

Cerebrospinal Fluid (1,3)-Beta-D-Glucan for the Diagnosis of Fungal Meningitis Associated with Contaminated Methylprednisolone Injections

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Abstract

Background: The prompt diagnosis and treatment of fungal meningitis is critical, but culture is insensitive. (1,3)-beta-D-glucan (BDG) is FDA-approved for serologic diagnosis of invasive fungal disease. However, BDG is not approved for cerebrospinal fluid (CSF) and the appropriate cutoff is unknown. We aim to validate the diagnostic accuracy of CSF BDG for fungal meningitis among patients exposed to contaminated methylprednisolone acetate (MPA).

Methods: A retrospective observational study was conducted at St. Joseph Mercy Ann Arbor and Vanderbilt University from November 2013 – February 2014. Patients were included if they received a contaminated MPA injection. Cases were classified as probable or proven meningitis according to Centers for Disease Control and Prevention guidelines. CSF BDG testing was performed according to the package insert for serum and validated using Clinical Laboratory Standards Institute procedures (MiraVista Diagnostics).

Results: Of 233 patients, 45 had meningitis (28 proven), 53 had spinal/paraspinal infection (19 proven), and 135 did not develop disease. Using the manufacturer's cutoff (> 80 pg/mL), the sensitivity and specificity were 96% and 95% for proven meningitis; and 84% and 95% for probable or proven meningitis. The Receiver Operating Characteristic analysis identified the optimal cutoff for proven meningitis to be 66 pg/mL (sensitivity 100%, specificity 94%); for probable or proven meningitis to be 66 pg/mL (sensitivity 91%, specificity 92%).

Conclusions: Our results suggest that CSF BDG is highly sensitive and specific for diagnosis of fungal meningitis associated with contaminated MPA injections. Further study is needed on the utility of CSF BDG for other types of fungal meningitis.

Introduction

- (1,3)-beta-D-glucan (BDG) is a component of the cell walls of many medically important fungi.
- The serum Fungitell assay (Associates of Cape Cod Incorporated, East Falmouth, MA, US) was approved by the FDA in 2004, the package insert reports a sensitivity (>80 pg/mL) of 65% (95% CI, 60% - 70%) and specificity (<60 pg/mL) of 81% (95% CI, 77% - 85%) for proven or probable invasive fungal disease.¹
- This assay has not been FDA-cleared for testing cerebrospinal fluid (CSF) and the appropriate cutoff for positivity is not known.
- In 2012, an unprecedented outbreak of fungal infections associated with the injection of contaminated methylprednisolone acetate (MPA) was identified with 751 cases of fungal disease reported by October, 2013.²
- We sought to validate the diagnostic accuracy of CSF BDG for both probable and proven fungal meningitis associated with contaminated MPA.

Methods

- Retrospective observational study was conducted at St. Joseph Mercy Ann Arbor and Vanderbilt University from November 2013 – February 2014.
- Patients were included if they received a contaminated MPA injection and CSF was available for analysis.
- Case definitions:** classified as probable or proven meningitis according to CDC guidelines. Controls were defined as persons who received an injection of contaminated MPA and did not meet the CDC case definitions.²
- CSF BDG testing:** performed according to the package insert for serum and validated using Clinical Laboratory Standards Institute procedures (MiraVista Diagnostics). The reportable range using serum specimens is 31 pg/mL to 500 pg/mL and the manufacturer recommends that <60 pg/mL be interpreted as negative, 60 pg/mL to 79 pg/mL intermediate, and that a value 80 pg/mL or higher be interpreted as positive.
- Data Analysis:** Sensitivity and specificity with 95% CI were calculated, Receiver Operating Characteristic (ROC) curves were created.

Results

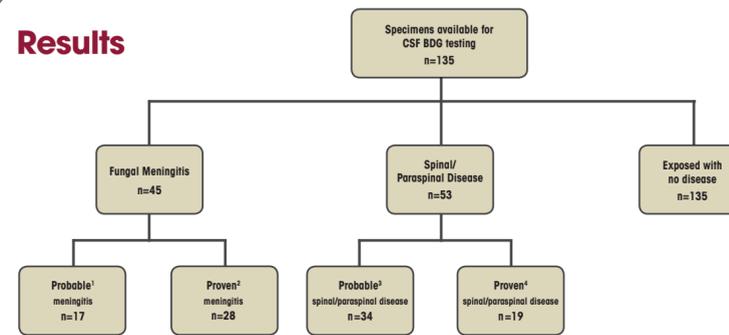


FIGURE 1 Flow chart showing (1-3)-beta-D-glucan testing of cerebrospinal fluid (CSF) testing in patients exposed to contaminated methylprednisolone acetate injection.

¹Probable meningitis defined as signs or symptoms of meningitis with CSF white blood cells > 5/ μ L, accounting for presence of red blood cells

^{2,4}Confirmed cases defined as patients who had probable disease plus microbiological, molecular, or histopathological evidence of a fungal pathogen

³Probable spinal or paraspinal disease defined as MRI evidence of osteomyelitis, abscess or other infection (e.g., soft tissue infection) of unknown etiology, in the spinal or paraspinal structures, at or near the site of epidural or paraspinal injection with contaminated methylprednisolone.

Results

- Using the manufacturer's cutoff (> 80 pg/mL), the sensitivity and specificity were 96% (95% CI, 80%-100%) and 95% (95% CI, 89%-98%) for proven meningitis; and 84% (95% CI, 70%-93%) and 95% (95% CI, 89%-98%) for probable or proven meningitis.
- The ROC analysis identified the optimal cutoff for proven meningitis to be 66 pg/mL, at which the sensitivity was 100% (95% CI, 87% - 100%) and the specificity was 94% (95% CI, 88% - 97%); for probable or proven meningitis to be 66 pg/mL, at which the sensitivity was 91% (95% CI, 79% - 98%) and a specificity of 92% (95% CI, 87% - 96%).



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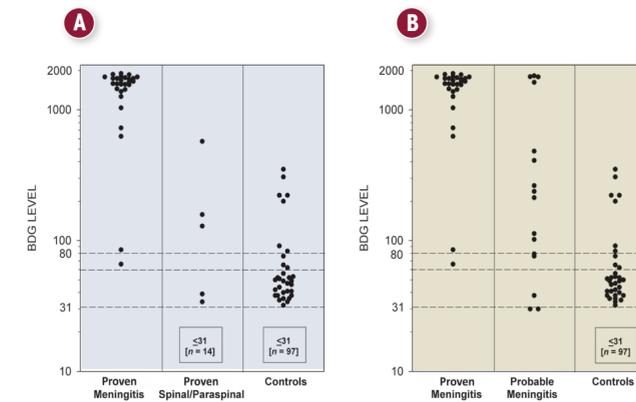


FIGURE 2 (A) CSF BDG in proven cases of fungal meningitis, spinal or paraspinal infection, and controls. (B) CSF BDG in proven cases of fungal meningitis, probable meningitis, and controls.

Conclusions

- CSF BDG is highly sensitive and specific for diagnosis of fungal meningitis associated with contaminated MPA injections.
- The accuracy of CSF BDG for the diagnosis of fungal meningitis in our study is higher than previous reports validating serum BDG for the diagnosis of invasive fungal disease.
- Further study is needed on the utility of CSF BDG for other types of fungal meningitis.

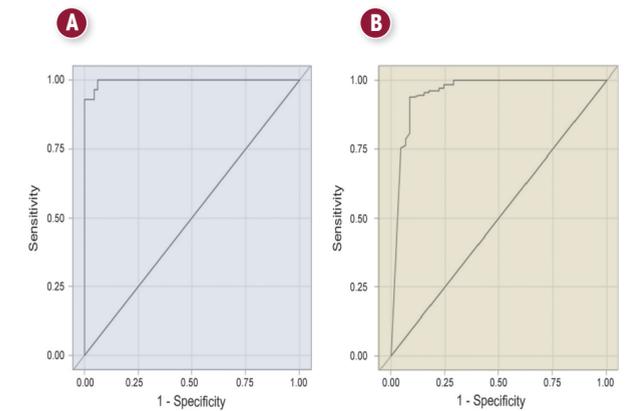


FIGURE 3 (A) Receiver operating characteristic (ROC) curve of CSF BDG cutoff values to distinguish proven meningitis from non-cases. Area under the ROC curve = 1.00 (95% CI, 0.99-1.00). (B) ROC curve of CSF BDG cutoff values to distinguish probable or proven meningitis from non-cases. Area under the ROC curve = 0.95 (95% CI, 0.91-0.99).

References

- Associates of Cape Cod Incorporated. Fungitell Package Insert 2013. Available from http://www.acciusa.com/pdfs/accProduct/Fungitell_multilang_pisheets/Fungitell%20Insert%20EN.pdf
- Centers for Disease Control and Prevention (CDC). Multistate Fungal Meningitis Outbreak Investigation 2013. Available from <http://www.cdc.gov/HAI/outbreaks/meningitis.html>.

