


To the Editor—We read with great interest the Brief Report by Watanabe et al [1] about the value of the (1→3) β-D-glucan (BG) assay as an adjunct for the diagnosis of Pneumocystis jiroveci pneumonia (PJP) in patients with AIDS. We congratulate the authors because their report has a large study population (111 patients with PJP and a control group with 425 patients). However, we would appreciate your taking into account the following observations.

First, we wonder whether the report is of a prospective study or a retrospective analysis of test performance in those patients with confirmed PJP.

Second, when using a control group, it is important to define accurately the risk factors of the matched control group, because the possible development of PJP is dependant on the host risk(s) for disease. From our point of view, in this setting, the control group should include human immunodeficiency virus (HIV)–positive patients with CD4+ cell counts ≤200 cells/ mm³ or a CD4+ cell percentage ≤14% with a clinical respiratory infection. These characteristics are not described by the authors in their control group.

Third, we would like to remark that the accuracy of a diagnostic test is defined by calculating the cutoff value, the sensitivity, the specificity, and the positive and negative predictive values. In their study, Watanabe et al [1] only report the sensitivity and specificity. In the clinical settings in which BG is used, negative predictive value is high, and it is consequently important to rule out the diagnosis of PJP and other invasive fungal diseases.

Fourth, bacterial pneumonia is a common respiratory infection in this subpopulation, with a 20% rate of positive blood culture results. Both gram-positive and gram-negative bacteremias have been reported to be the source of false-positive BG results [2]. The administration of some antibiotics may also be a cause of BG reactivity [3]. We miss these pertinent data in the cohort assessed by Watanabe et al [1], because both are possible confounding factors.

Fifth, Watanabe et al [1] state that serum BG levels are not suitable for monitoring the response to treatment and that they do not always return to normal levels during treatment. We agree that BG does not return to normal levels during the course of treatment, because 3 weeks is not enough time to achieve a serological cure, which usually requires several weeks after the end of treatment [4]. Our group [4] and others [5, 6] have reported that the kinetics of measured BG (Fungitell; Associates of Cape Cod) suggest that decreasing levels of BG correspond to a favorable response to treatment (Figure 1), whereas increasing levels are associated with treatment failure [4].

Therefore, we believe that prospective
studies are needed to further evaluate the accuracy of serum BG assay for the diagnosis and follow-up of PJP in HIV-positive patients.

Acknowledgments

We thank Dr. Malcolm A. Finkelman for his critical reading of this letter.

Financial support. Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, PI070107 (to A.d.P.), PI070134 (to M.S.C.), and PI070376 (to J.L.G.); and Department of Education, Universities and Research Basque Government, IT-264-07 (to J.P.); Río Hortega Research Educational Contract from the Instituto de Salud Carlos III (to J.L.G.); and Pfizer Spain (educational grant to A.d.P.).

Potential conflicts of interest. All authors: no conflicts.

Amalia del Palacio,1 Jara Llenas-García,2 María Soledad Cuéntara,1 Federico Pulido,2 Rafael Rubio,3 José Pontón,4 and Ángel del Palacio-Pérez-Medel5 1Servicios de Microbiología and 2Unidad VIH, Departamento de Medicina Interna del Hospital Universitario 12 de Octubre, and 3Servicio de Microbiología del Hospital Severo Ochoa, Leganés, Madrid, and 4Departamento de Inmunología, Microbiología y Parasitología, Facultad de Medicina y Odontología, Universidad del País Vasco, Bilbao, Vizcaya, Spain

References


Reply to del Palacio et al

To the Editor—We thank Palacio et al [1] for their interest in our study [2]. We would like to reply to their 3 comments.

First, our study [2] was performed retrospectively and analyzed >100 confirmed cases of Pneumocystis pneumonia (PCP).

Second, patients who had human immunodeficiency virus infection but did not have PCP were used as a control group, regardless of their CD4+ cell counts in our original study. Among the 425 control patients, 273 had CD4+ cell counts that were <200 cells/μL. If we analyzed data for these 273 patients, the median serum β-D-glucan level was 8.6 pg/mL (range, 1.0–283.0 pg/mL), which was almost the same as the median value for all 425 control patients. This data indicates that serum β-D-glucan level is not influenced by CD4+ cell counts.

Third, using the cutoff value of 23.2 pg/mL, positive predictive value and negative predictive value were 67.3% and 98.9%, respectively.

Fourth, the diagnosis of PCP was established by identification of Pneumocystis jirovecii in bronchoalveolar lavage (BAL) fluid with use of Diff-Quik (Dade Behring) staining method. We also examined the same sample by Gram stain and Zielh-Neelsen stain for the detection of bacteria and mycobacteria, respectively, in BAL fluid. In addition, there were no patients who had comorbidity due to bacterial pneumonia or pulmonary tuberculosis. Therefore, it is unlikely that our data were biased by confounding factors, such as bacterial pneumonia or administration of antibiotics.

Fifth, as we mentioned in our report [2], β-D-glucan levels generally decrease soon after treatment in patients who experience a good clinical course, as Palacio et al [1] have presented, and levels are normalized several months or years after treatment in all patients. However, β-D-glucan levels are elevated in ~20% of patients during the early phase of treatment, and β-D-glucan levels seldom return to the normal level within a 21-day treatment period. In accordance with the Centers for Disease Control and Prevention guidelines [3], treatment of PCP is usually completed by 21 days in our hospital, regardless of the β-D-glucan levels, and there were no patients who experienced relapse caused by the cessation of treatment after 21 days. Therefore, it is apparent that increase of β-D-glucan levels soon after treatment does not always indicate treatment failure. Consequently, we concluded that serum β-D-glucan is a useful adjunct marker for diagnosis of PCP but is not suitable for monitoring of the disease.

Acknowledgments

We thank all staff of the AIDS Clinical Center for the care of patients.


Potential conflicts of interest. All authors: no conflicts.

Tamayo Watanabe1,2 and Shinichi Oka1,2 1AIDS Clinical Center, International Medical Center of Japan, Tokyo, and 2Division of Infectious Diseases, Center for AIDS Research, Kumamoto University, Kumamoto, Japan

References