Section 1. Colombian consensus on the diagnosis and follow-up of invasive aspergillosis and *Aspergillus* disease in adult and pediatric 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. Voting on the questions of the Consensus modules (Delphi methodology).

MODULE	No. of voters	Average	Median	Minimum rated value	Maximum rated value	Percentage of agreement
Diagnosis of Invasive Aspergillosis (IA)/*Aspergillus* Disease	20	7.9	9	1/1	9/9	89
Antifungal prophylaxis for IFD/IA	20	6.1	9	1/1	9/9	76
Empirical Antifungal Treatment (EAT) and/or Diagnostic-driven antifungal treatment (DDAT) of IFD/IA	20	7.1	9	1/1	9/9	86
Targeted antifungal treatment of IA/IPA	20	7.6	9	1/1	9/9	92
Therapeutic management of IA in the pediatric and neonatal patient	18	8.8	9	1/1	9/9	99
Prevention of Infections Associated with *Aspergillus* spp. and Considerations for the Implementation of a Program for Optimized Use of Antifungals (POUA)	20	8.9	9	1/1	9/9	99
Diagnosis and Therapeutic Management of Extrapulmonary Aspergillosis	20	8.8	9	1/1	9/9	98
Diagnosis and Therapeutic Management of Chronic and/or Saprophytic Syndromes Associated with *Aspergillus* spp.	20	8.9	9	1/1	9/9	98
Diagnosis and Therapeutic Management of Allergic Syndromes Associated with *Aspergillus* spp.	20	8.6	9	1/1	9/9	98

Annex 2. Scoring by AGREE II methodology of the guides obtained from the literature search.

Module	Bibliographic references											
	(4)	(8)	(21)	(34)	(79)	(81)	(97)	(204)	(251)	(252)	(253)	(254)
Module 1: scope and objectives	91,3	92,2	91,0	88,9	96,3	90,5	89,6	83,3	97,9	94,4	93,5	81,9
Module 2: participation of those involved	69,4	56,7	68,8	66,7	72,2	65,1	58,3	51,1	74,3	71,3	71,3	61,1
Module 3: rigor in the evaluation	82,0	45,4	77,3	78,3	83,0	68,5	76,8	43,3	85,7	78,5	79,9	71,4
Module 4: clarity in presentation	90,9	82,2	89,6	89,4	95,4	90,5	88,9	62,8	95,1	89,8	98,1	88,2
Module 5: applicability	47,6	15,0	27,6	37,1	30,6	20,8	26,6	18,8	35,9	25,0	20,8	27,1
Module 6: editorial independence	82,1	86,7	90,6	74,2	95,8	91,7	53,1	60,0	93,8	97,2	95,8	93,8
Number of evaluators	14	5	8	10	6	7	8	10	8	6	6	8
Total average	77,2	63,0	74,1	72,4	78,9	71,2	65,6	53,2	80,5	76,0	76,6	70,6

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Annex 4. Table of declaration of conflicts of interest of the authors.

Abbreviation	Conflict of interest declared:	Who finances:
JOG	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Astellas. Colombia /Latin America 2017-2020
PRP	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Biotoscana, Stendhal Colombia /Latin America 2017-2020
CPG	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Merck Colombia, Amarey Nova medical, Biomerieux, Novartis, Abbott-Lafrancol, Takeda. Colombia/Latin America 2017-2020
AMC	Declares no conflict of interest.	Declares no conflict of interest.
SCM	Declares no conflict of interest.	Declares no conflict of interest.
BPE	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Amarey Novamedical, Takeda, Janssen, Technofarma, Rochen Biocare Colombia/Latin America 2017-2020
ELM	Has received financial support for research and scientific-welfare sponsorship.	Takeda, Sanofi Pasteur Colombia/Latin America 2017-2020
FG	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Gilead, Biomerieux. Colombia/Latin America 2017-2020
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DFC	Declares no conflict of interest.	Declares no conflict of interest.
FM	Declares no conflict of interest.	Declares no conflict of interest.
HFS	Declares no conflict of interest.	Declares no conflict of interest.
IB	Has been a consultant, lecturer, has received financial support for research and scientific-welfare sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Biotoscana, Stendhal Colombia /Latin America 2017-2020

Annex 5. Putative Invasive Pulmonary Aspergillosis[+].

1. Positive *Aspergillus* culture from clinical samples from the lower respiratory tract:
2. Compatible signs and symptoms (one of the following): • Refractory fever for at least 3 days, with adequate antibiotic treatment. • Recurrent fever after a period of defervescence of at least 48 hours, despite antibiotic treatment and without other apparent cause. • Pleuritic chest pain. • Pleuritic rubbing. • Dyspnea. • Hemoptysis. • Worsening of respiratory failure, despite adequate antibiotic treatment and ventilatory support.
3. Abnormal images on portable chest X-ray or chest CT:
4. 4a or 4b 4a. Host Risk Factors (one of the following conditions): • Neutropenia (ANC: 500 cells/µL), before or at the time of admission to the ICU. • Underlying hematologic or oncologic malignancy treated with cytotoxic drugs. • Corticosteroid treatment (prednisone-equivalent, ≥ 20 mg/d). • Congenital or acquired immunodeficiency. 4b. Semi-quantitative • Positive *Aspergillus* culture from BAL (+ or ++), without bacterial growth, together with microscopic observation of septate hyphae in the cytological study.

[+]*all four criteria must be present.*
It is considered as a fungal colonization of the respiratory tract: When > 1 criterion necessary for the diagnosis of a putative IPA is not met.
CT: computed tomography; ANC: Absolute neutrophil count; IPA: invasive pulmonary aspergilosis; ICU: Intensive Care Unit; BAL: Bronchoalveolar lavage.
Adapted from: García-Vidal C et al.[81], Meersseman W et al.[105], Blot SI et al.[236]

Annex 6. Serological tests available for diagnosis of Aspergillus disease.

Test	Description	Comments
Precipitation in gels	• Known as DID, ID or precipitin test. • An agarose gel is prepared with wells cut into the gel. The patient sample is added to the central well, and the Ags and control Abs are added into the outer wells. • If the target Abs are present in the sample, precipitation lines will be formed by interaction with the respective control Ags or Abs.	• All types of Abs precipitate, but IgG predominates. • The limitation of the test is the time it takes to complete (at least 5 days), it is tiresome and requires significant training. The interpretation of the results is subjective. • It does not require complex equipment (as compared to ELISA). • It is less sensitive than other Ab detection tests. • Commercial preparations of *A. fumigatus* Ags are available to perform the test.
CIE	• CIE is an improvement to the ID method, where movement through the gel is accelerated by the application of an electric current, and precipitation occurs within a few hours.	• CIE is preferred to ID because of its speed and because it requires a smaller amount of reference serum and antigenic extract to perform the test. • The sensitivity of CIE is similar to that of ID.
Complement fixation	• The patient sample is heated to destroy all existing complement proteins, then complement proteins and a standardized *Aspergillus* Ag is added. Finally, SRBCs are added pre-bound to the anti-SRBC Ab. • If the target Abs are present in the mixture, they will bind to the Ag that has been added and will form complexes, which react with the complement proteins until they are depleted to save the integrity of the SRBCs. • If *Aspergillus*-specific Abs are not present, complement proteins lyse the red blood cells, changing the color of the mixture.	• The technique is quite laborious and the interpretation of the results is subjective. • Semi-quantitative results can be obtained by serial dilutions of serum.

ELISA	• The patient sample is added to a mixture containing the specific Ag. • If Abs are present in the sample, they will bind to the Ag attached to the support. • Subsequently, the Abs are added with the conjugated enzyme, which binds to the primary Ab. • The color change is detected by optical density measurement. • Several types of ELISA are available: (a) competitive ELISA, where the labeled Ag competes with unlabeled Ag to bind with a limited amount of Ab and, (b) sandwich ELISA, where the Ag reacts with excess Abs from the solid phase, and bound Ag is treated with excess-labeled Ab.	• This technique allows the detection of individual types of Abs (IgG, IgM, IgA, etc.). • It can be performed manually, but requires a spectrophotometer in suitable conditions. • The technique is available in a fully automated way, which reduces costs and results are obtained in 2 hours. Results are positive in most sera, with a limit provided by the manufacturer to differentiate elevated from normal levels. However, they require expensive equipment and a reliable power supply. • The performance of ELISA tests is varied, and tests with a SE: 90% and SP: 85% are preferred. • Commercial tests available are: (a) Bio-Rad (SE:86-97.4%; SP: 89.6-98.2%), (b) Bordier (SE:97.4%; SP: 90.3%), (c) ImmunoCAP (SE: 83.8-97.9%; SP: 98%), and (e) Immulite (SE:92.9-96%; SP:98-99.3%).
Immunoblot	• Gel electrophoresis is used to separate *Aspergillus* Ags by molecular weight. • Ags are then transferred to a membrane to which human serum is added. • An identical series of reactions to ELISA is then performed, producing a color change visible to the naked eye at the location of the Ag on the membrane when positive.	• Complex equipment is not required, but it is a time-consuming test.
Immunochromatography (Lateral flow devices [LFDs])	• The technology is based on a series of capillary beds that can spontaneously transport a fluid. The patient sample is added to a first bed, which soaks everything with excess fluid. • The remains are transferred to a second bed, which contains the Ab with an enzyme conjugate, which bind to the Ags or Abs present in the analyzed sample. • The Ag-Ab complexes then pass to a third bed, which contains the capture Ab that bind to the complexes. • Only control Abs without Ag bind to an additional bed, thus serving as a control to ensure that the method has worked correctly.	• They are fast, easy to use (one-step), low operational cost, simple instrumentation, with little or no interference due to chromatographic separation, high specificity and improved sensitivity, long-term stability under different environmental conditions and portability of the device. • Only one commercial LFD device is available for the detection of specific *Aspergillus* IgG Abs. With SE: 88.9-91.6% and SP: 96.3-98%, being comparable with ELISA tests, although it does not allow quantitative results.

Ab: Antibody: Ag: Antigen; DID: Double immunodiffusion; ID: Immunodiffusion; CIE: Counterimmunoelectrophoresis; SRBC: Sheep red blood cells; ELISA: Enzyme-linked immunosorbent assay; SE: Sensitivity; SP: Specificity.
Adaptado de: Wilopo BAP y col.[9], Arvanitis M y col.[76], Richardson M y col.[85], Page ID y col.[86], Lindsley MD et al.[95].

Annex 7. 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 value; NPV: Negative predictive value.
Adaptado de: Donnelly JP y col.[77], García-Vidal C y col.[81], Maertens JA et al.[94], Patterson TF et al.[129], Arvanitis M et al.[172], Klein CN et al.[228]

Annex 8. Available methods for TDM.

Methods	Advantages	Limitations
Chromatographic (HPLC, UV, LC/MS-MS)	• Reference methods, with high sensitivity, specificity, fast analysis (3-5 hours). - HPLC/UV is a commercially available technology that can quantify multiple drugs in a single sample. - LC/MS-MS is a very sensitive and specific technology that can quantify multiple drugs in a single sample.	• It requires expensive equipment, maintenance and specialized personnel. • The response time is conditioned to the reception and centralization of the samples in reference centers. - HPLC/UV is subject to interference by different substances, and with slow execution times. - LC/MS-MS is expensive and not widely available.
Microbiological (bioassays)	• Cheaper and easier to perform. • Results in 24 hours (minimum reading and incubation time).	• Less sensitive, confusing results in combination therapy, requires cross-validation. • Interferences with other drugs, including other antifungals.

TDM: Therapeutic drug monitoring of antifungal agents; HPLC: High-performance liquid chromatography; UV: Ultraviolet light; LC/MS-MS: Liquid Chromatography/Mass Spectrometry.
Adapted from: Ashbee HR et al.[193], Cendejas-Bueno E et al.[240]

Annex 9. Therapeutic drug monitoring of antifungal agents (TDM).

Clinical scenarios where TDM may be indicated	Examples, comments
Populations with greater pharmacokinetic variability.	Impaired gastrointestinal function, liver dysfunction, pediatric population, elderly patients, obese patients, critically ill patients.
Change in pharmacokinetics	Change from intravenous to oral route, change in gastrointestinal function, change in liver function, physiological instability.
Drug interactions	Patient receiving drugs known to induce cytochrome P450 enzymes, especially CYP3A4, antacids, proton pump inhibitors (ITZ capsules, PCZ suspension), antiretroviral drugs. There should be records of the drugs administered to patients, using a database to detect drug interactions, before starting and stopping the administration of antifungals.
Poor prognosis disease	Extensive or bulky infection, lesions contiguous with critical structures, CNS infection, multifocal or disseminated infection.
Compliance concerns	Issue with longer-term consolidation therapy, secondary prophylaxis in outpatient setting.
Suspected breakthrough infection	If fungal disease progression occurs in the context of adequate antifungal exposure.
Suspected drug toxicity, especially neurotoxicity (VCZ).	Exposure-response relationships are described for other toxicities (e.g., hepatotoxicity), the utility of TDM to prevent the occurrence of neurotoxicity has not yet been fully established.

TDM: Therapeutic drug monitoring of antifungal agents; ITZ: Itraconazole; PCZ: Posaconazole; CNS: Central nervous system; VCZ: Voriconazole.
Adapted from: Ullmann AJ et al.[21], Ashbee HR et al.[193]

Annex 10. Drug-drug interactions of antifungal agents.

Drugs	Interaction with other drugs
D-AmB	• D-AmB can only be diluted in 5% glucose serum. • Co-administration with azoles, corticoids, cyclosporine, digitalis, flucytosine, foscarnet, nephrotoxic drugs, muscle relaxants and thiazides potentiate its nephrotoxicity. Suggested action: avoid other concomitant nephrotoxic drugs, therapeutic monitoring of immunosuppressive drugs, monitor renal function. • In patients with HIV infection, the association with pentamidine may produce reversible acute renal failure. • In neutropenic patients, simultaneous administration with granulocyte transfusions may cause pneumonitis. • May increase the pharmacological effect of some cytostatics (doxorubicin, carmustine, cyclophosphamide, fluorouracil). • Co-administration with 5FC or terbinafine may be synergistic against *Candida* spp. and *Cryptococcus* spp. The association with an echinocandin may be synergistic against *Aspergillus* spp, *Fusarium* spp. and mucorales.
L-AmB	• For drug interactions: see D-AmB.
LC-AmB	• For drug interactions: see D-AmB. • LC-AmB is considered a chemically unstable mixture, which degrades during infusion and increases AmB release. • It can favor digoxin toxicity due to hypokalemia, and its association with corticosteroids increases the risk of hypokalemia.
CAS	• CAS reduces tacrolimus plasma concentration by 20%, and cyclosporine raises CAS plasma concentration by 35%. Suggested action: no adjustment, monitor liver function. • A reduction in CAS plasma concentration has been observed in patients treated with efavirenz, nevirapine, phenytoin, rifampicin, dexamethasone and carbamazepine. Suggested action: no adjustment. • Co-administration with AmB can be additive or synergistic against *Candida*, *Aspergillus*, mucorales and *Fusarium*.
ANF	• Cyclosporine A elevates ANF plasma concentration by 22% (not considered clinically relevant). Suggested action: no adjustment. • It should be used with caution with nifedipine and sirolimus. • Co-administration with AmB may be additive or synergistic against *Candida*, *Aspergillus*, mucorales and *Fusarium*. Co-administration with an azole may be additive against *Candida*. Combination with ITZ, VCZ or PCZ may be synergistic against *Aspergillus* and other filamentous fungi.
MCF	• Cyclosporine A raises MCF plasma concentration by 10% (not considered clinically relevant), raises the area under the curve of sirolimus by 21% (without affecting its Cmax), and raises the Cmax of nifedipine by 42%. Suggested action: no adjustment. • No significant interactions have been described with cyclosporine, tacrolimus, mycophenolate mofetil, rifampicin, FCZ or ritonavir. • Although MCF is a substrate and inhibitor of CYP3A, hydroxylation by CYP3A is not a major metabolic pathway *in vivo*. • MCF is neither a substrate nor an inhibitor of P-glycoprotein. • Co-administration with AmB can be additive or synergistic against *Candida*, *Aspergillus*, mucorales and *Fusarium*.

FCZ	• FCZ is a cytochrome P450 and 3A4 inhibitor. • Rifampicin decreases serum FCZ concentration, and hydrochlorothiazide raises it. • May increase the anticoagulant effect of coumarins. • It can increase the serum concentration of cliclosporin, tacrolimus, diphenylhydantoin, barbiturates, amitriptyline, oral hypoglycemic agents, rifabutin, theophylline, zidovudine, alfentanil, methadone, ethinyl estradiol, anti-H1 ([terbinafine and astemizole]), with QT prolongation and risk of ventricular tachycardia), and cisapride (same effect as with anti-H1).
ITZ	• ITZ has many interactions, which is one of its limitations; it is a potent inhibitor of CYP3A4 and also of P-glycoprotein inhibitor. • Antacids (alkaline, anti-H2, anticholinergics, omeprazole, sucralfate), didanosine, rifampicin, rifabutin, phenytoin, phenobarbital, carbamazepine and isoniazid decrease the serum concentration of ITZ by impairing its absorption or increasing its hepatic metabolism. • May increase the anticoagulant effect of coumarins and potentiate the neurotoxicity of vincristine. • It raises the serum concentration of cyclosporine, tacrolimus, diphenylhydantoin, barbiturates, oral hypoglycemic agents, digoxin, felodipine and other dihydropyridine calcium antagonists, quinidine, several benzodiazepines (triazolam, alprazolam, midazolam and chlordiazepoxide), anti-H1 drugs (terbinafine and astemizole), with QT prolongation (and risk of polymorphic ventricular tachycardia), midazolam and chlordiazepoxide), anti-H1 drugs (terbinafine and astemizole), with QT prolongation (and risk of polymorphic ventricular tachycardia), cilostazol, cisapride, corticosteroids, buspirone and HIV pro protease inhibitors (saquinavir, ritonavir). • It may decrease the efficacy of hormonal contraceptives and should not be used with lovastatin (due to the possible risk of rhabdomyolysis); in case of association with atorvastatin, the dose of this drug should be reduced. • Association with cyclophosphamide and probably with busulfan leads to the formation of hepatotoxic metabolites. • Association with terbinafine can be additive or synergistic against *Candida*, *Cryptococcus*, *Aspergillus* and *Lomestospora prolificans*.
VCZ	• Phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital and ritonavir induce VCZ metabolism and reduce its serum concentration. Suggested action: If possible, avoid the combination, or perform TDM of VCZ. • VCZ is metabolized by CYP2C19, CYP2C9, and CYP3A4; VCZ increases the serum concentration of omeprazole, phenytoin, cyclosporine, tacrolimus, sirolimus (should be avoided), astemizole, cisapride, ergotamine alkaloids, quinidine, terfenadine, coumarin anticoagulants, statins, benzodiazepines, and prednisolone. Suggested action: decrease tacrolimus dose by 2/3, decrease cyclosporine dose by 1/2, therapeutic monitoring of immunosuppressive drugs, avoid combination with mTOR inhibitors or sirolimus, avoid combination when possible, or use these drugs with caution and at lower doses. • Cimetidine may increase the serum concentration of VCZ. • Co-administration with terfenadine, astemizole, cisapride, pimozide and quinidine is contraindicated, because it produces QT prolongation and *torsades de pointes*. Suggested action: avoid the combination.
PCZ	• PCZ has fewer interactions than ITZ and VCZ. • It is a potent CYP3A4 inhibitor, and elevates the serum concentration of cyclosporine, tacrolimus, rifabutin, midazolam, and possibly any drug that is metabolized by CYP3A4 (rifampicin, carbamazepine). Suggested action: decrease tacrolimus dose by 2/3, decrease cyclosporine levels by 1/4, therapeutic monitoring of immunosuppressive drugs. • The association of PCZ with cimetidine, phenytoin, rifabutin and sirolimus should be avoided. Suggested action: if possible, avoid the combination, or perform TDM of PCZ.
ISZ	• ISZ is contraindicated with congenital long QT syndrome. • It is a moderate inhibitor of CPY3A4 and CPY3A5, and an inducer of CPY2B6. • ISZ levels increase with co-administration with KTZ, rifampicin, rifabutin, carbamazepine, long-acting barbiturates, phenytoin, efavirenz, oxacillin, etravirine and ritonavir at high doses (> 200 mg q 12 hours). • It should be used with caution when associated with lopinavir/ritonavir, atorvastatin, cyclosporine, sirolimus, tacrolimus, midazolam, bupropion, mycophenolate, digoxin. Suggested action: therapeutic monitoring of tacrolimus and cyclosporine doses; no empirical reduction required while awaiting therapeutic monitoring of immunosuppressive drugs, consider early dose reduction with sirolimus.

D-AmB: Amphotericin B deoxycholate; L-AmB: Liposomal amphotericin B; LC-AmB: Amphotericin B lipid complex; CAS: Caspofungin; ANF: Anidulafungin; MCF: Micafungin; FCZ: Fluconazole; ITZ: Itraconazole; VCZ: Voriconazole; PCZ: Posaconazole; ISZ: Isavuconazole; KTZ: Ketoconazole; TDM: Therapeutic drug monitoring of antifungal agents; mTOR: *Mammalian Target of Rapamycin*.

Adapted from: García-Vidal C et al.[81], Mensa-Pueyo J, et al.[241], Jenks JD et al.[242], Ruiz-Camps I et al.[243], Bellmann R et al.[244], Cuenca-Estrella M[245], Lewis RE[246], Nett JE et al.[247], Gilbert D et al.[249], Ghannoum MA y Perfect JR (eds)[250].

Annex 11. Adverse effects with antifungal agents.

Drugs	Adverse effects
D-AmB	• Administration of D-AmB can produce fever, chills and shivering during infusion (which can be controlled by premedication with antipyretics, antihistamines or antiemetics), infusion-related nausea and vomiting (> 50% of treated patients), which usually disappear with repeated administration of the drug. • It causes elevation of creatinine (in 25-50% of patients); if creatinine levels rise > 2 mg/L, it is advisable to temporarily suspend its administration. • Continuous infusion administration for 24 hours may be better tolerated and less nephrotoxic, although there are few studies that determine that it maintains the same clinical efficacy, supplemental sodium intake of 70-150 mEq/day may decrease nephrotoxicity. • In patients receiving total doses greater than 5 g, co-administration with other nephrotoxic drugs may result in irreversible renal injury. • It can produce hypokalemia, hypomagnesemia, renal tubular acidosis, nephrocalcinosis, decreased glomerular flow and filtration, thrombophlebitis and normocytic-normochromic anemia (after 7-10 days of treatment, which improves with the administration of erythropoietin).
L-AmB	• Patients who experience acute toxicity with D-AmB usually tolerate the liposomal formulation well. • About 20% of patients report chest pain, with dyspnea and hypoxia, flank, abdominal, or leg pain, redness or urticaria related to the infusion. • Almost 10% of patients present acute toxicity or mild nephrotoxicity, almost always related to the simultaneous use of other nephrotoxic drugs. • Alterations in liver function (especially elevation of alkaline phosphatase) may be observed in up to 25% of patients, especially in liver transplant recipients. • Hypokalemia, allergic reactions, obnubilation, dyspnea, pancreatitis or ventricular fibrillation, attributable to the lipid vehicle, have been described in up to 30% of patients.
LC-AmB	• Administration of LC-AmB can produce fever and chills during infusion (which can be controlled by premedication with antiemetics, antihistamines or antipyretics), with infusion-related nausea and vomiting (10-20% of treated patients), which usually disappear with repeated administration of the drug. • LC-AmB must be infused before 6 hours and pre-agitated with high-frequency vortex and in doses no higher than 3 mg/kg/d. • It causes elevation of creatinine (in 20% of patients), due to decreased flow and glomerular filtration. • Co-administration of aminoglycosides, cyclosporine, tacrolimus, NSAIDs, foscarnet, cidofovir, cisplatin or cytosine arabinoside potentiate its nephrotoxicity. • It can produce hypokalemia, hypomagnesemia, renal tubular acidosis, nephrocalcinosis, thrombophlebitis, normochromic-normochromic anemia (after 7-10 days of treatment, which improves with the administration of erythropoietin).
CAS	• CAS is generally well tolerated; the overall incidence of adverse effects is 14% (similar to FCZ). • Phlebitis at the administration site, headache, histamine release-related signs (facial erythema or edema, urticaria, bronchospasm, nausea, abdominal pain and dyspnea), hypotension, toxicoderma (more frequent in patients receiving concomitant treatment with ITZ), fever and elevated transaminases (usually transient) may be observed.
ANF	• ANF is generally well tolerated, the overall incidence of adverse effects is 9%. • Phlebitis at the site of administration, headache, histamine release-related signs (facial erythema or edema, urticaria, bronchospasm, nausea, abdominal pain and dyspnea), hypotension, toxicoderma, fever, elevated transaminases and GGT ([gamma-glutamyl transpeptidase], usually transient), hypokalemia and hypomagnesemia may be observed.
MCF	• MCF is generally well tolerated. • Phlebitis at the site of administration, headache, nausea, vomiting, diarrhea, toxicoderma, fever, elevated transaminases and histamine release-related symptoms (skin rash, pruritus, vasodilatation and facial edema), leukopenia and thrombocytopenia may be observed.
FCZ	• FCZ is generally well tolerated and is probably the least toxic of the systemically used antifungals. • It produces digestive intolerance (anorexia, nausea, vomiting, diarrhea, abdominal pain), elevated transaminases in about 10% of cases (although it is considered less hepatotoxic than ketoconazole [KTZ]). • It causes elevation of transaminases in up to 20% of children and in HIV+ patients; several cases of associated hepatic necrosis have been described. • It produces pruritus, with or without rash (severe skin reactions including *Stevens-Johnson* syndrome have been described in some HIV-infected patients), and headache. • It can lead to superinfection by *C. krusei* and *C. glabrata*.
ITZ	• ITZ causes digestive intolerance (anorexia, nausea, vomiting, diarrhea, abdominal pain), especially with oral solution, due to the osmotic effect of cyclodextrin; pruritus and/or rash; reversible elevation of transaminases in 1-5% of cases (cholestatic hepatitis may occur in patients older than 50 years treated for more than 4 weeks), and peripheral neuropathy with prolonged treatments. • A dose ≥ 600 mg/d may cause adrenal insufficiency or symptoms of hyperaldosteronism (hypertension, edema, hypokalemia). • It is contraindicated in patients with heart failure (it has a negative inotropic effect).
VCZ	• VCZ causes gastrointestinal disturbances, elevated transaminases (10-15% of treated patients), hepatitis, reversible visual disturbances (photophobia, photopsias, blurred vision and changes in color perception) in up to 30% of patients, hallucinations (with serum concentration > 5.5 mg/L), toxicoderma (1-5% of treated patients) and phototoxicity.
PCZ	• PCZ causes fatigue, headache, eye pain, drowsiness, dry mouth, anorexia, abdominal pain, nausea, vomiting, flatulence, diarrhea, menstrual disorders, toxicoderma and elevated transaminases. • With prolonged administration, cases of adrenal insufficiency and QT prolongation have been observed. • It produces hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura (especially in patients treated simultaneously with cyclosporine or tacrolimus), and peripheral neuropathy in case of prolonged treatment.
ISZ	• ISZ causes nausea, vomiting, diarrhea, headache, elevated liver tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, back pain and QT prolongation.

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