [1] is particularly disconcerting because it closes with an unproven claim that appears to prey on the fears of physicians. We recommend treating ambulatory and hospitalized patients with CAP with drugs that are effective against legionnaires disease. We fail to see how our recommendations could possibly be construed as leading to unwarranted morbidity and mortality. In fact, these guidelines should substantially improve outcomes for patients with legionnaires disease.

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