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Detection of β-D-glucan for the diagnosis of invasive fungal infection in children with hematological malignancy

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Summary *Objectives:* The ß-D-glucan assay (BDG) has been added to the EORTC/MSG criteria for the diagnosis of invasive fungal infections (IFI), but data from pediatric populations is scarce. The aim of this study was to evaluate performance of BDG in a cohort of hemato-oncological children with hematological malignancy at risk for IFI.
Methods: 113 patients were included through an 18-month period. In addition to routine IFI screening, BDG was assayed once a week. IFIs were classified using EORTC/MSG criteria

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without including the BDG results. Performances were assessed after a ROC analysis for optimization and multivariate analysis to detect the causes of false positivity.
Results: 8 proven and 4 probable IFIs, and 7 possible IFIs were diagnosed in 9 and 7 patients, respectively. Sensitivity and specificity increased from 75% and 56% to 100% and 91.1%, respectively when considering the whole population and patients not having received any antifungals prior to the test. Multivariate analysis revealed that being younger than 7, severe colitis/mucositis, recent administration of polyvalent immunoglobulins and digestive colonization with *Enterococcus* sp were independent risk factors for false positivity.
Conclusions: BDG is a valuable test to detect IFI in pediatric patients not previously treated with antifungals and to detect the occurrence of chronic infection.

Introduction

Patients suffering from hematological malignancy are considered a population at high risk of developing invasive fungal infections (IFI). Nevertheless, epidemiological data in the particular setting of pediatrics is still limited. In a recent study including 244 high-risk children (acute leukemia, stem cell transplant), 55 patients (22.5%) developed a probable or proven IFI, consisting predominantly of invasive candidiasis (IC) (42%), followed by proven and probable invasive mold infections (33%).[1] It is well known that these infections are typically associated with high mortality rates, 38%, in the above study. This poor prognosis is partly due to the weak performance of the currently available diagnostic instruments, highlighting the requirement for developing fungal biomarker tests.[2] Indeed, conventional diagnostic methods are both poorly sensitive and require a period of incubation, leading to a delay in initiating an adequate antifungal therapy. Currently, specific biomarker commercial kits are available to diagnose invasive candidiasis, cryptococcosis and aspergillosis and the European Conference on Infections in Leukaemia ECIL has recently proposed recommendations for their use.[3]

In addition to these specific tests, the β D-glucan (BDG) assay is becoming widely used for diagnosing IFI in various clinical contexts, including hematology,[4,5] solid organ transplantation[6] and intensive care unit.[7] BDG is a cell wall polysaccharide produced by a wide range of fungi and can be detected in the patient's serum during the infectious process of IFI. Preliminary data led the EORTC—MSG to include this test as part of the biological criteria used for the definition of IFI.[8] Recently, two studies focusing on hematology—oncology adult patients reported a high sensitivity of 92—98% and a high specificity of 90—96%[9,10] and the ECIL group confirmed that this test is be useful in diagnosing IFI in adult patients with leukemia.[11] On the contrary, data on the use of this test in pediatric populations remains very limited and led the fourth ECIL to conclude that no specific recommendation could be proposed for BDG in the diagnosis management of IFI in children.[12]

The objective of this study was to evaluate the performances of BDG for the diagnosis of IFI in a hematology—oncology cohort of pediatric patients. Furthermore, BDG kinetics during the course of IFIs, causes of false positive results, and the impact of the use of different cut-offs were analyzed.

Patients and methods

Patients

Patients of 18-year old or less, admitted in the hematology—oncology pediatric ward of our institution between 01/01/2013 to 30/06/2014 (18 months), with either Acute Lymphoblastic Leukemia (ALL), Acute Myeloblastic Leukemia (AML), Burkitt leukemia, aplastic anemia, or admitted for an Autologous Hematopoietic Stem Cell Transplantation (AHSCT), were included. For each patient, demographic data (age, sex) and the type of hematological disease and other underlying conditions, were collected. Antifungal treatments received were also recorded, as well as the use of total parenteral and enteral nutrition, the administration of polyvalent immunoglobulins, and the occurrence and severity of colitis and/or mucositis, and of bacteremia and viral infections.

Antimicrobial management

The patients were handled according to the standard procedures of the ward. Systemic antifungal prophylaxis with 1 mg/kg/day micafungin was restricted to high-risk patients with expected prolonged neutropenia (>10 days) and the demonstration of *Candida* colonization in at least two stool samples. When fever occurred during the neutropenic phase, empiric antimicrobial therapy consisted in a combination of tazocillin (300 mg/kg/day of piperacillin, maximum 12 g/day) plus amikacin (15 mg/kg/day, maximum 1 g/injection). If fever persisted after 48 h, vancomycin (45 mg/kg/day, maximum 2 g/day) was added. According to the patient's condition, an empirical antifungal treatment was added between the 48th and the 96th hours of fever, or in the case of a new febrile episode after initial apyrexia, consisting in liposomal amphotericin B (3 mg/kg/day), or caspofungin (70 mg/m2 day 1, then 50 mg/m2).

Diagnosis of IFIs

Routine procedures were applied for the diagnosis of IFIs. Multisite sampling for bacterial and fungal cultures was performed once a week during the neutropenic phase. All patients were routinely screened twice a week for *Aspergillus* galactomannan (GM) (Platelia Aspergillus, BioRad, Marnes la