

## Single Academic Center Experience of Unrestricted $\beta$ -D-Glucan Implementation

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We investigated serum  $\beta$ -D-glucan (BDG) testing among non-neutropenic adult inpatients at an academic center where the test is unrestricted. BDG orders were inappropriate in 49% of cases due to absence of predisposing host factors or clinical picture consistent with fungal infection. Providers' knowledge about BDG was insufficient.

**Keywords.**  $\beta$ -D-glucan; fungal infection; implementation.

Detection of  $\beta$ -D-glucan (BDG) provides useful ancillary data in diagnosing invasive fungal infections (IFIs) and *Pneumocystis jiroveci* pneumonia (PJP) [1–3]. To be meaningful, however, the test must be applied in the correct setting (ie, in patients with a compatible clinical presentation and for a fungal infection that BDG can detect) [4, 5].

Up to 40% of BDG orders at our hospital come from nononcology, nontransplant units, which prompted us to investigate the appropriateness of BDG testing in this patient population (ie, patients without hematopoietic stem cell transplant [HSCT]/solid organ transplant [SOT]/hematologic malignancy), determine associated negative sequelae of unnecessary testing, and assess providers' knowledge about BDG testing.

### METHODS

Patients  $\geq 18$  years with at least 1 BDG ordered between January and July 2016 who were admitted to the Johns Hopkins Hospital (JHH), a 1194-bed tertiary care center in Baltimore, Maryland, were evaluated. Patients with HSCT, SOT, or active hematologic malignancy were excluded. The JHH Medical Microbiology

Laboratory performs the BDG assay (Fungitell, Associates of Cape Cod, Inc.) in-house daily, with results reported as follows: negative  $\leq 60$  pg/mL, indeterminate = 60–79 pg/mL, positive  $\geq 80$  pg/mL, “interfering substance” (eg, sample turbidity due to lipemia or bilirubin). BDG appropriateness was determined independently by 2 infectious diseases (ID) physicians. Testing was deemed appropriate if the clinical presentation was compatible with a fungal infection (clinical criteria) and there was a predisposing host factor (eg, immunosuppressant drug, travel to endemic area, low CD4 count,) (Supplementary Material) at the time of BDG ordering. Inappropriate BDG testing was further categorized into 4 groups: group 1: clinical presentation consistent with an infectious process but no predisposing factors for IFI (eg, community-acquired pneumonia in an otherwise healthy individual whose radiographic imaging was reported as atypical infection); group 2: clinical presentation not consistent with a fungal infection but immunosuppressing condition present (eg, patient on mycophenolate presenting with upper respiratory tract symptoms and positive respiratory syncytial virus); group 3: clinical presentation not consistent with infectious process and no risk factors for IFI (eg, patient in the medical intensive care unit develops hypotension due to gastrointestinal bleeding); and group 4: BDG lacked diagnostic value (eg, testing for mucormycosis in a patient receiving antifungal therapy). An anonymous paper-based survey was administered to fourth-year medical students, medical and surgical housestaff, and advanced practitioners evaluating their knowledge of BDG in detecting specific fungal organisms and causes of false-positive results.

Statistical significance was assumed at  $P$  value  $< .05$ . Categorical and continuous variables were compared using a chi-square test and Student  $t$  test as appropriate. Statistical analyses were performed using Stata software (version 13.0; StataCorp). The study was considered a quality improvement project and was exempt from review by the university's review board.

### RESULTS

A total of 334 adult inpatients received at least 1 BDG over the study period (Table 1).

The median time from hospital admission to obtaining a first BDG (interquartile range) was 1 (1–4) day. The majority of BDG tests were ordered by medicine services (319/334, 96%), and most of these were for patients outside of critical care units (264/319, 83%). BDG was most commonly ordered for evaluation of a new respiratory/mediastinal process (eg, pneumonia, pulmonary nodules, mediastinal lymphadenopathy; 221/334,

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**Table 1. Demographics and Clinical Characteristics of the Cohort by Appropriateness of  $\beta$ -D-Glucan Testing**

| Patient Characteristic                         | Appropriate BDG<br>(n = 169), No. (%) | Inappropriate BDG<br>(n = 165), No. (%) | P Value         |
|--|---------------------------------------|---|-----------------|
| Median age (IQR), y                            | 53 (38–61)                            | 56 (43–62)                              | .09             |
| Female sex                                     | 74 (44)                               | 76 (46)                                 | .63             |
| Medicine service                               | 162 (96)                              | 160 (97)                                | .7              |
| ICU at the time of testing                     | 32 (19)                               | 38 (24)                                 | .17             |
| CD4 < 200                                      | 44 (26)                               | 1 (0.6)                                 | <b>&lt;.001</b> |
| Neutropenia                                    | 0                                     | 0                                       |                 |
| Immunosuppressant medication                   |                                       |   |                 |
| High-dose steroid                              | 23 (14)                               | 6 (4)                                   | <b>&lt;.001</b> |
| Other <sup>a</sup>                             | 10 (6)                                | 9 (5)                                   | .57             |
| Chronic pulmonary disease                      | 32 (19)                               | 36 (22)                                 | .6              |
| Chronic kidney disease on dialysis             | 22 (13)                               | 24 (53)                                 | .2              |
| Chronic hepatitis C virus infection            | 26 (15)                               | 18 (41)                                 | .1              |
| Cirrhosis                                      | 11 (6.5)                              | 27 (71)                                 | <b>&lt;.005</b> |
| Rheumatologic condition                        | 24 (14)                               | 28 (54)                                 | .48             |
| Diabetes mellitus with hemoglobin A1c >7 mg/dL | 1 (0.6)                               | 8 (5)                                   | <b>.01</b>      |
| Active malignancy                              | 1 (0.6)                               | 4 (2.3)                                 |                 |
| Total parenteral nutrition                     | 10 (6)                                | 2 (1.2)                                 | <b>.02</b>      |
| Candida colonization                           | 55 (32)                               | 45 (27)                                 | .20             |
| Respiratory                                    | 43                                    | 32                                      |                 |
| Other  | 12                                    | 13                                      |                 |

The bolding meant to highlight statistically significant results.

Abbreviations: BDG,  $\beta$ -D-glucan; ICU, intensive care unit; IQR, interquartile range.

<sup>a</sup>High-dose steroid: prednisone doses  $\geq 20$  mg/d for  $\geq 3$  weeks. Other: biologic agents, mycophenolate, azathioprine, and cyclosporine.

66%). In 17% (60/334) of cases, BDG was ordered to evaluate nonspecified systemic illnesses manifesting as fever or leukocytosis. BDG orders were considered inappropriate in 49% (165/334) of patients. Patients in group 1 (n = 79, 48%) and group 3 (n = 56, 48%) most commonly underwent inappropriate testing, followed by group 2 (n = 28, 17%) and group 4 (n = 2, 1.2%). Inappropriate BDG testing occurred more commonly in patients with cirrhosis (71% inappropriate vs 29% appropriate,  $P < .01$ ) and uncontrolled diabetes (89% vs 11% respectively,  $P < .01$ ). ID was consulted in 42% (142/334) of patients. Among patients with an ID consult, only 18% of inappropriate tests were recommended by ID.

There were 23 cases of proven IFI (6 candidemia, 14 invasive aspergillosis, 2 mucormycosis, 2 cryptococcosis, and 1 chromoblastomycosis) and 4 cases of PJP in this cohort. BDG was positive in 17/24 cases expected to give a positive result. There were 39 patients with a positive BDG who did not have serological, microbiologic, or histopathologic data supportive of fungal infection; in most of these cases (n = 34), a cause of false-positive results was identified: 8 patients had received albumin, intravenous immunoglobulin (IVIG), or both before testing, 3 were on total parenteral nutrition (TPN), 2 had Gram-negative bacteremia, 8 were on hemodialysis, and 33 had received antibiotics reported to cause false-positive results. In 5 patients, a positive BDG with no other evidence of IFI/PJP led to 39 days of unnecessary antifungal therapy. Uninterpretable BDG results occurred in 17% (57/334) of patients: 13 indeterminate and 44 with interfering substance. Of these patients,

38% underwent repeat testing and 30% had a second inconclusive BDG. Inappropriate testing (without including repeat tests, unnecessary antifungals, or length of stay triggered by false-positive results) represented an annual cost of \$45 257. This figure is an underestimate given that we did not study pediatric, transplant, or hematologic malignancy patients.

Forty-seven medical providers completed an in-person survey about indications and false-positive BDG results. Respondents correctly identified BDG as a fungal marker of *Candida* and *Pneumocystis jiroveci* in 63% and 54% of cases, respectively, whereas 56% of participants misidentified BDG as a fungal marker of *Mucorales*. Most participants (40/47) failed to identify causes of false-positive BDG results.

## DISCUSSION

We evaluated BDG use in non-neutropenic patients at an academic center where the test is unrestricted. We found that approximately half of BDG orders were inappropriate, due to either lack of risk factors for IFI/PJP or absence of a clinical picture consistent with a fungal infection. The majority of BDG tests were ordered by medicine services in non-critically ill patients. ID consultation was associated with less inappropriate testing. Providers' knowledge on the utility of the test and factors influencing results was poor.

Decisions around testing and interpreting BDG results are challenging for the non-ID expert. Providers must determine the likelihood of a disease they may not be as familiar with and do so in patient populations in whom predictive algorithms

are ill defined (eg, in chronic obstructive pulmonary disease [COPD] patients or individuals with cirrhosis). Furthermore, the risk of fungal infection varies based on immunosuppressant drug used and underlying disease. For example, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) blockers have been considered a risk factor for fungal infections [6]; however, the risk differs by type of TNF- $\alpha$  blocker, with monoclonal TNF- $\alpha$  inhibitors carrying a higher risk for endemic mycosis than soluble TNF- $\alpha$  receptor agents. Similarly, some monoclonal antibodies (eg, alemtuzumab) have been associated with IFI whereas others (eg, vedolizumab) do not seem to increase the risk for fungal infection [7, 8].

In our study, patients with cirrhosis and uncontrolled diabetes were more likely to receive inappropriate BDG testing. Previous studies have shown that fungal colonization is higher in patients with cirrhosis in the intensive care unit compared with other patient groups; however, the risk of fungal infection differed according to cirrhosis severity [9]. Factors such as diabetes, malnutrition, and COPD have been associated with higher risk of invasive aspergillosis [10]; thus, balancing early detection of fungal infection with inappropriate testing is challenging.

Most BDG testing recommended by ID consults was appropriate in this evaluation, suggesting that ID involvement through consultation or provision of pre-authorization for testing would improve BDG utilization. The small proportion of inappropriate tests recommended by ID may be explained by incorrect recommendations by fellows who either are unaware of the test characteristics or are influenced by their experience using the test while on the transplant consult service.

We observed that up to 30% of orders were completely avoidable (the patient did not have risk factors for IFI, and the clinical presentation was not suggestive of infection), and an order entry-based intervention may prevent this type of inappropriate testing. We also observed that frequently BDG was ordered along with other diagnostic tests in response to an abnormal radiographic report in asymptomatic patients, and optimization of radiographic reports may result in fewer BDG orders. Our survey revealed poor understanding of the utility of BDG and of causes of false-positive results by non-ID experts, indicating that provider education may also help reduce inappropriate testing.

To improve BDG testing at JHH, we developed a BDG section of the JHH Guidelines for Antibiotic Use, which are widely used by prescribers [11]. We included a list of indications for BDG in the EMR and a message stating that orders without appropriate indications will be audited. We elected not to require pre-authorization for BDG testing because of existing demands on the ID consult attending and stewardship team and because the complexities of identifying the correct patient population for testing require knowledge not held by microbiology technicians.

Our study has limitations. It was conducted at a single center and may not be generalizable to other institutions with differences in medical practice culture that influence ordering patterns. Also, we surveyed a relatively small number of medical providers. However, these individuals had varying levels of clinical experience and belonged to different medical teams; hence, we feel that the sample surveyed was diverse.

In conclusion, at our large academic center, BDG implementation without a concomitant intervention to guide its use resulted in a large proportion of unnecessary BDG testing in non-neutropenic, non-critically ill patients. Guidance on patient selection for BDG testing is needed for optimal test use.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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