JAMA Diagnostic Test Interpretation

Aspergillus Galactomannan for Diagnosing Invasive Aspergillosis

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A 67-year-old man with granulomatous polyangiitis (Wegener granulomatosis) complicated by end-stage renal disease requiring hemodialysis and mild pulmonary fibrosis, was hospitalized with a 2-week history of worsening dyspnea and dry cough. He was taking 20 mg prednisone and 150 mg azathioprine daily.

On examination, he was afebrile and had diffuse rhonchi and expiratory wheezes. A chest computed tomography (CT) scan revealed bilateral nodular infiltrates and a 1.3-cm cavitary nodule in the right upper lobe. Bronchoscopy was performed on day 2. Blood and bronchoalveolar lavage fluid test results are presented in the **Table**.

Table. Laboratory Test Results

Specimen	Test	Result
Serum and urine	*Histoplasma* antigen	Negative
Serum and urine	*Blastomyces* antigen	Negative
Serum	Galactomannan	Negative (<0.5 ODI)
	Fungitell	Positive (94 pg/mL)
Transbronchial biopsy	Pathology	Organizing pneumonia; no organisms seen
Bronchoalveolar lavage	Galactomannan	Positive (6.7 ODI)
	Calcofluor stain	Septate hyphae
	Fungal culture	*Aspergillus fumigatus*

Abbreviation: ODI, optical density index.

HOW WOULD YOU INTERPRET THIS PATIENT'S TEST RESULTS?

A. The patient has proven invasive pulmonary aspergillosis.

B. The patient has probable invasive pulmonary aspergillosis.

C. The patient does not meet criteria for invasive pulmonary aspergillosis.

D. The patient is not at risk for invasive pulmonary aspergillosis and the results reflect colonization.

Answer

B. The patient has probable invasive pulmonary aspergillosis.

Test Characteristics

Invasive aspergillosis primarily occurs in patients who have specific risk factors, such as prolonged neutropenia, history of allogeneic hematopoietic cell or solid organ transplantation, use of high-dose corticosteroids or inherited severe immunodeficiency. Dense, well-circumscribed nodular lesion(s) on CT scan, with or without surrounding hazy infiltrate (halo sign) and cavitary lesions, are characteristic but not specific for invasive pulmonary aspergillosis.

The *Aspergillus* galactomannan enzyme immunoassay detects polysaccharides that are present in the cell wall of *Aspergillus* species and that can be found in serum and bronchoalveolar lavage fluid during invasive infection.[1,2]

The role of the galactomannan assay in the diagnosis of invasive aspergillosis has been studied most often in neutropenic patients and allogeneic hematopoietic cell transplant recipients.[2,3] In these patient groups, the reported sensitivity of the assay in serum is 70% to 82% and specificity is 81% to 92%, and in bronchoalveolar lavage fluid, sensitivity is 73% to 100% and specificity is 68% to 92%.[2] In solid organ transplant recipients, sensitivity is 21% to 86% and specificity is 80% to 89% in serum, and in broncholveolar lavage fluid, sensitivity is 60% to 90% and spedificity is 90% to 96%.[4,5] The sensitivity of the assay is higher in bronchoalveolar lavage fluid than in serum, especially in lung transplant recipients.[6]

False-negative results occur in patients who are receiving antifungal agents other than fluconazole.[7] False-positive results occur in patients who are colonized but not infected with *Aspergillus* species and in those who have infection with *Fusarium* species, *Histoplasma capsulatum*, and *Blastomyces dermatitidis* because these fungi have similar galactomannans in their cell walls.

False-positive reactions with piperacillin-tazobactam have been reported in the past, but manufacturing changes have eliminated this problem. Other reported causes of false-positive results include severe mucositis, severe gastrointestinal graft vs host disease, blood products collected in certain commercially available infusion bags, multiple myeloma (IgG type), and flavored ice pops or frozen desserts containing sodium gluconate.

The time required to receive galactomannan test results is 2 to 7 days if the test is sent to a reference laboratory. The cost to Medicare is $90.

Application of Test Results to This Patient

This patient was at high risk for invasive pulmonary aspergillosis because of prolonged therapy with prednisone. Based on radiological findings and a positive galactomannan assay in bronchoalveolar lavage fluid, he was diagnosed with probable invasive pulmonary aspergillosis and started on voriconazole (**Box**).[8,9] Two days later, *Aspergillus fumigatus* was recovered in bronchoalveolar lavage fluid culture. *Pseudomonas aeruginosa* was also present in the culture but was considered to be only colonizing the airways.

Box. Simplified EORTC-MSG Diagnostic Criteria for Proven, Probable, and Possible Invasive Pulmonary Aspergillosis[a]

Proven Invasive Pulmonary Aspergillosis

Presence of host risk factors and radiological criteria and histopathologic or cytopathologic evidence of septate hyphae suggestive of *Aspergillus* species and compatible tissue damage in a specimen taken from a sterile site; or

Recovery of *Aspergillus* species by culture from a sterile site

Probable Invasive Pulmonary Aspergillosis

Presence of host risk factors and radiological criteria and recovery of *Aspergillus* species in culture from a nonsterile site; or

Evidence of septate hyphae suggestive of *Aspergillus* species in a specimen from a nonsterile site; or

Aspergillus galactomannan detected in serum or bronchoalveolar lavage fluid; or

(1,3) β-D-glucan detected in serum

Possible Invasive Pulmonary Aspergillosis

Presence of host risk factors and radiological criteria in the absence of microbiological evidence and no alternative diagnosis to explain these findings

Abbreviation: EORTC-MSG, European Organization for Research and Treatment of Cancer-Mycoses Study Group.

[a] Adapted from De Pauw et al.[8]

Proven invasive pulmonary aspergillosis requires proof of tissue invasion by histopathological examination or positive culture from a normally sterile site.[8] In this patient, the diagnosis of proven invasive pulmonary aspergillosis could not be made because the transbronchial lung biopsy did not show hyphae invading lung tissue. For patients who have hematological malignancies or have received a hematopoietic stem cell transplant, lung biopsy is rarely performed because of thrombocytopenia, and thus, most cases of invasive pulmonary aspergillosis in these patient groups are deemed probable or possible (Box).

What Are Alternative Diagnostic Testing Approaches?

The Fungitell assay detects (1,3) β-D-glucan, another cell wall component of many different fungi. A positive Fungitell result supports the diagnosis of an invasive fungal infection but is not specific for aspergillosis.[10]

Patient Outcome

The patient was discharged home to continue therapy with voriconazole. Eight weeks later, a chest CT showed marked improvement. He completed 16 weeks of antifungal therapy with voriconazole. Three months later, he remained asymptomatic.

Clinical Bottom Line

- When invasive pulmonary aspergillosis is suspected, the following tests should be ordered immediately: a high-resolution CT scan of the thorax, serum galactomannan, and consultation for bronchoscopy with bronchoalveolar lavage for galactomannan assay, fungal stain, and culture.
- The sensitivity of the galactomannan assay for invasive pulmonary aspergillosis is higher in bronchoalveolar lavage fluid than in serum.
- In patients who have risk factors and radiologic findings suggesting invasive aspergillosis, a positive galactomannan in serum or bronchoalveolar lavage fluid confirms a diagnosis of probable invasive pulmonary aspergillosis.
- In patients with risk factors for invasive aspergillosis and radiologic findings consistent with invasive pulmonary aspergillosis, antifungal therapy should be started while awaiting cultures and galactomannan test results.

ARTICLE INFORMATION

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REFERENCES

1. Hope WW, Kruhlak MJ, Lyman CA, et al. Pathogenesis of *Aspergillus fumigatus* and the kinetics of galactomannan in an in vitro model of early invasive pulmonary aspergillosis. *J Infect Dis*. 2007;195(3):455-466.

2. Miceli MH, Maertens J. Role of non-culture-based tests, with an emphasis on galactomannan testing for the diagnosis of invasive aspergillosis. *Semin Respir Crit Care Med*. 2015;36(5):650-661.

3. Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the *Aspergillus* double-sandwich enzyme immunoassay. *Clin Infect Dis*. 2007;44(10):1329-1336.

4. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay. *Clin Infect Dis*. 2006;42(10):1417-1427.

5. Husain S, Clancy CJ, Nguyen MH, et al. Performance characteristics of the platelia *Aspergillus* enzyme immunoassay for detection of *Aspergillus* galactomannan antigen in bronchoalveolar lavage fluid. *Clin Vaccine Immunol*. 2008;15(12):1760-1763.

6. Zou M, Tang L, Zhao S, et al. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. *PLoS One*. 2012;7(8):e43347.

7. Duarte RF, Sánchez-Ortega I, Cuesta I, et al. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis*. 2014;59(12):1696-1702.

8. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46(12):1813-1821.

9. Patterson TF, Thompson GR III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis. *Clin Infect Dis*. 2016;63(4):e1-e60.

10. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, et al. β-D-glucan assay for the diagnosis of invasive fungal infections. *Clin Infect Dis*. 2011;52(6):750-770.