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Diagnostic performance of four lateral flow assays for detecting cryptococcal glucuronoxylomannan antigen

KEYWORDS
POCT;
Cryptococcal GXM antigen test;
Sensitivity;
Specificity

Dear Editor,

We read with great interest the Wang et al. article describing a renal transplant recipient who had disseminated cryptococcosis and demonstrating that assessing cryptococcal glucuronoxylomannan (GXM) antigen (Dynamiker Biotechnology Co., Ltd, Tianjin) can serve as a primary microbiological tool for early diagnosis of cryptococcosis.[1] *Cryptococcus* infections are generally lethal.[2] The cryptococcal GXM antigen test using CSF or blood confirms cryptococcosis, and point-of-care tests (POCTs) are now the preferred test.[3] We compared the specificity and sensitivity of four available cryptococcal GXM antigen tests in a series of clinical isolates.

Four POCT lateral flow assays (LFAs) for detecting cryptococcal GXM antigen were evaluated, including the Dynamiker test (Dynamiker Biotechnology Co., Ltd, Tianjin), Kangtai test (Kangtai Biotechnology, Wenzhou), Liming test (Liming Biological, Nanjing), and IMMY test (Immuno Mycologics, USA). A total of one hundred clinical isolates in twenty-eight genera/species were identified by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) and internal transcribed spacer (ITS) with the universal primers ITS1 (5′-TCCGTAG GTGAACCTGCGG-3′) and ITS4 (5′-TCCTCCGCTTATTGA-TATGC-3′).[4] Thirty-one *Cryptococcus* species, seventeen *Trichosporon* species, twelve *Candia* species, twenty-three other yeasts (*Saccharomyces cerevisiae*, *Hannaella zeae*, *Rhodotorula minuta*, *Magnusiomyces capitatus*, *Rhodotorula mucilaginosa*, *Moniliella pollinis*, *Kluyveromyces marxianus*, *Pichia kudriavzevii*, *Wickerhamomyces anomalus*, *Lodderomyces elongisporus*, *Cyberlindnera fabianii*, *Sporidiobolus salmonicolor*, *Yarrowia keelungensis and Kluyveromyces blattae*), two *Malassezia* species, thirteen other fungi (*Mycotypha microspora*, *Prototheca*, *Basidiobolus*, *Fusarium delphinoides*, *Talaromyces marneffei*, *Histoplasma capsulatum*, *Diutina ranongensis*, *Conidiobolus coronatus*, *Moesziomyces bullatus*, *Exophiala dermatitidis)* and two bacteria *(Rothia*, *Capnocytophaga cynodegmi*) were included.

The isolates were passaged once after resuscitation, incubated for approximately 24 h on SDA, and then detected by the four tests. The specificity of the tests was evaluated using isolate suspensions of a concentration of 0.5 McFarland, of which 0.5 McFarland-positive isolate suspensions were prepared as a series of 10-fold dilutions to evaluate sensitivity.

All one hundred isolates were detected by the four tests, and the positive results were completely consistent with each other. Among the thirty-one isolates of *Cryptococcus* species, 80.65% (25/31) were detected, including the two main etiologic agents: *C. neoformans* and *C. gattii*. Additionally, 76.47% (13/17) of *Trichosporon* isolates were positive, with a total specificity of 81.16% (56/69). The detection limit of the four tests was 1.0×10^1 CFU/ml for *Cryptococcus* isolates, which was lower than that of *Trichosporon* species. There were six *Cryptococcus* isolates with inconsistent sensitivity results among the four tests at the highest dilution. The Dynamiker test showed the highest sensitivity at the indicated dilution (six *Cryptococcus* isolates were all positive) (Table 1). In addition, no hook effect was found.

Significantly, due to GXM in the cell wall of *Trichosporon*, which can lead to cross-reaction with cryptococcal antigens, false positivity should be considered by clinicians when interpreting cryptococcal GXM antigen results.[5]

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Table 1 Sensitivity results of four point-of-care lateral flow assays for detecting cryptococcal glucuronoxylomannan antigen.

Organism (no. of isolates tested)	Dynamiker	Kangtai	Liming	IMMY
	Detection limit range (CFU/mL)			
C. neoformans (8)	4.0×10^2-2.0×10^4	4.0×10^2-2.0×104	4.0×10^2-1.0×105	1.0×10^3-2.0×10^4
C. neoformans var. *grubii* (3)	1.8×10^3-6.0×10^3	1.8×103-3.0×104	1.8×103-3.0×104	6.0×10^3-3.0×10^4
C. gattii (2)	1.0×10^1-1.3×10^2	1.0×101-1.3×103	1.0×10^2-1.3×103	1.0×10^2-1.3×10^3
C. albidus (1)	1.0×10^3	1.0×104	1.0×104	1.0×10^4
C. laurentii (1)	1.0×10^3	1.0×10^3	1.0×10^3	1.0×10^3
C. uzbekistanensis (1)	3.0×10^4	3.0×105	3.0×105	3.0×10^5
C. curvatum (1)	8.0×10^4	8.0×104	8.0×104	8.0×10^4
T. dermitis (1)	2.0×10^3	2.0×104	2.0×104	2.0×10^4
Trichosporon mucoides (1)	4.0×10^2	4.0×103	4.0×103	4.0×10^3
T. asahii (2)	5.0×10^3-1.1×10^6	5.0×103-1.1×106	5.0×103-1.1×106	5.0×10^3-1.1×10^6
T. montevideense (1)	1.2×10^6	1.2×106	1.2×106	1.2×10^6
T. inkin (1)	2.0×10^5	2.0×105	2.0×105	2.0×10^5
T. ovoides (3)	9.0×10^5-1.7×10^6	9.0×105-1.7×106	9.0×105-1.7×106	9.0×10^5-1.7×10^6
T. dohaense (2)	5.1×10^4-1.9×10^5	5.1×104-1.9×105	5.1×104-1.9×105	5.1×10^4-1.9×10^5
T. coremiiforme (1)	7.0×10^3	7.0×103	7.0×103	7.0×10^3
T. guehoae (1)	2.0×10^3	2.0×103	2.0×103	2.0×10^3
Organism (designation of isolates tested)	Dilution (0.5 M×)	Inconsistent results among the four tests		
C. gattii(A3530)	10^{-4}	+	+	-	-
C. uzbekistanensis(A5648)	10^{-1}	+	-	-	-
C. gattii(A5677)	10^{-4}	+	+	-	-
C. albidus(A5680)	10^{-2}	+	-	-	-
C. neoformans(A5676)	10^{-3}	+	+	+	-
C. neoformans var. *grubii* (A5923)	10^{-3}	+	+	+	-

Note: Abbreviations: '*C.*', *Cryptococcus*; '*T.*', *Trichosporon*.

Considering that different cryptococcal GXM antigen tests and taxonomic diversity of the involved pathogen/species may affect timely diagnosis of cryptococcal infections, we reported that the four cryptococcal GXM antigen tests all showed high consistency, with great sensitivity (80.65%) and specificity (81.16%). Further clinical investigations should be conducted to highlight the clinical value of these tests.

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