ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

SUPLEMENTARY ONLINE MATERIAL

Colombian consensus on the diagnosis, treatment and prevention of *Candida* spp. disease in children and adults*,+

Annex 1. Vote on questions of the modules of the consensus (Delphi methodology).

Module	No. of Voters	Mean	Median	Minimum Scored Value	Maximum Scored Value	Percentage of Applicability
DIAGNOSIS OF INVASIVE CANDIDIASIS (IC)	13	7.3	7	3/1	9/9	77
DIAGNOSIS OF CANDIDEMIA	13	7.2	7	2/1	9/9	88
ANTIFUNGAL PROPHYLAXIS FOR CANDIDEMIA/IC	11	7.0	8	1/1	9/9	95
CANDICEMIA/IC IN NON-NEUTROPENIC PATIENTS	13	6.3	7	3/1	9/9	94
CANDICEMIA/IC IN NEUTROPENIC PATIENTS	13	6.8	7	2/1	9/9	95
TARGETED ANTIFUNGAL TREATMENT FOR CANDIDEMIA/IC	13	6.8	7	2/1	9/9	95
CANDICEMIA/IC IN NEONATE PATIENTS	9	8.4	9	3/1	9/9	100
MANAGEMENT OF CANDIDEMIA/IC IN SPECIAL SITUATIONS	13	6.5	7	2/1	9/9	90
INTRAABDOMINAL/PERITONEAL IC	13	6.5	7	2/1	9/9	94
Candida spp. URINARY TRACT INFECTIONS	13	6.7	7	2/1	9/9	94
Candida spp. RESPIRATORY TRACT INFECTION	13	6.7	7	2/1	9/9	94
PREVENTION OF *Candida* spp. IFDs	9	9.0	9	9/9	9/9	100

Annex 2. Score of guidelines found in the bibliographical search by AGREE II methodology[38,40,42,46,70,72,108,178,388–392].

MODULE	Bibliographical References												
	1	2	3	4	5	6	7	8	9	10	11	12	13
MODULE 1: Scope and Objectives	81.6	75.3	70.6	80.6	80.6	71.5	75.9	72.2	78.4	48.5	75.0	73.6	80.6
MODULE 2: Participation of persons involved	56.4	48.5	55.6	56.3	60.2	68.1	69.8	66.7	67.9	49.0	54.2	52.8	55.6
MODULE 3: Rigor of Evaluation	62.0	40.0	45.8	87.5	58.3	65.9	75.9	64.8	76.6	47.9	60.9	60.4	59.9
MODULE 4: Clarity of the Presentation	87.6	79.3	85.7	92.1	88.9	77.1	90.1	85.8	88.9	86.4	93.1	97.2	91.7
MODULE 5: Applicability	30.1	31.1	36.9	46.4	55.6	30.2	41.7	49.5	52.8	37.5	33.3	17.7	27.1
MODULE 6: Editorial Independence	64.7	65.9	90.5	99.4	55.6	100.0	100.0	100.0	86.1	75.8	100.0	100.0	100.0
NUMBER OF EVALUATORS	13	11	7	14	6	8	9	9	9	11	4	4	4
TOTAL MEAN	**61.9**	**51.5**	**57.9**	**77.0**	**64.7**	**65.1**	**73.1**	**69.2**	**74.0**	**53.8**	**64.7**	**62.0**	63.9

Annex 3. Table of Authors' affiliation

Last Name, Name	Affiliation	Abbreviation
Oñate G, José M	Internal Medicine-Infectious Diseases Specialist, Imbanaco Medical Center, Clínica de Occidente de Cali, Universidad del Valle.	JO
Rivas P, Pilar	Associate Professor, Group Head Coordinator, Microbiology Department, Faculty of Medicine, Universidad Nacional de Colombia, Bogota, Colombia.	PR
Pallares G, Christian	Coordinator, Infections and Epidemiological Surveillance Committee, Imbanaco Medical Center; Lecturer, Office of the Vice-Chancellor for Research, Universidad el Bosque, Bogota, Colombia.	CHP
Saavedra T, Carlos H	Professor, Internal Medicine Department and Infectious Diseases Research Group, Faculty of Medicine, Universidad Nacional de Colombia.	CS
Camacho M, Germán	Pediatric Infectious Diseases Specialist, HOMI Foundation, Hospital Pediátrico de la Misericordia, Fundación Hospital Infantil Universitario de San José; Lecturer, Pediatrics Department, Faculty of Medicine, Universidad Nacional de Colombia, Bogota, Colombia.	GC
Martínez B, Ernesto	Internal Medicine Department, Universidad del Valle, Hospital Universitario del Valle Evaristo García ESE, Clínica Farallones, Cali.	EM
Coronell R, Wilfrido	Pediatric Infectious Diseases Specialist, PhD in Tropical Medicine; Lecturer, Universidad de Cartagena, Cartagena, Colombia.	WC
López M, Eduardo	Center for Pediatric Infectious Diseases Studies, Pediatrics Department, Universidad del Valle, Imbanaco Medical Center	EL
Roncancio V, Gustavo E	Internal Medicine-Infectious Diseases Specialist, Clínica Cardiovascular, Medellin.	GR
Berrio M, Indira	Hospital General de Medellin, Luz Castro de Gutiérrez, Corporación para Investigaciones Biológicas, CIB.	IB
Zuluaga DL, Iván	Internal Medicine-Infectious Diseases Specialist; Scientific Director, SICAC IPS; Scientific Advisor, Organización Sanitas IPS; Internal Medicine Postgraduate Lecturer, Universidad Libre de Barranquilla.	IZ
Segura Ch, Janier	Internal Medicine-Infectious Diseases Specialist, Clínica Amiga, Imbanaco Medical Center.	JS
Álvarez P, Jorge E	Internal Medicine-Infectious Diseases Specialist, Hospital Universitario del Valle, Universidad del Valle.	JA
Romero A, Andrés F	Pediatric Infectious Diseases Fellow, Pediatrics Department, Universidad del Valle.	AR
Álvarez-Moreno, Carlos A	Professor, Internal Medicine Department, Faculty of Medicine, Universidad Nacional de Colombia, Clínica Universitaria Colombia, Clínicas Colsanitas, Bogota, Colombia.	CA
Vélez L, Juan D	Internal Medicine-Infectious Diseases Specialist, Fundación Clínica Valle del Lili.	JV
Cortes L, Jorge A	Associate Professor, Internal Medicine Department and Infectious Diseases Research Group, Faculty of Medicine, Universidad Nacional de Colombia.	JC
Parra-Giraldo, Claudia M	Human Proteomics and Mycoses Unit, Infectious Diseases Group, Microbiology Department, Faculty of Sciences, Pontificia Universidad Javeriana, Bogota D.C, Colombia.	CMP

Annex 4. Table of conflict of interest disclosed by authors

Abbreviation	Conflict of interest disclosed:	Sponsor:
JO	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2016-2017
PR	She was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). Colombia /Latin America 2016-2017
CHP	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Merck Colombia, Amarey Nova medical, Biomerieux, Novartis, Abbott-Lafrancol, Takeda. Colombia /Latin America 2010-2017
CS	Declares no conflict of interest.	Declares no conflict of interest
GC	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Procaps, Colombian Association of Infectology (ACIN), Pan American Health Organization (PAHO), Sanofi. 2015-2016
EM	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Stendhal, Gilead/Gador, GSK, ABBVIE. 2015-2017
WC	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Sanofi. 2016-2017
EL	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Astellas, Takeda, Stendhal. 2016-2017
GR	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2014-2017
IB	He was a speaker and received scientific sponsorship.	Merck Sharp and Dohme (MSD), Procaps. 2016-2017
IZ	She received scientific sponsorship.	Procaps. 2017
JS	She received scientific sponsorship.	Pfizer S.A.S, Sanofi. 2016-2017
JA	Declares no conflict of interest.	Declares no conflict of interest
AR	Declares no conflict of interest.	Declares no conflict of interest
CA	He was a speaker, and received research funding and scientific sponsorship.	Merck Sharp and Dohme (MSD), Procaps. 2016-2017
JV	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2015-2017
JC	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2015-2017
CMP	Declares no conflict of interest.	Declares no conflict of interest

Annex 5. Recommendations for the identification of yeast-like specie[43].

Identification of *Candida* species
• As a minimum requirement, colony micromorphology observation complemented by macromorphology using the CHROMagar *Candida*® medium, is recommended. • For second-level hospitals, it is recommended that one or more of the methods below should be used for the identification of species: o Micromorphology of the colonies. o Macromorphology (CHROMagar *Candida*® medium). o Biochemical tests: ▯ In-house conventional methods. ▯ Manual commercial systems with limited databases (e.g. Auxacolor® or Uni-Yeast Tek®). • For third-level hospitals, where transplant recipients, hematological and/or immunocompromised patients are treated, the following are recommended as minimum requirements: o Micromorphology complemented by biochemical tests (API 20 C AUX®, API ID32C®, YST Vitek 2®, RYI MicroScan® or Yeast ID Panels®). o Molecular methods in specific situations. • Molecular methods (PCR and MALDI-TOF) should be considered for the identification of emerging pathogens and when investigating outbreaks of fungal infections.

Adapted from: Colombo AL et al[43].

PCR: Polymerase chain reaction; MALDI-TOF MS: Matrix assisted laser desorption ionization Time-of-Flight.

Annex 6. Chromogenic media for the identification of *Candida* species[43].

Characteristics of colonies per species after incubation in CHROMagar *Candida*® medium, at 37 °C, for two days	
Species	**Color and morphology**
Candida albicans	Green.
Candida tropicalis	Dark blue to grey blue (with pink halo in agar).
Candida krusei	Pale pink to purple (intense tone with pale edges) and a dry texture.

Adapted from: Colombo AL et al[43].

Annex 7. Automated methods for the identification of yeast-like fungus species

Method*	Basis	Comment
YST Vitek 2® cards	Analysis cards with 63 wells for the detection of fungal metabolism Reading by fluorescence.	Identification of 51 yeast-like species and organisms, including *Candida dubliniensis*. Requires additional tests (mainly morphological) when the identification has low discrimination. Time to identification: 15 hours
YT MicroPlate® system	Identification panels with 94 biochemical tests	Identifies up to 267 different species belonging to 53 genus Time to identification: up to 72 hours
RYI MicroScan® panel	Microdilution plate with 96 wells that uses 27 dehydrated substrates Identification is performed by conventional and chromogenic tests	Rapid identification of 40 yeast-like species and organisms May require additional tests (mainly morphological) when the identification has low discrimination. Time to identification: 4 hours
Yeast ID® Panel	Identification panels based on conventional biochemical, chromogenic and fluorogenic tests.	Identification of 64 species of yeast and yeast-like organisms Requires establishing the source culture medium of the fungal isolate in order for the determination of secondary morphological characteristics Time to identification: 16 hours

*Information taken from the manufacturer package inserts.

Annex 8. Considerations on in vitro antifungal susceptibility commercial tests[258].

ATB Fungus (bioMérieux), is based on the CLSI microdilution method. Applicable for *Candida* spp. and *Cryptococcus neoformans*
• It is an easy to perform, reproducible and affordable technique.
• It has a good consistency with reference methods (CLSI-EUCAST), mainly with amphotericin B and 5-fluorocytosine.
• Limitations
  ° Does not include echinocandins
  ° There are discrepancies between fluconazole and itraconazole

AST-YS01 Vitek® 2 (bioMérieux), is based on the CLSI microdilution method. Applicable for *Candida* spp. and *C. neoformans*.
• Is an automated and easy technique that allows determining the MIC.
• It has a good consistency with reference methods (CLSI-EUCAST).
• Limitations
  ° There are discrepancies when testing antifungal agents with uncommon yeast isolates.
  ° It does not include all echinocandins nor itraconazole.

Sensititre™ YeastOne™ (Trek Dg. System) is a colorimetric dilution method based on the CLSI microdilution method.
• It incorporates Alamar blue, an oxidoreductase dye that turns red when there is growth and remains blue when there is no growth.
• Good reproducibility. One advantage is a more objective reading because turbidity should not be read but only the change in color.
• Limitations
  ° Color change may be difficult to appreciate in some isolates.
  ° Paradoxical effect (growth in concentrations above MIC) is common with itraconazole and echinocandins.

Neo-Sensitabs™ (Rosco Diagnostic) and SensiDisks (Bio-Rad), are tablets containing the antifungal agent in crystallized form. Its main advantage is the stability of the tablets (up to 4 years at 4-8°C).
• They are an inexpensive, reproducible and easy to perform resource in routine laboratory tests.
• They are useful for knowing the susceptibility to systemic antifungal agents.
• Limitations
  ° Issues with azole readings: presence of colonies inside the halo.
  ° Issues with the interpretation of some isolates.
  ° High percentage (>5%) of errors with fluconazole (some resistant isolates were identified as susceptible).

E-test® (bioMérieux) and MIC™ (Oxoid), are quantitative systems of diffusion in agar that allow the determination of MIC. Applicable for *Candida* spp., *C. neoformans* and filamentous fungi. • They are rapid, reproducible techniques that allow the determination of MIC. • They are useful for the determination of filamentous fungi in vitro susceptibility • Limitations   ° Subjectivity and difficulty in yeasts and filamentous fungi MIC readings

Adapted from: Rivas P et al[258].

CLSI: Clinical and laboratory standards institute; EUCAST: European committee on antimicrobial susceptibility testing; MIC: Minimum inhibitory concentration.

Annex 9. Clinical cut off points for common antifungal agents againstCandida species[38,55].

Species	Antifungal agent	Cut off points, µg/mL*			
		S	DDS	I	R
C. albicans	Fluconazole	≤2	4		≥8
	Itraconazole	≤0.12	0.25–0.5		≥1
	Voriconazole	≤0.12		0.25–0.5	≥1
	Posaconazole				
	Anidulafungin	≤0.25		0.5	≥1
	Caspofungin	≤0.25		0.5	≥1
	Micafungin	≤0.25		0.5	≥1
C. glabrata	Fluconazole		32		≥64
	Itraconazole				
	Voriconazole				
	Posaconazole				
	Anidulafungin	≤0.12		0.25	≥0.5
	Caspofungin	≤0.12		0.25	≥0.5
	Micafungin	≤0.06		0.12	≥0.25
C. parapsilosis	Fluconazole	≤2	4		≥8
	Itraconazole				
	Voriconazole	≤0.12		0.25–0.5	≥1
	Posaconazole				
	Anidulafungin	≤2		4	≥8
	Caspofungin	≤2		4	≥8
	Micafungin	≤2		4	≥8
C. tropicalis	Fluconazole	≤2	4		≥8
	Itraconazole				
	Voriconazole	≤2	4		≥8
	Posaconazole				
	Anidulafungin	≤0.25		0.5	≥1
	Caspofungin	≤0.25		0.5	≥1
	Micafungin	≤0.25		0.5	≥1
C. krusei	Fluconazole				
	Itraconazole				
	Voriconazole	≤0.5		1	≥2
	Posaconazole				
	Anidulafungin	≤0.25		0.5	≥1
	Caspofungin	≤0.25		0.5	≥1
	Micafungin	≤0.25		0.5	≥1

Adapted from: Pappas PG et al.; Albataineh MT et al[38,55].

Blank spaces mean that there are insufficient data to establish clinical cut off points.

I: intermediate; MIC; Minimum Inhibitory Concentration; R: Resistant; S: Susceptible; DDS: Dose-Dependent Susceptible.

*CLSI clinical cut off points adopted by CLSI.

Annex 10. Emerging Candida species associated with human infections[10].

Anamorph stage	Telemorph stage	Clinical relevance and particularities
C. africana	Not described	Closely related to *C. albicans*. This species exhibits an intrinsic susceptibility pattern. It is probably less pathogenic than *C. albicans* and were found almost exclusively in female urinary tract samples.
C. auris	Not described	Related to *C. haemulonii*. FCZ MIC is higher than that of *C. albicans*. Multi-resistant species and very durable in the environment. Resistant to the usual hospital disinfectants.
C. bracarensis	Not described	Closely related to *C. glabrata*. Its susceptibility pattern is similar to that of *C. glabrata* (high azole MIC compared with that of *C. albicans*).
C. ciferrii	*Trichomonascus ciferrii*	Uncertain clinical significance. Inherent resistance to several antifungal agents.
C. dubliniensis	Not described	Closely related to *C. albicans*. With an intrinsic susceptibility pattern similar to that of the abovementioned species; however, it has the potential for acquired resistance.
C. fabianii	*Cyberlindnera fabianii*	Uncertain clinical significance. FCZ MIC is higher than that of *C. albicans*.
C. famata	*Debaromyces hansenii*	This species is an uncommon fungemia-causing agent. Recent data question whether this species is a human pathogen (it does not grow at 37°C and there are no cases confirmed by sequencing analysis).
C. guilliermondii	*Meyerozyma guilliermondii*	Closely related to *C. fermentati* and *C. palmioleophila*. Echinocandin and azole MIC is high
***C. haemulonii* (including *C. duobushaemulonii*)**	Not described	May be a human pathogen associated with surface infections and central venous catheter fungemia, in particular in Brazil, the Caribbean and some regions in Asia. Azole and AB MIC is high. Related to *C. auris*.
C. hellenica	*Zygoascus meyerae*	There have been reports of fungemia and respiratory infections caused by this species. Reduced susceptibility to FCZ, ITZ and CAS. It is susceptible to VCZ.
C. inconspicua	Not described	Closely related to *C. norvegensis*. Its susceptibility pattern is similar to that of *C. krusei* (intrinsically susceptible to FCZ).
C. intermedia	Not described	It is an oropharingeal colonization agent associated with bloodstream infections and peritonitis. It is susceptible to all antifungal agents except for 5FC.
C. kefyr	*Kluyveromyces marxianus*	No inherent resistance to antifungal agents has been described.
C. lipolytica	*Yarrowia lipolytica*	Uncertain clinical significance. FCZ MIC is higher than that of *C. albicans*.
C. lusitaniae	*Clavispora lusitaniae*	AB tends to be inefficient (even with MIC ≤1 mg/L).
C. metapsilosis	Not described	Closely related to *C. parapsilosis*. Its susceptibility pattern is similar to that of the abovementioned species (high echinocandins MIC).
C. nivariensis	Not described	Closely related to *C. glabrata*. Its susceptibility pattern is similar to that of *C. glabrata* (reduced susceptibility to azole).
C. norvegensis	*Pichia norvegensis*	Closely related to *C. inconspicua*. Its susceptibility pattern is similar to that of *C. krusei* (intrinsically susceptible to FCZ).
C. orthopsilosis	Not described	Closely related to *C. parapsilosis*. Its susceptibility pattern is similar to that of the abovementioned species (high echinocandins MIC).
C. palmioleophila	Not described	Phenotypically related to *C. guilliermondii*. Azole MIC is high but echinocandin MIC is low (unlike *C. guilliermondii*).
C. pelliculosa	*Wickerhamomyces anomalus* (formerly known as *Pichia anomala, Hansenula anomala*)	FCZ MIC is higher than that of *C. albicans*.
C. pulcherrima	*Pichia kudriavzevii* (formerly known as *Metschnikowia pulcherrima*)	Its clinical significance is uncertain.
C. rugosa	Not described	FCZ MIC is higher than that of *C. albicans*.
C. subhashii	Not described	Its clinical significance is uncertain.
C. viswanathii	Not described	Its clinical significance is uncertain.
C. zeylanoides	Not described	Its clinical significance is uncertain.

Adapted from Arendrup MC et al[10].
MIC: Minimum inhibitory concentration; FCZ: Fluconazole; AB: Amphotericin B; ITZ: Itraconazole; CAS; Caspofungin; VCZ: Voriconazole; 5FC: 5-Flucitosine.

Annex 11. Serum biomarkers for the diagnosis of candidemia/IC[37,41,56,57].

Diagnostic Test	Description	Optimal sample	S (%)	Sp (%)	Comments and interpretation
Mannan and Anti-Mannan Platelia™ *Candida* Ag Plus® Platelia™ *Candida* Ab Plus® (Bio-Rad Laboratories)	ELISA for the detection of *Candida* spp. Abs. and Ags.	Serum and plasma	54-94	59-95	It yields results 6 days earlier than detection in blood cultures, even though its use as an early marker of IC is still uncertain. High susceptibility to most of the species; it is not reliable for the detection of certain species such as *C. parapsilosis* o *C. guilliermondii*. PPV 17-94%; NPV 89-94%. Its high NPV makes it a good alternative disease exclusion test, which would avoid unnecessary antifungal treatment. Interpretation of results: A negative MN Ag. result does not exclude the diagnosis of IC, mannanemia is a short-term condition. Anti-MN-Ab and MN Ag titers are supplementary. Serum of patients at risk of IC without MN-Ag may have high titers of anti-MN-Ab and vice-versa.
(1,3)-β-D-glucan Fungitell (Associates of Cape Cod Inc., USA). Wako WB003 (Wako Pure Chemical Industries, Japan). Fungitec G (Seikagaku Kogyo Corporation, Japan). B-G Star (Maruha Corporation, Japan).	ELISA for the detection of (1,3)-β-D-glucan, a panfungal component of the cell wall	Serum	65-81	57-83	Is a panfungal *Candida* non-specific marker. It yields results 7 days earlier than detection in blood cultures. Its diagnostic usefulness varies and depends on the studied population of patients. PPV 22-63%; NPV 77-96%. It is considered particularly useful in patients with intraabdominal infections, in whom culture sensitivity is reduced. Interpretation of results: Optimal results are obtained when two consecutive tests are positive. One positive result does not allow the identification of the species causing the infection. There is a correlation between a positive test and proven IC.
CAGTA *Candida albicans* IFA IgG® (Vircell, Spain)	Indirect immunofluorescence assay based on the detection of antibodies against *C. albicans* germ tube surfaces	Serum	77-89	91-100	CAGTA is not affected by *Candida* colonization or antifungal treatment. It is useful in the diagnosis of *Candida*-deep seated infections. Using an early CAGTA detection based-approach may reduce the mortality of critical patients at risk of IC, especially in surgical patients. Interpretation of results Positive in IC caused by: *C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. glabrata, C. guilliermondii, C. dubliniensis.*

Adapted from: Arvanitis M et al.; León C et al.; Ayats J et al.; Colombo AL et al[37,41,56,57].
ELISA: Enzyme-linked immunosorbent assay; Ab: Antibody; Ag.: Antigen; S: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; MN: Mannan; BD: (1,3)-β-D-glucan; CAGTA: Anti-mycelium antibodies.

Annex 12. Available molecular and proteomic biomarkers for the diagnosis of candidemia/IC[37,39,55,66,68].

Test	Basis	Optimal sample	S (%)	Sp (%)	Comments and interpretation
LightCycler SeptiFast™ (Roche, Germany)	Multiplex PCR for the detection of bacteria and fungi DL: 30–100 CFU/mL	Clinical samples or samples of negative cultures	61	99	It is possibly less susceptible for *Candida* spp. compared with similar tests It has better susceptibility compared with conventional blood cultures It is supplementary for diagnosis in high-risk patients Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: *C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata.*
FilmArray blood culture identification (Film-Array™ - BioFire DX) (bioMerieux)	Nested PCR Multiplex	Positive blood culture	95-100	99.5-100	It requires minimum preparation of the sample It has a quick turnaround time It requires the use of specialized equipment Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: *C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata.*
T2 *Candida* (T2Biosystems Inc)	NAAT followed by hybridization and T2 magnetic resonance assay DL: 1-3 CFU/mL	Whole blood	91	98	It requires minimum preparation of the sample It has a low limit of detection NPV ≈100% It is expensive and requires the use of specialized equipment Interpretation of results: Even though this test has the potential to significantly improve IC diagnosis and management, additional evaluations are required to determine a more profitable implementation. It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: *C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata.*
PNA FISH (*Yeast Traffic Light* PNA FISH™)	Nucleic acid sequence probes for the detection of *C. albicans/C. parapsilosis, C. glabrata/C. krusei* or *C. tropicalis*	Positive blood culture	92-100	95-100	It is very susceptible and specific It has a quick turnaround time Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: *C. albicans/ C. parapsilosis; C. tropicalis; C. krusei/C. glabrata.*
MALDI-TOF MS (bioMerieux, France or Bruker Daltonics, Germany)	Concentration of yeast sediment followed by MALDI-TOF MS mass spectrophotometry analysis	Positive cultures or directly from clinical samples, including positive blood cultures	0-100	¿?	The reports on its performance vary, probably due to differences in the preparation of samples (Sepsityper vs. *in-house* methods) It is convenient for laboratories that use equipment already Interpretation of results: Detected species: multiple species, depending on the spectra available on libraries
PCR/ESI-MS (Iridica™, Abbott, USA)	PCR followed by electrospray ionization - mass spectrometry Amplicon (PCR/ESI-MS)	Positive cultures or directly from clinical samples, including positive blood cultures	83	94	High susceptibility and specificity It is expensive and requires the use of specialized equipment Interpretation of results: Detected species: multiple species

Adapted from: Arvanitis M et al.; Brady AC et al.; Vanichanan J et al.; Powers-Fletcher MV et al.; Albataineh MT et al[37,39,55,66,68].
DL: Detection Limit; S: Sensitivity; Sp: Specificity; (%): Percentage; NAAT: Nucleic acid amplification test; PNA FISH: Fluorescent *in situ* hybridization using peptide nucleic acid; MALDI-TOF MS: Matrix assisted laser desorption ionization time-of-flight; PCR/ESI-MS: PCR + mass spectrometry + electrospray ionization.

Annex 13. Pharmacokinetics/Pharmacodynamics of Systemic Antifungal Agents[65,124,149,148,150,151].

Antifungal agent		Pharmacokinetics	
ECHINOCANDINS	Caspofungin	C_{max}	12 mg/L (with 50 mg IV.)
		AUC_{24h}	75 mg x h/L (with 50 mg/day IV.)
		$T^{½}$	9-11 h
		Protein binding	97%
		DV	0.3 L/kg
	Anidulafungin	C_{max}	7.2 mg/L (with 100 mg IV.)
		AUC_{24h}	105 mg x h/L (with 100 mg/day IV.)
		$T^{½}$	26 h
		Protein binding	99%
		DV	0.56 L/kg
	Micafungin	C_{max}	7 mg/L (with 100 mg IV.)
		AUC_{24h}	103 mg x h/L (with 100 mg IV.)
		$T^{½}$	15 h
		Protein binding	>99%
		DV	0.3 L/kg
POLYENES	Amphotericin B deoxycholate	C_{max}	2 mg/L (with 50 mg IV.)
		AUC_{24h}	17 mg x h/L (with 50 mg IV.)
		$T^{½}$	24 h
		Protein binding	>90%
		DV	4 L/kg
	Liposomal amphotericin B	C_{max}	80 mg/L (with 5 mg/kg/day IV.)
		AUC_{24h}	555 mg x h/L (with 5 mg/kg/day IV.)
		$T^{½}$	24-30 h
		Protein binding	90%
		DV	0.15 L/kg
	Amphotericin B lipid complex	C_{max}	1.7 mg/L (with 5 mg/kg/day IV.)
		AUC_{24h}	14 mg x h/L (with 5 mg/kg/day IV.)
		T ½	19-45 h
		Protein binding	90%
		DV	130 L/kg

Antifungal agent		Pharmacokinetics	
AZOLES	Fluconazole	C_{max}	6 mg/L with 100 mg OA; 20-30 mg/L with 400 mg OA
		AUC_{24h}	412 mg x h/L with 400 mg/day IV.
		$T^{½}$	30 h, 18 h in children (there are no data in severe kidney failure)
		Protein binding	11%
		DV	0.6-0.8 L/kg
	Itraconazole	C_{max}	0.25-1 mg/L with 200 mg OA; 1.9 mg/L with 200 mg OA
		AUC_{24h}	15 mg x h/L with 200 mg/day IV.
		$T^{½}$	20-42 h
		Protein binding	99%
		DV	9 L/kg
	Voriconazole	C_{max}	3-6 mg/L with 4 mg/kg IV.; 2-3 mg/L with 200 mg OA (both in steady state)
		AUC_{24h}	16 mg x h/L with 4 mg/day IV.
		$T^{½}$	6 h (there are no data in severe kidney failure)
		Protein binding	60%
		DV	4.6 L/kg
	Posaconazole	C_{max}	0.22 mg/L
		AUC_{24h}	7.7-33.8 mg x h/L
		$T^{½}$	35 h
		Protein binding	98-99%
		DV	4.9-18.8 L/kg
	Isavuconazole	C_{max}	7.2 mg/L
		AUC_{24h}	121.4
		$T^{½}$	130
		Protein binding	99%
		DV	450 L
FLUCYTOSINE		C_{max}	45 mg/L with 2 g OA
		AUC_{24h}	825 mg x h/L with 6 g/day IV.
		T ½	3-5 h (in severe kidney failure: 200 h)
		Protein binding	< 10%
		DV	0.6 L/kg

Adapted from: Mensa-Pueyo J. et al.; Gilbert DN et al.; Ruiz-Camps I. et al.; Cuenca-Estrella M; Lewis RE; Bellmann R et al[65,124,149,148,150,151].

C_{max} : Maximum concentration (Serum peak concentration); AUC_{24h}: Area under the curve (total drug, including that bound to proteins) 24h; $T^{½}$: Elimination half-life; DV: Distribution volume; MEC: Minimum effective concentration; MIC: Minimum inhibitory concentration; h: Hours; g: Grams; min: Minutes; IV.: Administered intravenously; OA: Oral administration; kg: Kilogram; L: Liter; mEq: Milliequivalent; g: gram; min: Minutes; SOT: Solid organ transplant; HPCT: Hematopoietic progenitor cells transplant; CNS: Central nervous system.

Annex 14. Antifungal treatment per isolated Candida species.

Species	Antifungal agent of choice	Alternative agent	Comments
C. albicans	In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).	AmB-D or AmB-L, standard dose.	Depending on the susceptibility and after appropriate clinical/microbiological response is achieved, de-escalation to FCZ (800 mg loading dose, then 400 mg daily) or VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate, if echinocandin were used as the starting therapy.
C. parapsilosis	In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).	AmB-D or AmB-L, standard dose.	
C. tropicalis	In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).	AmB-D or AmB-L, standard dose.	
*C. auris**	AmB-L (3 mg/kg daily) for 5 d + Equinocandin, standard dose, for 3 weeks.	Not established.	
C. glabrata	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.	
C. krusei	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.	Depending on the susceptibility de-escalation to VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate.
C. lusitaniae	FCZ (800 mg loading dose, then 400 mg daily). VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily).	Echinocandin, standard dose.	
C. guilliermondii	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.	Depending on the susceptibility and after appropriate clinical/microbiological response is achieved, de-escalation to FCZ (800 mg loading dose, then 400 mg daily) or VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate.
C. haemulonii	Not established.	Not established.	High FCZ and AmB-D in vitro MICs, with good echinocandin activity; however, published evidence is insufficient.

(Adapted by experts of the consensus)

**https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-treatment.html.* Take into account the hemodynamic situation of the patient and the in vitro sensitivity of the specific isolation, for the start of combined treatment.
FCZ: Fluconazole; VCZ: Voriconazole; AmB-D: Amphotericin B deoxycholate; AmB-L: Liposomal amphotericin B; CAS: Caspofungin; ANI: Anidulafungin; MIC: Micafungin; Day/days; h: Hours; mg: Milligrams; kg: Kilograms.

Annex 15. PK/PD Parameters of Antifungal Agents[65,124].

Antifungal agent	In Vitro Activity	In Vitro PAE	Efficacy Predictive Parameters
Polyenes (Amphotericin B)	**Fungicidal** Concentration-dependent against *Candida* spp., *Cryptococcus* and *Aspergillus* spp.	**Long-term** Concentration-dependent against yeasts and filamentous organisms.	C_{max}/MIC: 4-10
Triazoles (Fluconazole, Itraconazole, Voriconazole, Posaconazole)	**Fungistatic** Concentration-dependent against *Candida* spp. and *Cryptococcus* spp. **Fungistatic** Time- and concentration-dependent against *Aspergillus* spp.	**Long-term** Time- and concentration-dependent against *Candida* spp. and *Cryptococcus* spp. but not against filamentous organisms.	AUC/MIC: ≥25 against *Candida* spp. C_{min}: > 500 against *Aspergillus* spp. with Itraconazole and Voriconazole Posaconazole requires plasma concentration: 1000-1500 mg/L
Echinocandins (Caspofungin, Anidulafungin, Micafungin)	**Fungicide** Concentration-dependent against *Candida* spp. **Fungistatic** Concentration-dependent against *Aspergillus* spp.	**Long-term** Concentration-dependent against *Candida* spp.	C_{max}/MIC: > 4 against *Candida* spp. AUC/MIC: > 250 in tissue and plasma C_{max}/MEC (effective): 10 against *Aspergillus* spp.

Adapted from: Lewis RE; Bellmann R et al[65,124].

PAE: Post-antifungal effect.

Annex 16. Candida species and predisposing factors for IFD in pediatric patients[189].

Species	Risk Factor for IFD
C. albicans	Intensive Care Units, CVC, treatment with antibiotics or corticosteroids, surgery
C. parapsilosis	Prematurity, CVC, PN
C. tropicalis	Immunosuppression, neoplastic diseases
C. glabrata	Prior treatment with FCZ, severe immunosuppression
C. krusei	Prior treatment with FCZ, immunosuppression, neoplastic diseases

Adapted from: Figueras C et al[189].
CVC: central venous catheter; PN: Parenteral nutrition: FCZ: Fluconazole.

Annex 17. Algorithm of antifungal prophylaxis with fluconazole in preterm neonates[98].

High-risk groups	< 1000 g at birth or born < 27 weeks	1000-1500 g at birth
Criterium	< 5 days of age CVC or endotracheal tube	> 3 days of therapy with antibiotics CVC
Dose	3 mg/kg IV. (twice a week)	3 mg/kg IV. (twice a week)
Duration	Until the patient no longer requires venous access	Same as that of treatment with antibiotics, or while the CVC is in place
Monitoring	Weekly liver function tests All isolates should undergo susceptibility tests	Weekly liver function tests All isolates should undergo susceptibility tests
Empiric treatment of *Candida* invasive infections	AmB	AmB
Level of evidence	A-I	B-II

Adapted from: Kaufman DA[98].

AI and BII abbreviations refer to the level of evidence/degree of standard recommendation.
CVC: Central Venous Catheter; IV.: Administered Intravenously; AmB: Amphotericin B.