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## Detecting Invasive Fungal Disease in Surgical Patients: Utility of the (1 3)- $\beta$ -d-Glucan Assay

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# Detecting Invasive Fungal Disease in Surgical Patients: Utility of the (1→3)-β-D-Glucan Assay

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## Abstract

**Background:** The specificity and sensitivity of the (1→3)-β-D-glucan (BDG) assay in surgical patients needs further investigation. We hypothesized that the BDG assay would have lower sensitivity/specificity compared with that of medical patients.

**Methods:** We reviewed patients who had undergone laparotomy, gastrectomy, hepatectomy, or colectomy and had a BDG assay post-operatively.

**Results:** A total of 71 patients met study criteria. There were 29 (40.8%) who had proven/probable invasive fungal infection. Sensitivity for BDG level ≥80 diagnosed within one week of the assay draw was 77.3% (95% confidence interval [CI], 54.6–92.2%), and specificity was 44.9% (95% CI, 30.7–59.8). The positive predictive value was 38.6% (95% CI, 31.0–46.9%), and negative predictive value was 82.5% (95% CI, 65.7–91.0%). A BDG assay result of 149 pg/mL had a classification rate of 63.4%. Therefore, a BDG assay result ≥150 pg/mL has a sensitivity of 78.6% and a specificity of 41.4%.

**Conclusion:** A BDG assay can be useful for ruling out invasive fungemia in post-operative patients.

**Keywords:** β-D-glucan assay; invasive fungemia; surgical patients

DESPITE THE ADVENT of new anti-fungal agents [1], invasive fungal infections continue to carry a high mortality rate [2,3]. The population at risk for invasive fungal infection, because of potent iatrogenic immunosuppression for solid organ or hematopoietic stem transplantation, continues to increase [4,5]. In addition, increasing use of life sustaining-therapies in the intensive care unit (ICU) has led to more nosocomial fungal infections [6,7]. Early diagnosis of invasive fungal infection is imperative because early administration of anti-fungal medications can improve survival [8]. Prompt diagnosis of fungal infection, however, remains a clinical challenge because it can often necessitate invasive procedures or can be difficult to discern from fungal colonization.

The 1-3-β-D-glucan (BDG) assay can be used as a serum marker for many invasive fungal infections [9]. The BDG assay is a component of the cell wall of most fungi, with the exception of zygomycetes and cryptococci [10]. Previous studies have shown that the BDG assay has good diagnostic accuracy for invasive fungal infection [10]. Several studies

have been performed in both medical and surgical patients showing the accuracy of BDG assay in the diagnosis of invasive fungal infection [11–14]. We hypothesized that BDG assay in surgical patients would have lower sensitivity and specificity compared with that of medical patients.

## Methods

### Study population

All patients, age 18 and older, undergoing four common operations (laparotomy, gastrectomy, hepatectomy, or colectomy) between 2010 and 2014 at two academic medical centers were reviewed retrospectively. Those patients who had a BDG assay post-operatively within 30 days of operation were then identified. If multiple assays were performed, the single highest level was selected. Patients were classified as having either proven/probable invasive fungal disease or as having possible/no invasive fungal disease based on the European Organization for Research and Treatment of Cancer–Mycoses Study Group classification [9]. All 29

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TABLE 1. BASELINE PATIENT CHARACTERISTICS

Characteristic	Total (n=71)	Probable or Proven IFD (n=29)	Possible or No IFD (n=42)	p	Total (n=71)
Age (median)	63 (54-68)	65 (54-70)	62 (46-70)	0.88	63 (46-68)
Female gender	22 (31%)	8 (28%)	14 (33%)	0.40	22 (31%)
Diabetic	17 (24%)	8 (28%)	9 (21%)	0.37	17 (24%)
Hemodialysis	13 (18%)	7 (24%)	6 (14%)	0.23	13 (18%)
Malignancy	15 (21%)	9 (31%)	6 (14%)	0.08	15 (21%)
Immunosuppression	34 (48%)	11 (38%)	23 (55%)	0.27	34 (48%)
Neutropenia	4 ( 6%)	3 (10%)	1 ( 2%)	0.18	4 ( 6%)
IVIG	1 ( 1%)	0 ( 0%)	1 ( 2%)	0.59	1 ( 1%)
GVHD	5 ( 7%)	0 ( 0%)	5 (12%)	0.07	5 ( 7%)
Transplant	25 (35%)	8 (28%)	17 (40%)	0.19	25 (35%)
Albumin	12 (17%)	7 (24%)	5 (12%)	0.15	12 (17%)
Laparotomy	25 (35%)	10 (34%)	15 (36%)	0.56	25 (35%)
Hepatectomy	12 (17%)	5 (17%)	7 (17%)	0.57	12 (17%)
Gastrectomy	3 ( 4%)	2 ( 7%)	1 ( 2%)	0.36	3 ( 4%)
Colectomy	30 (42%)	11 (38%)	19 (45%)	0.36	30 (42%)

IFD= invasive fungal disease; IVIG= intravenous immunoglobulin; GVHD= graft versus host disease.

patients in the proven/probable invasive fungal disease had blood culture results that were positive for fungus. Patients who did not have a BDG assay during the same hospitalization or who had a BDG assay more than 30 days post-operatively were excluded.

The outcomes measured included development of invasive fungal infection within seven days of testing and the development of invasive fungal infection by the end of hospitalization. We chose the seven-day period because we thought that this would be enough time in which to diagnose a fungal infection if one was present. A BDG assay level  $\geq 80$  pg/mL was used as the cutoff for an elevated level as established in previous studies [15,16].

### Statistical analysis

All data analyses were performed using STATA 15.0 software (College Station, TX: StataCorp LP). Continuous variables are presented as median with interquartile range, and categorical variables are reported as percentages of the total number of data points available for that field. The Mann-Whitney test and Fisher exact test were used to analyze continuous and categorical variables. Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were also calculated using the pre-determined cutoff value. A receiver operating characteristic (ROC) curve analysis was performed plotting sensitivity versus specificity and the area under the curve was calculated. For this, different cutoff values were used to determine the maximum sensitivity and specificity.

### Results

A total of 71 patients met study criteria. Of these, 29 (40.8%) had proven/probable invasive fungal infection; all had blood culture results that were positive for fungus. Of these, 22 (75.9%) received a diagnosis within one week after BDG assay was performed and the remaining seven (24.1%) before the end of hospitalization. A total of 42 (59.2%) patients had no/possible fungal infection.

### Baseline patient characteristics

Baseline patient characteristics are shown in Table 1. When comparing the two cohorts, there was no significant difference with respect to patient age (28% vs. 33%,  $p=0.88$ ) or female gender (28% vs. 21%,  $p=0.40$ ). A total of 48% of patients were immunosuppressed, with no difference between the two cohorts (38% vs. 55%,  $p=0.27$ ). The most common surgical procedure performed was colectomy (42%), followed by laparotomy (35%), hepatectomy (17%), and gastrectomy (4%). Distribution of type of operation was not significantly different when comparing the two cohorts, as shown in Table 1.

### Elevated $\beta$ -D-glucan Levels

Sensitivity of an elevated BDG level for invasive fungal disease diagnosed within one week of the assay was 77.3% (95% CI, 54.6–92.2%) as shown in Table 2. Specificity was 44.9% (95% CI, 30.7–59.8%) for patients with a diagnosis within one week of assay performance. The positive predictive value was 38.6% (95% CI, 31.0–46.9%), and negative predictive value was 81.5% (95% CI, 65.7–91.0%) as shown in Table 2.

Sensitivity of an elevated BDG level for invasive fungal disease diagnosed by the end of hospitalization was 69.0% (95% CI, 49.2–84.7%) as shown in Table 3. Specificity was 42.9% (95% CI, 27.7–59.0%) for patients with a diagnosis diagnose by the end of hospitalization. The positive predictive value was 45.5% (95% CI, 36.8–54.4%), and negative predictive value was 66.7% (95% CI, 51.2 – 79.2%) as shown in Table 3.

### ROC curve

The area under the ROC curve was 0.56. After testing different cutoff values, a BDG assay result of 149 pg/mL had

TABLE 2.  $\beta$ -D-GLUCAN ASSAY  $\geq 80$  PG/ML AT  $< 7$  DAYS

Sensitivity	77.3% (54.6%–92.2%)
Specificity	44.9% (30.7%–59.8%)
Positive predictive value	38.6% (40.0%–46.9%)
Negative predictive value	81.5% (65.7%–91.0%)

TABLE 3. BDG ASSAY  $\geq 80$  PG/M $\text{L}$  BY END OF HOSPITALIZATION

Sensitivity	69.0% (49.2%–84.7%)
Specificity	42.9% (27.7%–59.0%)
Positive predictive value	45.5% (36.8%–54.4%)
Negative predictive value	66.7% (51.2%–79.2%)

the highest classification rate of 63.4%. Therefore, a BDG assay result  $\geq 150$  pg/mL has a sensitivity of 78.6% and a specificity of 41.4%.

## Discussion

Previous studies have shown that BDG levels can be a useful adjunct for diagnosing many invasive fungal infections, whether in medical or surgical patients [10–14]. These studies suggest that BDG should be used in patients with appropriate pre-test probability and a clinical picture that can be consistent with fungal infection. The BDG assays are still helpful even when anti-fungal agents have been initiated. While previous studies have shown that BDG assay may have lower sensitivity in certain populations, such as those with hematologic malignancy, little data exist regarding its sensitivity and specificity in surgical patients [5,10,17]. Our study demonstrated that the BDG assay has good sensitivity, but low specificity in post-operative patients.

This study found that BDG assay in surgical patients has good sensitivity, making it a useful adjunct for ruling out many invasive fungal infections in patients who have had recent operations. For patients with a diagnosis of invasive fungal infection within seven days of elevated BDG assay, sensitivity was found to be 77.3%. This finding is similar to that found in medical patients where a large meta-analysis determined that BDG assay has a sensitivity of 79.1% [10].

Previous studies have shown that sensitivity of BDG varies among different subgroups. How this sensitivity differs among different categories of surgical patients needs further characterization. Patients with upper gastrointestinal perforations are known to be at higher risk for invasive fungal infection. How a BDG assay should be interpreted in a patient having elective gastric resection may be different from an assay in a patient who underwent emergency laparotomy for a perforated gastric ulcer. Similar to the present study, previous studies performed in surgical patients have been underpowered and unable to determine whether the BDG assay is more accurate in patients with specific types of operations [11–14].

While sensitivity for BDG assay in surgical patients appears to be high, the test is not specific in patients with recent operations (44.9%). This is in contrast to previous studies that have shown high specificity among the general population. A meta-analysis determined that the pooled specificity after analyzing 16 studies was 85.3% [10]. Factors known to cause false positive results among BDG assays include medications, hemodialysis, and immunoglobulin therapies [18].

It is theorized that exposure to surgical gauze may be another cause of false positive results. Kanamori et al. [19] exposed purified water to six different types of commonly used surgical gauze ex-vivo; in all samples but one, markedly elevated BDG levels were measured. The high false positive rate among surgical patients needs further investigation. Determining what other factors are contributing to false positive

results in surgical patients may allow clinicians to better select patients who may benefit from a BDG assay.

While BDG assay value  $\geq 80$  pg/mL has good sensitivity, our findings of a low area under the ROC curve suggest that an optimal cutoff value for the BDG assay does not exist in surgical patients. Further studies are needed to determine whether a cutoff different from that typically used in medical patients should be used in surgical patients suspected of invasive fungemia. While specificity for BDG assay in surgical patients is poor overall, our findings do indicate that a BDG value  $\geq 150$  pg/mL has good specificity (78.6%) for diagnosing invasive fungal infections.

This study had several limitations, including those related to two-institution, retrospective analysis. All data were obtained from chart review, which introduces selection bias and some incomplete data collection. Because one of the inclusion criteria for the study was the requirement of a BDG assay, there is a significant selection bias for patients included in the study. In addition, this analysis had a small sample size, thus limiting the power of the study. Patients did not have a BDG assay on a daily basis; therefore, we could not determine median time from BDG assay to infection.

Because of the retrospective nature of the study, we could not examine other factors for fungemia such as total parenteral nutrition, colonization sites, or exposure to carbapenems. The study is also limited by surgeon preferences, because some surgeons may be more likely to order a BDG assay early in the hospital course, while others may fail to order the assay even when warranted.

## Conclusion

This study demonstrates high sensitivity and low specificity of the BDG assay in surgical patients. A BDG assay can be useful for ruling out invasive fungemia in post-operative patients because it has high sensitivity and negative predictive value. Its poor specificity and positive predictive value, however, suggests that patients with a positive assay must have further investigation in determining whether anti-fungal agents should be initiated. When the BDG assay values are very high ( $\geq 150$  pg/mL) in surgical patients, however, the test has good specificity for invasive fungemia and anti-fungal agents should be initiated.

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## Author Disclosure Statement

No competing financial interests exist.

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