Letter to the Editor

Serum (1→3)-β-D-Glucan Assay for the Diagnosis of Pneumocystis jiroveci Pneumonia

We read with interest the recent article by Del Bono et al. (2), and we would appreciate your taking into account the following observations.

(i) Current diagnosis of Pneumocystis jirovecii pneumonia (PJP) relies on direct visualization of Pneumocystis from stained respiratory specimens (1, 3, 4, 6, 8). No combination of symptoms, signs, radiological findings, and blood chemistry results is diagnostic of PJP (4, 5), and consequently, all new adjunct diagnostic techniques such as the (1,3)-β-D-glucan (BG) assay should be validated prospectively in cases of proven PJP and not in clinically presumptive cases.

(ii) We agree that invasive diagnostic procedures are sometimes (but not always) difficult to perform due to the severe clinical status of patients, but other alternative noninvasive diagnostic procedures are possible, such as oral washes combined with PCR (1, 3, 4). PCR has been shown to have greater sensitivity and specificity, but the interpretation of results may be conflicting, because asymptomatic P. jiroveci carriage is possible in both immunocompetent and immunocompromised individuals (4, 7, 8).

(iii) When used matched control groups, it is important to define the risk factors accurately, since the possible development of PJP is dependent on the host’s risk factor(s) for disease (4, 8). From our point of view, in this setting, the control group(s) should include, exclusively, immunocompromised patients with pneumonia of known etiology (different from PJP); healthy volunteers are inadequate. Although a second control group was immunocompromised patients with non-PJP pneumonia, there are not data about the type of immunosuppression, the CD4 cell counts, and the etiology of their pneumonia.

(iv) In an autopsy study of 328 miners with PJP (9), 32.6% had concomitant respiratory infection with Cryptococcus neoformans, other fungi, viruses, and bacteria. Of note, PJP was unsuspected prior to death in 89% of cases. Del Bono et al. (2) state that they exclude patients with no evidence of bacterial pneumonia, although the methodology is not described and they do not provide data on other possible confounding etiologies and on long-term follow-up with patients.

(v) Although the accuracy of a diagnostic test is defined by calculating the sensitivity, specificity, and positive and negative predictive values, Del Bono et al. (2) do not report these data.

(vi) The diagnostic criterion for PJP based on a favorable response to specific therapy is not widely admitted (9). Furthermore, clinical response to treatment of one infection may make clinicians less likely to look for coinfection with other organisms (9).

We agree with Wong et al. (9) that in populations with high HIV prevalence rates, PJP should always be considered in a differential diagnosis, even when tuberculosis or bacterial pneumonia is suspected. In this setting, a highly elevated serum BG value adds to the suspicion of PJP (3). While this may be adequate for empirical or preemptive therapy initiation, quantitative diagnostic performance assessment requires a higher standard of evidence.

We maintain that evidence-based prospective studies with different patient subpopulations, in which BG levels are sequentially quantified, are needed for further evaluation of the usefulness of BG detection in PJP.

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Authors’ Reply

We thank del Palacio and colleagues for their interest in our study (2). (1,3)-β-D-glucan analysis is a promising assay for *Pneumocystis jiroveci* pneumonia (PCP) diagnosis as shown by several studies (3, 4).

We agree that the assay should be validated in cases of proven PCP, as already done in a retrospective study described in a recently published article (5). However, the aim of our study was not to validate the (1,3)-β-D-glucan assay but simply to assess its potential clinical role for patients with suspected PCP unable to undergo invasive procedures, that is, a patient population for which the clinical judgment was the only diagnostic tool. Thus, due to the peculiar characteristics of our study patients, we could not provide any sensitivity or specificity data, since we did not include any case of proven PCP. For patients with suspected PCP, we ruled out other causes of pneumonia on a clinical, noninvasive basis, including results from sputum examination and a serologic or antigenic assay for PCP but for whom PCP diagnosis was ruled out on a clinical basis, including either a favorable response to antimicrobials with no known activity against *P. jiroveci* or the later clinical evidence of a convincing alternative diagnosis. The non-PCP group included 15 patients with the following underlying conditions: 9 patients with hematologic malignancies undergoing immunosuppressive or steroidal therapy; 1 patient with ovarian cancer, 1 with Wegener’s granulomatosis, 1 renal transplant patient, and 1 patient with chronic obstructive pulmonary disease, all receiving long-term steroidal and/or other immunosuppressive medications; and 2 HIV-infected patients with fewer than 200 CD4 cells/µL. All patients had clinical conditions not compatible with bronchoscopy or did not give their informed consent for the procedure.

All patients fulfilled the inclusion criteria. All had pneumonia, all had clear risk factors for PCP, and none of them underwent any invasive diagnostic test.

Within the boundaries of our study, the (1,3)-β-D-glucan assay has been shown to be a significant contributor in strengthening the possible diagnosis of PCP and therefore may be used as an adjunctive test for those patients with presumptive PCP unable to undergo bronchoscopy. These are the same conclusions del Palacio and colleagues stated in a letter published in 2008 (1). We do not think anything has changed in PCP diagnosis since then.

In conclusion, the role the (1,3)-β-D-glucan assay may play in PCP diagnosis is similar to the role the galactomannan assay plays in invasive aspergillosis diagnosis: that of a reliable and reproducible test used for shifting the diagnosis from possible to probable, while taking into consideration all the clinical data.

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