

Galactomannan Antigenemia for the Diagnosis of Invasive Aspergillosis in Neutropenic Patients with Hematological Disorders

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Objectives: Invasive aspergillosis (IA) is among the most common invasive fungal infections in neutropenic patients with hematological disorders in the authors' institution, King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand. Previous studies have reported the *Aspergillus* galactomannan enzyme immunosorbent assay (GM EIA) may be a useful diagnostic tool for IA. The authors evaluated the performance of the GM EIA for the diagnosis and monitoring of the course of IA in KCMH.

Material and Method: The authors prospectively performed the study from June 2002 to January 2004 in a consecutive series of adult neutropenic patients with hematological disorders who were at risk for developing IA. During hospitalization, serum galactomannan levels were measured once or twice weekly using the Platelia *Aspergillus* EIA test kit. The sensitivity and specificity of the GM EIA were calculated according to the proportion of patients with true and false positive and negative tests.

Results: There were 50 treatment episodes in 44 patients with 5 proven, 12 probable, and 33 possible or no IA. The cutoff GM index of > 0.75 was determined with a sensitivity of 94.1% and a specificity of 78.8%. There was a close relationship between clinical outcome and the kinetics of GM indices.

Conclusion: The GM EIA is a useful diagnostic tool for the diagnosis and monitoring of the course of IA in the presented institute.

Keywords: Galactomannan antigen, Galactomannan enzyme immunosorbent assay, Invasive fungal infection, Invasive aspergillosis, Febrile neutropenia

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Invasive fungal infections (IFIs) particularly invasive aspergillosis (IA) have been one of the major causes of morbidity and mortality in patients with hematological disorders who receive chemotherapy or undergo hematopoietic stem cell transplantation (HSCT)⁽¹⁻³⁾. Early diagnosis of IA may improve the clinical outcome, but it usually requires invasive procedures to obtain specimens for culture and histopathologic examination^(4,5). Unfortunately, such procedures are often precluded by thrombocytopenia or by the critical condition of the patients. Hence, a definite

diagnosis is rarely made before death or during the stage of infection in which the patient has a low fungal burden and therapy may be successful^(6,7). Over the past decade, there are two advances in the diagnosis of IA including high-resolution computed tomogram (HRCT) scanning of the chest and the detection of galactomannan (GM)⁽⁸⁻¹⁰⁾. GM is a polysaccharide cell-wall component of *Aspergillus* species that is released during the growth. A commercially available double-sandwich EIA for the detection of GM has recently been developed⁽¹¹⁾. The assay employs the rat monoclonal antibody EB-A2 recognizing the 1-5-b-D-galactofuranoside side chains of the GM molecule. The GM EIA has been demonstrated in several clinical studies to be a reliable diagnostic tool for IA. However,

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the reported sensitivity and specificity vary between 57%-100% and 66%-100%, respectively⁽¹⁰⁾. These disparate results may be explained by different study designs and case definitions; heterogeneity of the study population; use of low-risk controls; limited numbers of serum samples; and different cut-off levels of measuring GM.

At the authors' institution, King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand, IA is among the most common IFIs in neutropenic patients with hematological disorders. Unfortunately, culturing of blood or body fluids usually has a low diagnostic yield, and does not discriminate between invasive disease, colonization, and contamination^(4,5,12). Therefore, the authors needed to make an early diagnosis of IA by non culture method. To evaluate the potential of GM EIA for the diagnosis and monitoring of the clinical course of IA, we conducted a prospective study in neutropenic patients with hematological disorders who were at risk for developing IA.

Material and Method

Patients

The authors prospectively performed the study from June 2002 to January 2004 in a consecutive series of adult patients with hematological disorders who were at risk for developing IA at KCMH, Bangkok, Thailand. Eligible patients were 1) receiving chemotherapy with an expected duration of neutropenia of less than 500 cells/ μ L of at least 7 days or 2) undergoing allogeneic bone marrow or peripheral blood stem cell transplantation. Those patients, who were undergoing autologous bone marrow transplantation or less than 16 years old, were excluded from the present study. The present study was approved by the institutional review board of KCMH. Informed consent was obtained from patients or their legal guardians.

All patients were hospitalized, and antifungal prophylaxis with itraconazole oral solution (200-400 mg/day) was given twice a day throughout the period of neutropenia. Broad-spectrum antibiotics were empirically initiated at the first febrile episode of neutropenic patient according to the guidelines of Infectious Diseases Society of America. Patients, who had persistent fever after 5-7 days of appropriate antibiotic treatment, received amphotericin B (amphotericin B deoxycholate: 0.8-1.2 mg/kg/day or liposomal amphotericin B: 3-5 mg/kg/day) until the resolution of fever and neutropenia.

During hospitalization, blood samples were obtained once or twice weekly until death or discharge

from the hospital. Serum samples were stored at -70 °C until further analysis. All patients were surveyed for the development of IA including daily history taking; physical examination; chest x-ray at admission followed by weekly chest x-ray; repeated blood, urine, and sputum cultures as clinically indicated; and weekly surveillance cultures on stool and urine samples. In cases of clinical suspicion of IA, a diagnostic work-up was initiated including high-resolution pulmonary computed tomogram scan, bronchoalveolar lavage (BAL) or transbronchial biopsy if feasible. Clinical specimens were submitted for bacteria, fungal and mycobacterial cultures; and special staining for *Mycobacterium*, fungus and *Pneumocystis jirovecii*. Other diagnostic procedures were carried out on clinical indication. Necropsy or autopsy was pursued in all fatal cases unless there was a refusal by the patient's family.

Case definitions and classification

IA was diagnosed on the basis of the international definitions of IFI according to the Mycoses Study Group the European Organization for Research and Treatment of Cancer (EORTC-MSG) criteria⁽¹³⁾. IA was classified into four categories including proven, probable, possible, and no IA. Briefly, proven IA included all patients who had histologically proven disease or whom had a positive culture for *Aspergillus* obtained by percutaneous aspiration. Probable IA included all patients who had the development of a new opacity on their chest x-ray or HRCT, and repeated isolation of the same species of *Aspergillus* from the sputum or BAL. Possible IA included all patients who had the development of a new opacity on the chest x-ray or HRCT, and with no evident etiology.

Measurement of GM

Serum galactomannan levels were measured using the *Platellia Aspergillus* EIA test kit (Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France), as described previously⁽¹⁴⁾. Results were recorded as the ratio of the optical density (OD) of the sample to that of the threshold control samples. An OD index of 1.0 or more in two consecutive samples was considered positive. After all samples had been analyzed, data were combined with the clinical data, which had been collected independently.

Statistical analysis

The sensitivity and specificity of the GM EIA were calculated according to the proportion of patients with true and false positive and negative tests. Calcula-

Table 1. Characteristics of 17 patients with proven and probable invasive aspergillosis (IA)

No.	Age (yrs), sex	Hematological disorder	Treatment	IA category	Site	Duration of neutropenia (days)	Duration of hospitalization (days)	Duration of antifungal treatment (days)	Recovery from neutropenia (days)	GM index	Outcome
1.	53, M	AML	CT	Proven	Disseminated	22	34	19	Yes	6.64	Survived
2.	76, M	M M	CT	Proven	Lung	7	21	14	Yes	2.79	Survived
3.	50, M	AML	CT	Proven	Sinus	19	27	7	Yes	1.02	Survived
4.	18, M	Relapsed AML	CT	Proven	Disseminated	7	7	7	No	3.78	Died
5.	31, F	AA	HSCT	Proven	Lung, sinus	55	55	28	No	2.66	Died
6.	20, F	AML	CT	Probable	Lung, sinus	33	84	14	Yes	2.19	Survived
7.	58, F	ALL	CT	Probable	Lung, sinus	13	60	4	Yes	4.45	Survived
8.	29, M	AML	CT	Probable	Disseminated	50	54	13	No	4.13	Died
9.	55, F	AML	CT	Probable	Lung, sinus	27	84	62	Yes	2.67	Survived
10.	47, F	AML	CT	Probable	Lung	9	49	20	Yes	23.62	Survived
11.	34, M	CML → AML	CT	Probable	Lung	9	9	7	No	1.53	Died
12.	58, M	AML	CT	Probable	Lung	13	13	13	No	2.67	Died
13.	18, M	AA	HSCT	Probable	Lung	42	50	32	Yes	0.43	Survived
14.	31, M	ALL	HSCT	Probable	Lung, sinus	No neutropenia	53	7	Yes	1.41	Survived
15.	44, F	AML	CT	Probable	Lung	39	53	24	No	1.65	Died
16.	68, F	AML	CT	Probable	Lung	7	9	7	Yes	1.28	Survived
17.	29, F	AML	CT	Probable	Lung	91	91	43	No	1.67	Died

M: Male, F: Female, AML: acute myeloid leukemia, ALL: acute lymphocytic leukemia, AA: aplastic anemia, CML: chronic myeloid leukemia, CT: chemotherapy, HSCT: hematopoietic stem cell transplantation, GM-EIA: galactomannan EIA, ampho B: amphotericin B

lations were also performed based on the certainty of IA (proven, probable, or possible).

Results

Characteristics of the study population

According to the EORTC-MSG criteria, 50 consecutive treatment episodes in 44 patients were classified as proven IA (5 cases), probable IA (12), and possible or no IA (33). There were 23 male and 27 female patients. The number, demographic data, underlying hematological disorder, clinical characteristics, antifungal treatment, GM index, and clinical outcome of 17 patients with proven and probable IA are summarized in Table 1. The sites of proven and probable IA

were the lung (9 cases), lung and paranasal sinuses (4), paranasal sinuses (1), and multiple organs (3). There were 42 acute myeloid leukemia (AML), 5 HSCT, 2 acute lymphocytic leukemia (ALL), and 1 multiple myeloma (MM).

By the end of the study, eight patients had died and 42 had survived. The median duration of fever was 9.5 days (range: 0-60 days). The median duration of neutropenia was 20 days (range: 7-91 days), and the median duration of amphotericin B administration was 6 days (range: 0-60 days).

Calculating the cutoff GM index

The receiver-operator characteristic (ROC) curve and table of statistics for some selected cutoff GM index are shown in Fig. 1 and Table 2, respectively. The optimal trade-off inflection point for GM lay between 1.00 (sensitivity: 88.2%, specificity: 97%) and 1.25 (sensitivity: 88.2%, specificity: 100%). The sensitivity and specificity were 94.1% and 78.8% with a cutoff GM index of ≥ 0.75 if the test was used as the screening test.

Kinetics study of GM index during the clinical course of IA

The GM index was monitored at least once weekly during the clinical course after antifungal treatment in all patients with proven and probable IA. In all ten patients who survived, GM indices decreased to baseline values at the end of the clinical course (Fig. 2A). In contrast, all seven patients who died had persistently elevated GM indices until death (Fig. 2B).

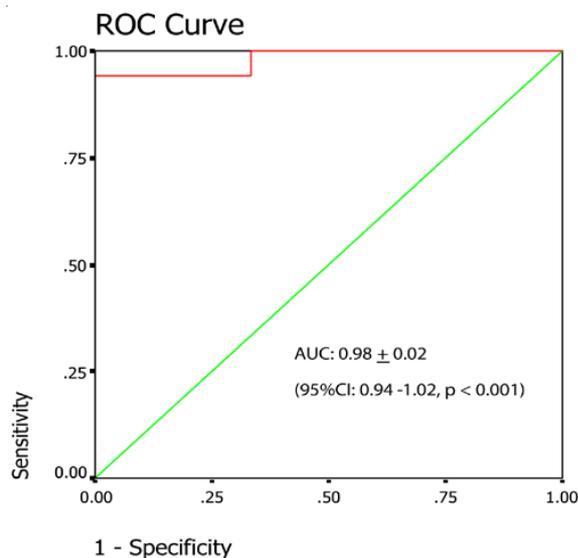


Fig. 1 Receiver-operator characteristic (ROC) curve values for some selected cutoff galactomannan (GM) index for the group of patients with proven and probable invasive aspergillosis as a standard

Discussion

There is still much uncertainty and controversy regarding the reliable methods for establishing the diagnosis of most IAs in febrile neutropenic patients^(4,5,8,9). Most clinicians approach this uncer-

Table 2. Sensitivity, specificity and predictive values for some selected cutoff galactomannan (GM) index for the group of patients with proven and probable invasive aspergillosis as a standard

GM index	Sensitivity	Specificity	PPV	NPV
0.50	0.941	0.667	0.593	0.957
0.75	0.941	0.788	0.696	0.963
1.00	0.882	0.970	0.938	0.941
1.25	0.882	1.000	1.000	0.943
1.50	0.765	1.000	1.000	0.892

PPV: positive predictive value, NPV: negative predictive value

tainty by empirically treating patients with suspected IA before infection becomes overwhelming and therapy may be unsuccessful. On the other hand, a substantial diagnosis is certainly still needed to avoid over-treat-

ment. The EORTC-MSG has recently developed standardized definitions of IFI in immunocompromised patients with cancer and HSCT for use in the context of clinical and epidemiological research⁽¹³⁾. Because

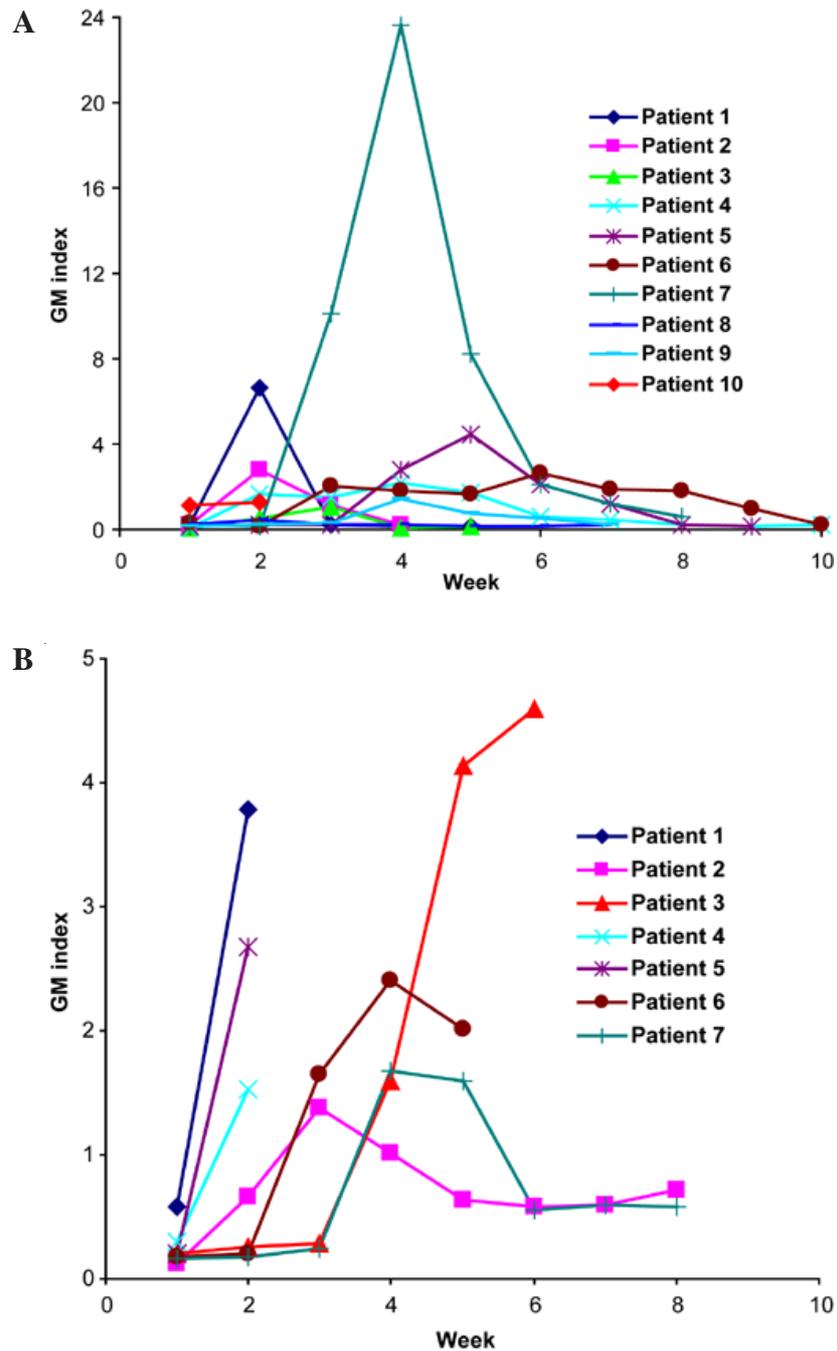


Fig. 2 Kinetics of galactomannan (GM) antigenemia detected by GM EIA in all ten patients with proven and probable invasive aspergillosis who survived (A) and seven patients who died (B)

culture has a poor sensitivity in the diagnosis of IA, and does not always distinguish between invasive disease, colonization, and environmental contamination in immunocompromised patients, several non-culture methods involving the detection of antigen, metabolites or nucleic acids have been devised^(4,9,15). The committee also proposed the use of *Aspergillus* antigen testing as one of microbiological criteria to support a probable diagnosis of IA⁽¹³⁾. A commercially available sandwich EIA for the detection of GM has recently developed using the rat monoclonal antibody EB-A₂^(10,11). The threshold for detection of GM by EIA is 1.0 ng/mL⁻¹ serum, compared to a 15.0 ng/mL⁻¹ threshold by the earlier latex agglutination method^(11,16). In all studies so far, the sensitivity of GM EIA varied considerably between 57% and 100%, and the specificity of the assay was between 66% and 100%⁽¹⁰⁾. The sensitivity and specificity of GM EIA in the present study ranged from 76.5% to 94.1% and from 66.7% to 100%, based on the GM index between 0.50 and 1.50. Several reasons that probably explain the reported differences in performance of the assay include the difference in the fungus (strain, growth phase and kinetics of GM release), the host (preexisting condition, site and extent of fungal disease and antifungal treatment) and the definition (definition of case, cutoff GM index and results)^(10,17). A cutoff GM index of ≥ 1.50 is recommended by the manufacturers. The Food and Drug Administration of the United States has approved a cutoff GM index as low as 0.50⁽¹⁰⁾. The improved sensitivity of GM EIA in the present study might be counterbalanced by a decreased of specificity when the cutoff GM index is lowered. Because the present study was aimed to evaluate the test for use in the initial screening of patients at risk to develop IA, a cutoff GM index of ≥ 0.75 seems to yield the optimal trade-off, with a sensitivity of 94.1% and a specificity of 78.8%. Furthermore, GM antigenemia preceded clinical diagnosis of proven and probable of IA on the basis of HRCT findings by a median of 5 days in five presented patients (data not shown). This observation is similar to those described by previous studies^(14,18). Therefore, a prospective screening for GM antigenemia in febrile neutropenic patients allows early diagnosis of IA, especially when this method is performed in combination with other diagnostic procedures.

The usefulness of kinetics monitoring of the GM indices for evaluating the clinical outcome after antifungal treatment has been described^(14,19,20). As shown in Fig. 2A and 2B, there was a close parallel between GM indices and clinical outcome. All patients,

who had persistently high GM indices after antifungal treatment, eventually died, whereas those whose GM indices decreased to baseline values survived. Most patients who died also did not have recovery from neutropenia. The present results suggest that measurement of GM indices along with neutrophil counts is useful for predicting the clinical course and outcome of IA. The mechanism of which circulating level of GM decreases in the setting of appropriate antifungal treatment, and neutrophil recovery may involve an inhibition of hyphal growth of *Aspergillus*. It is also possible that amphotericin B will alter the kinetic release of GM into circulation⁽¹⁰⁾.

The present study has some limitations, even though it has relatively homogenous population regarding hematological disorders, diagnostic procedures, and treatment modality. The use of potentially contaminated antibiotics including piperacillin-tazobactam and other beta-lactams may have affected the false positivity of the GM EIA results⁽²¹⁾. The number of proven cases of IA was too low because the critical condition of many patients did not permit an invasive diagnostic procedure. Addition of the probable cases of IA might have influenced the validation of GM EIA. The authors did not include possible cases of IA in the analysis of validity of GM EIA to avoid misinterpretation of the results due to the relatively less specificity of the possible IA group. As the ROC analysis, the mean area under the ROC curve (AUC) was very good (0.98). The authors intend to use the cutoff GM index of ≥ 0.75 as an aid for the diagnosis of IA. The positive result will trigger further investigations for disease such as HRCT, bronchoalveolar lavage or tissue biopsy.

In conclusion, GM EIA can be used as an aid for the diagnosis as well as for monitoring and predicting clinical outcome of IA. In future, the authors intend to compare other non-culture methods such as real-time polymerase chain reaction or nucleic acid sequence-based amplification with GM EIA for the diagnosis of IA in febrile neutropenic patients.

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แอนติเจนกาแลกโตแมนแนนในเลือดสำหรับการวินิจฉัยการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลมในผู้ป่วยโรคเลือดที่มีเม็ดเลือดขาวต่ำ

ชัชฌา สวนกระต่าย, พิชัย คณิตจรัสกุล, เกษิณี อรุณย์มงคล

วัตถุประสงค์: การติดเชื้อราแอสเปอร์จิลลัสเป็นการติดเชื้อราแบบลูกกลมที่พบได้บ่อยในผู้ป่วยโรคเลือดที่มีเม็ดเลือดขาวต่ำในโรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร ประเทศไทย หลาย ๆ การศึกษารายงานการตรวจแอนติเจนกาแลกโตแมนแนนของแอสเปอร์จิลลัสโดยใช้วิธีเอนไซม์อิมมูโนซอร์เบนต์ว่าน่าจะมีประโยชน์ในการช่วยวินิจฉัยการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลม จึงเป็นที่มาของการศึกษาการตรวจแอนติเจนกาแลกโตแมนแนนสำหรับการวินิจฉัยและใช้ติดตามการรักษาการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลมในโรงพยาบาลจุฬาลงกรณ์

วัสดุและวิธีการ: เป็นการศึกษาแบบไปข้างหน้าระหว่างปี พ.ศ. 2545 ถึง พ.ศ. 2547 ในผู้ป่วยผู้ใหญ่ทุกรายที่มีโรคเลือดที่มีเม็ดเลือดขาวต่ำ และมีโอกาสเสี่ยงสูงต่อการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลม มีการวัดระดับแอนติเจนกาแลกโตแมนแนนสัปดาห์ละ 1-2 ครั้งในผู้ป่วยทุกรายที่รับไว้ในโรงพยาบาล โดยใช้ชุดทดสอบของผลาทีเลียแอสเปอร์จิลลัสเอนไซม์อิมมูโนซอร์เบนต์ การคำนวณความไวและความจำเพาะของการตรวจแอนติเจนกาแลกโตแมนแนนโดยวิธีเอนไซม์อิมมูโนซอร์เบนต์ขึ้นกับสัดส่วนผู้ป่วยที่มีและไม่มีเชื้อราแอสเปอร์จิลลัสแบบลูกกลม และได้และไม่ได้ผลบวกต่อการตรวจ

ผลการศึกษา: มีผู้ป่วยทั้งหมด 44 ราย แต่มีเม็ดเลือดขาวต่ำจากการรักษาทั้งหมด 50 ครั้ง โดยแยกเป็นการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลม ประเภทแน่นอน 5 ราย ประเภทน่าจะเป็น 12 ราย และอีก 33 รายเป็นประเภทอาจเป็นไปได้หรือไม่มีการติดเชื้อ ตรวจพบแอนติเจนกาแลกโตแมนแนนในเลือดโดยใช้วิธีเอนไซม์อิมมูโนซอร์เบนต์ทั้งใช้ค่าจุดตัด > 0.75 เป็นผลบวก มีความไวและความจำเพาะเป็นร้อยละ 94.1 และร้อยละ 78.8 ตามลำดับ และมีความสัมพันธ์อย่างใกล้ชิดระหว่างผลการรักษาทางคลินิกและการเปลี่ยนแปลงของแอนติเจนกาแลกโตแมนแนนนี้

สรุป: การตรวจแอนติเจนกาแลกโตแมนแนนโดยวิธีเอนไซม์อิมมูโนซอร์เบนต์เป็นการตรวจที่จำเป็นสำหรับการวินิจฉัยและติดตามการรักษาการติดเชื้อราแอสเปอร์จิลลัสแบบลูกกลมในโรงพยาบาลจุฬาลงกรณ์ได้ดี
