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 current tests are insensitive. (1,3)-Beta-d-Glucan (BDG) is FDA-approved for rapid 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 or paraspinal disease (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 probable or proven meningitis; and 84% (95% CI, 70%-93%) 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.

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 wall 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.2 This assay has not been FDA-validated for cerebrospinal fluid (CSF) and the appropriate cutoff for positivity is not known. We aim to validate the diagnostic accuracy of CSF BDG for probable or proven meningitis to be 66 pg/mL (sensitivity 100%, specificity 94%); for spinal or paraspinal disease the sensitivity and specificity were 96% and 95% for proven meningitis; and 84% and 95% for probable or proven 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 specimen is 0-80 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
Using the manufacturer’s cutoff (> 80 pg/mL), the sensitivity and specificity were 94% (95% CI, 83%-100%) and 95% (95% CI, 89%-98%) for probable 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, sensitivity 100%, specificity 94%; for probable meningitis to be 66 pg/mL (sensitivity 91%, specificity 92%).

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.

References

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