Nonmolecular Methods for the Diagnosis of Respiratory Fungal Infections

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KEYWORDS

• Galactomannan • β-glucan • *Cryptococcus* antigen test • Invasive aspergillosis
• Pulmonary cryptococcosis • *Pneumocystis jirovecii* pneumonia • Mucormycosis

KEY POINTS

- Nonmolecular fungal biomarkers are part of the diagnostic workup of invasive fungal pneumonia in conjunction with other clinical, radiologic, and microbiological criteria.
- Good evidence supports the use of the galactomannan (GM) test in serum or bronchoalveolar lavage fluid for the diagnosis and follow-up of invasive aspergillosis in patients who have hematologic cancer.
- The 1,3-β-D-glucan (BG) test in serum can detect a broad spectrum of invasive fungal pathogens, including *Pneumocystis jirovecii*.
- GM and BG testing cannot be recommended in patients who do not have cancer, because of their modest performance in this population; their inability to detect mucormycosis is another limitation.
- Detection of the cryptococcal antigen in serum is a cornerstone of the diagnosis of disseminated cryptococcosis, but its sensitivity is lower in patients who do not have human immunodeficiency virus, with disease limited to the lung.

INTRODUCTION

Fungal pneumonias are an important cause of mortality among an increasing diversity of immunosuppressed populations, such as patients who have hematologic cancer, transplant recipients, patients with human immunodeficiency virus (HIV) or individuals with chronic pulmonary or autoimmune diseases. Their diagnosis is difficult and often only presumptive, relying on a combination of clinical, radiologic, and microbiological

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factors. Nonmolecular fungal markers in serum or other biological samples represent a noninvasive diagnostic tool, which can help in therapeutic decisions. The performance of nonmolecular fungal diagnostic tests for each type of fungal pneumonia is discussed in this article. This review provides the reader with a general overview of the performance and limitations of these tests, as well as some recommendations for their use in specific contexts (summarized in **Table 1**).

MICROBIOLOGY/EPIDEMIOLOGY

Pneumonia is the leading infectious cause of death in developed countries.[1] Among the broad variety of respiratory pathogens, fungi account for only a small proportion of community-acquired and nosocomial pneumonias.[2,3] However, fungal respiratory infections are of particular concern in the expanding population of immunosuppressed patients, and the spectrum of opportunistic fungi causing infections in predisposed individuals is constantly increasing, as shown in **Table 2**. *Aspergillus* represents the leading cause of invasive pulmonary fungal infection (IFI) and death in patients who have cancer, especially those with hematologic malignancies, and in transplant recipients.[4,5] Members of the subphylum Mucormycotina (previously referred to as the Zygomycetes and responsible for mucormycosis) and other emerging non-*Aspergillus* molds account

Table 1
Nonmolecular diagnostic tests for the diagnosis of fungal pulmonary infections

Disease	Available Tests	Comments
Invasive aspergillosis	Galactomannan (serum)	Good evidence supports use in patients with hematologic malignancies Caveat: negative test does not exclude disease (relatively low sensitivity) Not routinely recommended in other populations at risk of IFI
	Galactomannan (BAL)	Good evidence supports use in patients with hematologic malignancies as well as in other populations at risk of IFI Caveat: cannot differentiate *Aspergillus* pulmonary colonization from IA
	BG (serum)	Good evidence supports use in patients with hematologic malignancies Caveat: negative test does not exclude disease (low sensitivity) Not routinely recommended in other populations at risk of IFI
Other mold pulmonary infections	BG (serum)	Not routinely recommended. Does not detect agents of mucormycosis
Pneumocystis jirovecii pneumonia	BG (serum)	Good evidence supports use in patients with HIV and patients who do not have HIV
Pulmonary cryptococcosis	Cryptococcal antigen (serum)	Good evidence supports use in patients with HIV and patients who do not have HIV Caveat: lower sensitivity in patients who do not have HIV and in nondisseminated disease

Abbreviations: BAL, bronchoalveolar lavage fluid; BG, 1,3-β-D-glucan; IA, invasive aspergillosis; IFI, invasive fungal infection.