J Infect Chemother (2011) 17:473–477
DOI 10.1007/s10156-010-0198-6

ORIGINAL ARTICLE

Clinical viability of Fungitell, a new (1→3)-β-D-glucan measurement kit, for diagnosis of invasive fungal infection, and comparison with other kits available in Japan

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Received: 1 July 2010 / Accepted: 1 December 2010 / Published online: 6 January 2011

Abstract Fungitell, a (1→3)-β-D-glucan (β-D-glucan) measurement kit, was approved in the United States in 2004. Three other kits for measurement of β-D-glucan, Fungitec G test MK (G-MK), β-Glucan test Wako (Wako), and β-Glucan test Maruha (Maruha), are commonly used for diagnosis of invasive fungal diseases in Japan. We evaluated the clinical viability of the Fungitell kit and compared it with the 3 kits generally used in Japan. The plasma β-D-glucan values measured with each kit showed some differences, possibly because different β-D-glucan standards, blood pretreatment methods, and kinds of horseshoe crab (a raw material for the main reagent) are used in each kit. Measures of diagnostic efficiency, for example the sensitivity, specificity, and positive and negative predictive values, varied among the kits. Although the areas under the receiver operating characteristic curves of the kits were not significantly different, the sensitivity of the Fungitell kit was the highest, followed by that of the G-MK kit. The sensitivity of the Wako and Maruha kits was low, but the specificity of these tests was higher than that of the G-MK or Fungitell kits. These inconsistent β-D-glucan measurements could interfere with diagnosis of invasive fungal infection. Early establishment of an international standard method for measurement of β-D-glucan is required.

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Keywords (1→3)-β-D-glucan · Invasive fungal infection · Diagnostic marker

Introduction

Recently, invasive fungal infections (IFI) have been increasing in severely immunocompromised patients. In many cases, it is extremely difficult to make an early diagnosis because of the poor condition of the patient or a tendency to bleed, so serological markers have been used widely for early diagnosis in Japan along with mycological diagnostic methods. A method for measuring (1→3)-β-D-glucan (β-D-glucan) was established in 1995 by Seikagaku Corporation (Tokyo, Japan) as a diagnostic test for invasive fungal infection [1], and it has been widely used in Japan. Three kits are currently available in Japan—the Fungitec G test MK (G-MK; Seikagaku Corporation, Tokyo, Japan), the β-Glucan test Wako (Wako; Wako Pure Chemical Industries, Osaka, Japan), and the β-Glucan test Maruha (Maruha; Maruha Nichiro Foods, Tokyo, Japan) [2]. In addition, the Fungitell (Associates of Cape Cod, MA, USA) β-D-glucan assay kit was approved in the USA in 2004.

Measurement of β-D-glucan was introduced to the revised guideline for treatment of aspergillosis published by the IDSA [3], and is recommended as one of the indirect mycological criteria for diagnosis of probable and possible invasive fungal infection (excluding cryptococcosis and zygomycosis) in the diagnostic guideline published by the European organization for research and treatment of cancer/invasive fungal infections cooperative group and national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) [4] in 2008. Thus, β-D-glucan measurement was once only used clinically in

Japan, but it has recently begun to be accepted in western countries.

This is the first report on the viability of the Fungitell compared with the 3 kits currently used in Japan.

Materials and methods

Subjects

A total of 121 patients who underwent measurement of plasma β-D-glucan practically between April 23rd and June 4th, 2003 at Kawasaki Medical School Hospital were investigated using stored plasma samples. When multiple plasma samples were available, the sample showing the highest value with the G-MK was evaluated.

Diagnostic classification

The 121 patients were retrospectively classified into 5 categories according to the 2007 Japanese guideline for management of deep-seated mycoses [5], at the time when the target plasma sample was obtained from each patient. The diagnostic categories were:

1 Proven IFI: the clinical course corresponded to IFI, and fungi were detected by mycological or histopathological analysis of sterile materials.
2 Probable IFI: the clinical course corresponded to IFI, and there were typical features of IFI on imaging, and a positive serodiagnostic test (except for the β-D-glucan).
3 Possible IFI: the clinical course corresponded to IFI, but there were no findings supporting the diagnosis.
4 Non-IFI: the clinical course did not correspond to IFI, and there was no active inflammation or infection by organisms other than fungi was proven.
5 Unknown: not corresponding to any of the above criteria.

β-D-Glucan assay

β-D-Glucan levels in the 121 stored plasma samples were re-measured with each of the 4 test kits (G-MK, Fungitell, Wako, and Maruha) according to each manufacturer's instructions.

Data analysis

β-D-Glucan values measured with the 4 kits and the concordance of each judgment (positive or negative) were evaluated. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each kit were calculated using the standard cut-off values for the kits (the values for the G-MK, Fungitell, Wako, and Maruha were 20, 80, 11, and 11 pg/mL, respectively). Proven IFI and probable IFI patients were classified as the case group and non-IFI patients were used as the control group. Possible IFI and unknown patients were excluded from this evaluation. A receiver operating characteristic (ROC) curve was drawn for each kit, and the area under the curve was calculated.

Results

Patient characteristics

The subjects included 79 males and 42 females aged 15–91 years (mean ± SD: 62.8 ± 15.7 years, median: 66 years). There were 13 patients with proven IFI (10.7%), 3 with probable IFI (2.5%), 8 with possible IFI (6.6%), 95 with non-IFI (78.5%), and 2 unknown cases (1.7%). Details of the 16 proven and probable IFI are as follows: 5 patients had chronic necrotizing pulmonary aspergillosis (CNPA), 4 had pulmonary aspergilloma, 3 had candidemia, and 1 each had candidal urinary tract infection, pulmonary candidiasis, peritoneal candidiasis, and invasive pulmonary aspergillosis.

For evaluation of the sensitivity, specificity, PPV, and NPV of each test kit, cases of pulmonary aspergilloma were excluded because the plasma β-D-glucan level is not usually elevated in patients with noninvasive fungal infection such as aspergilloma. Pathogenic fungal species isolated from the proven IFI patients were *Asperigillus fumigatus* in 5 cases, *A. niger* in 2 cases, *Aspergillus* sp. in 1 case, *Candida albicans* in 2 cases, *C. parapsilosis* in 2 cases, and *C. glabrata* in 1 case.

Comparison of β-D-glucan values measured with the 4 kits

A comparison of β-D-glucan values measured with the 4 kits is shown in Fig. 1. The best correlation was recognized when the plasma β-D-glucan values measured with the G-MK and Maruha kits were compared ($r = 0.943879$). That was followed by the correlation of β-D-glucan values measured with the Wako and Maruha kits ($r = 0.891189$). However, the Fungitell–Wako and Fungitell–Maruha correlations obtained were relatively low.

Concordance of each combination

The concordance of judgment (positive or negative) of each combination of kits is shown in Table 1. Concordance between the Fungitell and G-MK and between the Wako and Maruha was higher than for the other combinations.