Diagnostic Accuracy of Serum Galactomannan Assay in Children with Acute Myeloid Leukemia: Effect of the Revised EORTC/MSGERC 2020 Criteria

Akut Myeloid Lösemili Çocuklarda Serum Galaktomannan Testinin Tanısal Doğruluğu: Revize Edilmiş EORTC/MSGERC 2020 Kriterlerinin Etkisi

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To the Editor,

Patients with acute myeloid leukemia (AML) are at high risk of invasive fungal infections (IFIs) due to profound and prolonged neutropenia as a result of induction chemotherapy protocols [1]. Invasive aspergillosis (IA) became the most common form of IFI after the introduction of fluconazole prophylaxis [1]. The serum galactomannan (GM) assay has emerged as an important diagnostic tool for the early detection of IA. This study aimed to determine the accuracy of the serum GM test and the effect of the revised 2020 European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSGERC) definitions on IA incidence in children with AML.

We retrospectively reviewed the cases of 71 pediatric patients treated for AML between January 2005 and December 2022 in the Pediatric Hematology Department of Ege University. IA was defined according to the 2008 EORTC/MSG criteria and compared with the new 2020 criteria [2,3]. GM testing was conducted twice a week during the neutropenia period. True-positive antigenemia was defined as a positive GM test with the diagnosis of proven or probable IA (Table 1).

Thirty-six of the patients were male (50.7%) and 35 (49.3%) were female. The median age was 55 months (range: 1-214 months). Thirty-three (46.4%) of the patients were classified as being of high risk. A total of 275 febrile neutropenia episodes were evaluated and IA was thought to account for 11.2% of them. Probable and possible IA events were 2.54% and 8.7%, respectively. There were no proven IA events. Since 2013, 47 (66%) patients had received mold-active antifungal prophylaxis with voriconazole and a significant decrease in the rate of IA was achieved with this prophylaxis [19 (6.9%) attacks before the pre-prophylaxis period, 12 (4.3%) attacks after prophylaxis began; p=0.015].

A total of 1528 serum samples from 65 patients with at least one serum GM result were analyzed. The median number of GM tests was 16 (range: 2-89). Thirty-one (47.6%) patients had positive GM antigenemia, which corresponded to 5.1% (n=79) of all serum samples. GM was truly positive in 16.1% of these cases.

According to the 2008 EORTC/MSG criteria, the sensitivity of the serum GM test was 62.5% [95% confidence interval (CI): 24.49-91.48%] and the specificity was 54.39% (95% CI: 40.66-67.64%) with a positive predictive value of 16.13% (95% CI: 9.49-26.08%), a negative predictive value of 91.18% (95% CI: 80.37-96.31%), and accuracy of 55.38% (95% CI: 42.53-67.73%) for proven/probable IA.

According to the 2020 EORTC/MSGERC criteria, the sensitivity was 25% (95% CI: 0.63-80.59%) and the specificity was 81.97% (95% CI: 70.02-90.64%) with a positive predictive value of 8.33% (95% CI: 1.51-35.02%), a negative predictive value of 94.34% (95% CI: 90.34-96.74%), and accuracy of 78.46% (95% CI: 66.51-87.69%) for proven/probable IA (Table 2).

Acet-Öztürk et al. [4] reported that the use of 2020 EORTC/MSGERC criteria resulted in a significant 27.3% reduction in probable IA diagnoses. Similarly, with the new 2020 criteria, the specificity of the serum GM test increased and the number of patients in the probable IA group decreased by 42% (3/7 cases) with the GM test alone in our study; however, the lack of an *Aspergillus* PCR test was a limitation. Siopi et al. [5] reported that episodes of probable IA were reduced by 33% with GM alone and by 11% when GM + PCR were used as mycological criteria.

False positivity of the serum GM test remains a significant disadvantage. However, the contribution of our high mold-effective prophylaxis rate to the false negative rate cannot be denied.

Table 1. Comparison of 2008 EORTC/MSG and 2020 EORTC/MSGERC criteria for probable invasive aspergillosis.

	2008 EORTC/MSG criteria	2020 EORTC/MSGERC criteria
Host factors	• Recent history of neutropenia (<0.5x10^9 neutrophils/L or <500 neutrophils/mm^3 for >10 days) temporally related to the onset of fungal disease • Receipt of an allogeneic stem cell transplant • Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks • Treatment with T-cell immunosuppressants • Inherited severe immunodeficiency (chronic granulomatous disease, severe combined immunodeficiency, etc.)	• Recent history of neutropenia (<0.5x10^9 neutrophils/L for >10 days) temporally related to the onset of invasive fungal disease • Hematologic malignancy • Receipt of an allogeneic stem cell transplant • Receipt of a solid organ transplant • Prolonged use of corticosteroids at ≥0.3 mg/kg for ≥3 weeks in the past 60 days • Treatment with T-cell immunosuppressants (including calcineurin inhibitors) • Treatment with B-cell immunosuppressants such as Bruton's tyrosine kinase inhibitors, e.g., ibrutinib • Inherited severe immunodeficiency such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency • Acute graft-versus-host disease of grade III or IV involving the gastrointestinal system, lungs, or liver that is refractory to first-line treatment with steroids
Clinical features	• **Lower respiratory tract fungal disease** Presence of 1 of the following 3 signs on CT: · Dense, well-circumscribed lesions(s) with or without a halo sign · Air-crescent sign · Cavity • **Tracheobronchitis** · Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen upon bronchoscopic analysis • **Sinonasal infection** Imaging showing sinusitis plus at least 1 of the following 3 signs: · Acute localized pain (including pain radiating to the eye) · Nasal ulcer with black eschar · Extension from the paranasal sinus across bony barriers, including into the orbit • **Central nervous system infection** 1 of the following 2 signs: · Focal lesions on imaging · Meningeal enhancement on MRI or CT	• **Pulmonary aspergillosis** Presence of 1 of the following 4 patterns on CT: · Dense, well-circumscribed lesions(s) with or without a halo sign · Air crescent sign · Cavity · Wedge-shaped and segmental or lobar consolidation • **Tracheobronchitis** · Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis • **Sinonasal diseases** · Acute localized pain (including pain radiating to the eye) · Nasal ulcer with black eschar · Extension from the paranasal sinus across bony barriers, including into the orbit • **Central nervous system infection** 1 of the following 2 signs: · Focal lesions on imaging · Meningeal enhancement on magnetic resonance imaging or CT
Mycological evidence	• Cytology (direct microscopy or culture) • Mold in sputum, BAL, bronchial brush, or sinus aspirate samples •Galactomannan antigen ≥0.5 in plasma, serum, BAL, or CSF •β-D-glucan detected in serum	• Mold recovered by culture from sputum, BAL, bronchial brush, or aspirate • Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold • Tracheobronchitis *Aspergillus* recovered by culture of BAL or bronchial brush; microscopic detection of fungal elements in BAL or bronchial brush indicating mold • **Sinonasal diseases** Mold recovered by culture of sinus aspirate samples; microscopic detection of fungal elements in sinus aspirate samples indicating mold • **Galactomannan antigen** Antigen detected in plasma, serum, BAL, or CSF; any 1 of the following: · Single serum or plasma: ≥1.0 · BAL fluid: ≥1.0 · Single serum or plasma: ≥0.7 and BAL fluid: ≥0.8 · CSF: ≥1.0 • ***Aspergillus* PCR** Any 1 of the following: · Plasma, serum, or whole blood with 2 or more consecutive positive PCR tests · BAL fluid with 2 or more duplicate positive PCR tests · At least 1 PCR test positive for plasma, serum, or whole blood and 1 PCR test positive for BAL fluid *Aspergillus* species recovered by culture from sputum, BAL, bronchial brush, or aspirate

BAL: Bronchoalveolar lavage, CSF: cerebrospinal fluid, CT: computed tomography, MRI: magnetic resonance imaging, PCR: polymerase chain reaction.

Table 2. Comparison of serum galactomannan test performance in the diagnosis of invasive aspergillosis according to 2008 EORTC/MSG and 2020 EORTC/MSGERC criteria.

	2008 EORTC/MSG criteria	2020 EORTC/MSGERC criteria
Sensitivity (95% CI)	62.5% (24.49-91.48)	25% (0.63-80.59)
Specificity (95% CI)	54.39% (40.66-67.64)	81.97% (70.02-90.64)
PPV (95% CI)	16.13% (9.49-26.08)	8.33% (1.51-35.02)
NPV (95% CI)	91.18% (80.37-96.31)	94.34% (90.34-96.74)
Accuracy (95% CI)	55.38% (42.53-67.73)	78.46% (66.51-87.69)

EORTC/MSG: European Organization for the Research and Treatment of Cancer/Mycoses Study Group; EORTC/MSGERC: European Organization for the Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

In conclusion, diagnostic criteria should be reviewed over time and further investigations are essential for accurate diagnostic tests in the early diagnosis of IA.

Keywords: Galactomannan, Aspergillosis, Invasive fungal infections, Acute myeloid leukemia, Children

Anahtar Sözcükler: Galaktomannan, Aspergilloz, İnvazif mantar enfeksiyonları, Akut myeloid lösemi, Çocuk

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