Section 3. Colombian consensus on the diagnosis and treatment of extrapulmonary aspergillosis in adult patients*

***From the Colombian Association of Infectious Diseases (ACIN) Mycosis Group, for the Development of the Colombian Consensus on the Management of Invasive Fungal Disease**

Annex 1. Biomarkers for the diagnosis of an IA.

Test	Clinical sample	Cut-off point (ODI)	SE (%)	SP (%)	Comments and Interpretation
AGA	**Serum**	≥ 0.5 ≥ 1.0 ≥ 1.5	78-79 65-78 48-64	81-86 91-94 95	• AGA, a double-sandwich EIA (Platelia *Aspergillus*, Bio-Rad, Marnes-La-Coquette, France), using a monoclonal EB-A2 Ab, is a well-established and extensively studied method for the diagnosis of proven/probable IA and can be used in various body fluids. • It is included as an EORTC/MSG mycologic criterion for diagnosis of a probable IA • It can be performed in local clinical laboratories, it does not yet have an external quality control, an ODI of positivity is not directly recommended, following the recommendation given by the manufacturer. • The recommended optimal ODI for diagnosis (detected in plasma, serum, BAL or CSF): - Any of the following: - Individual serum or plasma: ≥ 1.0 - BAL: ≥ 1.0 - Individual serum or plasma: ≥ 0.7 and BAL ≥0.8 - CSF: ≥1.0
	BAL	≥ 0,5 ≥ 1,0	86 85	89 94	• There is a lack of consensus regarding the accepted ODI, as the diagnostic yield varies according to the population studied (i.e., hematologic malignancy, SOT, ICU, etc.). - A higher ODI (> 1.0) correlates with better diagnostic yield and higher sensitivity than with AGA from serum. • The combination of AGA measurement from BAL with molecular methods (PCR targeting *A. fumigatus* or *Aspergillus* spp.) improves the diagnostic yield (SE and SP of 97% for AGA or PCR positive).
(1,3)-β-D-glucan (BDG)	**Serum**	>60-80 pg/mL	76	85	• BDG is a cell-wall polysaccharide component of many pathogenic fungi, including *Candida*, *Fusarium* and *Pneumocystis* species, with the exception of mucorales and some *Cryptococcus* species. • It is included as an EORTC/MSG mycologic criterion for diagnosis of probable IFD; unfortunately, it is not pathogen-specific and cannot differentiate between fungal species; furthermore, pretest preparations may limit its routine applicability. • It has good sensitivity and specificity. However, the PPV is poor, associated with a high false positive rate, with an NPV of around 80-90%. - It may be slightly more sensitive than AGA from serum, although it is limited by its low specificity. - Its diagnostic accuracy is inferior to the detection of AGA from BAL.

LFD	**Serum**	N/A	82	98	• The *Aspergillus* LFD test is useful for the diagnosis of an IA at the POC (point-of-care). It uses a murine monoclonal Ab, JF4, highly specific against growing *Aspergillus* species (different from that used in the Platelia AGA *Aspergillus* assay). • It is a rapid test (≈ 15 min) easy to manipulate and does not require specific laboratory equipment, In addition, no cross-reactions with drugs or contaminating infections have yet been observed that have been shown to cause false-positive reactions. A limitation is that in many countries it is not available. • The *Aspergillus* LFD test has superior sensitivity and specificity compared to serum AGA and BDG tests. - It has more accurate results than standard serological markers, although interpretation of the results is subjective. - It has better diagnostic yield than AGA when used as a screening test rather than as a confirmatory test. - It is useful for confirming or excluding IA when combined with other tests (such as AGA and PCR).
	BAL	N/A	66-100	81-94	• The *Aspergillus* LFD test from BAL has been evaluated in several studies, including multicenter studies and in different patient populations. • In critically ill patients, it has a sensitivity and specificity comparable to the AGA test from BAL.
PCR	**Serum**	N/A	84-88	75-76	• Fungal DNA detection tests, such as PCR, allow rapid diagnosis of IA compared to conventional methods. - In house techniques and commercial platforms are available that detect panfungal targets or species-specific genes. - In high-risk patients, PCR-based methods based on serum, plasma, whole blood and/or BAL have been implemented, with high sensitivity and specificity. • It is included as an EORTC/MSG mycologic criterion for diagnosis of proven/probable IA. • PCR shows moderate diagnostic accuracy when used as a screening test, but with a high NPV which allows IA to be ruled out. - With a low PPV, if disease prevalence is low, the ability to rule out IA is limited. • *Aspergillus* PCR - Any of the following: - 2 or more consecutive positive PCR tests from plasma, serum or whole blood. - 2 or more positive duplicate PCR tests from BAL. - At least 1 positive PCR test from plasma, serum or whole blood together with 1 positive PCR test from BAL
	BAL	N/A	91-92	90-96	

IA: invasive aspergillosis; AGA: *Aspergillus* galactomannan antigen; EIA: Enzyme immunoassay; Ab: Antibody: Ag: Antigen; SE: Sensitivity; SP: Specificity; N/A: Not applicable; BDG: (1,3)-β-D-glucan; ODI: Optical Density Index; SOTR: Solid Organ Transplant Recipient; HSCT: Hematopoietic stem-cell transplantation; GVHD: graft-versus-host disease; BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid; PCR: Polymerase chain reaction; IPA: Invasive pulmonary aspergillosis; LFD: Lateral Flow Device (*Aspergillus*); PPV: Positive predictive v alue; NPV: Negative predictive value.
Adapted from: Donnelly JP et al.[65], Maertens JA et al.[70], Patterson TF et al.[72], García-Vidal C et al.[76], Klein CN et al.[177], Arvanitis M et al.[178].

Annex 2. Treatment of IA based on previous treatment or administered prophylaxis.

Antifungal pretreatment or prophylaxis	Antifungal of choice	Alternative antifungal	Comments
PCZ	L-AmB	L-AmB + echinocandin VCZ + ANF ISZ	TDM before starting treatment. If possible, initiate treatment according to the results of the AST.
VCZ	L-AmB VCZ + ANF	L-AmB + echinocandin ISZ	TDM before starting treatment. If possible, initiate treatment according to the results of the AST. If possible, de-escalate to VCZ.
Echinocandin[+]	VCZ VCZ + ANF	L-AmB L-AmB + echinocandin ISZ	If possible, initiate treatment according to the results of the AST.
LC-AmB	VCZ VCZ + ANF	L-AmB + echinocandin ISZ PCZ	If possible, initiate treatment according to the results of the AST.

[+]*Caspofungin, anidulafungin, micafungin*
VCZ: Voriconazole; PCZ: Posaconazole; ISZ: Isavuconazole; L-AmB: Liposomal Amphotericin B; LC-AmB: Amphotericin B lipid complex; ANF: Anidulafungin; TDM: Therapeutic drug monitoring of antifungal agents; AST: Antifungal sensitivity testing.
Adapted from: García-Vidal C et al.[76], Ruiz-Camps I et al.[179].