ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

GUÍAS DE PRÁCTICA CLÍNICA

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

José M. Oñate[1], Pilar Rivas-Pinedo[2,+], Ximena Castañeda-Luquerna[3], Jorge I. Marín-Uribe[4], Indira Berrio[5], Hugo Fernández-Suarez[6], Juan P. Osorio-Lombana[7], Sonia I. Cuervo-Maldonado[8], Carlos H. Saavedra-Trujillo[9], Adriana Marcela Celis[10], Carlos A. Álvarez-Moreno[11], Julio C. Gómez-Rincón[12], Sonia Restrepo-Gualteros[13], Germán Camacho-Moreno[14], Leonardo Enciso-Olivera[15], Bonell Patiño-Escobar[16], Fredy Guevara[17], Jaime Patiño-Niño[18], Franco Montufar[19], Eduardo López-Medina[20], Dinno Fernández-Chico[21], José F. García-Goez[22], Christian Pallares G[23]

Abstract

The clinical manifestations of *Aspergillus* spp. associated diseases are variable and depend on the interaction between the inoculating dose (which is not known and probably varies widely), the patient's ability to resist infection at both local and systemic level, and the virulence of the etiologic agent. The major difficulty in establishing a clinical classification scheme lies in the existence of a broad and continuous spectrum of disease, associated with a complicated diagnosis and clinical management. An IA can present as a localized infection in one organ, or as part of a disseminated infection, which presents itself in a varied spectrum of clinical pictures. However, no clinical trials have been completed to evaluate the different specific therapeutic approaches according to the type of involvement in these patients. The most common clinical forms of invasive aspergillosis (IA) occur in the lung and paranasal sinuses, chronic pulmonary aspergillosis (CPA) can be complicated by spreading to contiguous structures such as the pleural space, pericardium, chest wall and mediastinal structures such as the esophagus and great vessels. It frequently spreads beyond the respiratory tract, and can affect the skin, CNS, eyes, liver, kidneys and other structures.

Keywords: aspergillosis; *Aspergillus*; guidelines; invasive aspergillosis; *Aspergillus* diagnosis; voriconazole; posaconazole; isavuconazole; caspofungin; micafungin; anidulafungin; amphotericin B; extra pulmonary aspergillosis; central nervous system; endocarditis; sinusitis; osteomyelitis; endophthalmitis.

Sección 3. Consenso colombiano para el diagnóstico y tratamiento la aspergilosis extrapulmonar en pacientes adultos*

***Del Grupo de Micosis de la ACIN, para el Desarrollo del Consenso Colombiano para el Manejo de la Enfermedad Fúngica Invasora**

Resumen

Las manifestaciones clínicas de las enfermedades asociadas con *Aspergillus* spp. son variables y dependen de la interacción entre la dosis de inoculación (que se desconoce y probablemente varía ampliamente), la capacidad del paciente para resistir la infección a nivel local y sistémico, y la virulencia del agente etiológico, donde la mayor dificultad para establecer un esquema de clasificación clínica radica en la existencia de un espectro amplio y continuo de enfermedad, asociado a un diagnóstico y manejo clínico complicado. Una aspergilosis invasiva (AI) puede presentarse como una infección localizada en un órgano, o como parte de una infección diseminada, que se presentan en un variado espectro de cuadros clínicos, sin embargo, no se han completado ensayos clínicos que evalúen los diferentes abordajes terapéuticos específicos, de acuerdo al tipo de compromiso en estos pacientes. Las formas clínicas más comunes de AI tienen lugar a nivel de pulmón y de senos paranasales, una aspergilosis pulmonar crónica (APC) puede complicarse al extenderse a estructuras contiguas como el espacio pleural, el pericardio, la pared torácica y las estructuras mediastínicas como el esófago y los grandes vasos. La capacidad de diseminación más allá del tracto respiratorio es frecuente, y puede comprometer afectar piel, SNC, ojos, hígado, riñones y otras estructuras.

Palabras clave: aspergilosis; *Aspergillus*; guias de práctica clínica; aspergilosis invasiva; diagnostico de *Aspergillus*; voriconazol; posaconazol; isavuconazol; caspofungina; micafungina; anidulafungina; anfotericina B; aspergilosis extra pulmonar; Sistema nervioso central; endocarditis; sinusitis; osteomielitis; endoftalmitis.

1 Department of Internal Medicine, Universidad del Valle. Clínica de Occidente. Centro Médico Imbanaco. Cali, Colombia. https://orcid.org/0000-0002-6180-792X
2 Medical and Diagnostic Mycology, Department of Microbiology, School of Medicine, Universidad Nacional de Colombia. Bogotá, Colombia. https://orcid.org/0000-0002-6034-3182
3 Clínica de la Mujer. Virrey Solís, Special Plans. Bogotá, Colombia. https://orcid.org/0000-0003-1384-7625
4 Department of Critical Care Medicine and Infectious Diseases, Clínica San Marcel. Manizales, Colombia. https://orcid.org/00000002-6443-5076
5 Medical and Experimental Mycology Group, Corporación para Investigaciones Biológicas (CIB). Hospital General de Medellín. Medellín, Colombia. https://orcid.org/0000-0001-8234-607X
6 Diagnostic Imaging Unit, Centro Médico Imbanaco. Cali, Colombia. https://orcid.org/0000-0002-5199-9665
7 Fundación Clínica Shaio. Bogotá, Colombia. https://orcid.org/0000-0003-3541-9867
8 Instituto Nacional de Cancerología E.S.E. Department of Internal Medicine, Universidad Nacional de Colombia. Bogotá, Colombia. https://orcid.org/0000-0001-5676-880X
9 Clínica Universitaria Colombia, Clínica Colsanitas. Department of Internal Medicine, Universidad Nacional de Colombia. Bogotá, Colombia. https://orcid.org/0000-0003-0068-6631
10 Cellular and Molecular Research Group of Pathogenic Microorganisms (CeMoP). Department of Biological Sciences, Universidad de los Andes. Bogotá, Colombia. https://orcid.org/0000-0003-3057-1966
11 Department of Internal Medicine, School of Medicine, Universidad Nacional de Colombia. Clínica Universitaria Colombia. Clínica Colsanitas. Bogotá, Colombia. https://orcid.org/0000-0001-5419-4494
12 Instituto Nacional de Cancerología E.S.E, Sub-Integrated Health Services Sub-Network Centro Oriente E.S.E., GREICAH, Research Group on Infectious Diseases in Cancer and Hematological Disorders. Universidad El Bosque. Bogotá, Colombia. https://orcid.org/0000-0001-5841-1409
13 HOMI, Fundación Hospital Pediátrico de la Misericordia, Hospital Universitario San Ignacio. Department of Pediatrics, Universidad Nacional de Colombia. Bogotá, Colombia. https://orcid.org/0000-0003-3870-4102
14 HOMI, Fundación Hospital Pediátrico de la Misericordia. Fundación Hospital Infantil Universitario de San José. Department of Pediatrics, Universidad Nacional de Colombia. Bogotá, Colombia. https://orcid.org/0000-0003-0472-798X
15 Hospital Universitario Nacional de Colombia. Hospital Universitario de la Samaritana. Bogotá, Colombia. https://orcid.org/0000-0001-5540-1969
16 Department of Laboratory Medicine, University of California, San Francisco. CA, USA. https://orcid.org/0000-0003-2622-4822
17 Clínica Colsanitas. Fundación Santa Fe de Bogotá. Universidad del Rosario. Bogotá, Colombia. https://orcid.org/0000-0002-6256-4130
18 Fundación Valle del Lili. Universidad ICESI. Cali, Colombia. https://orcid.org/0000-0003-1022-3606
19 Clínica León XIII. Universidad de Antioquia. Medellín, Antioquia. https://orcid.org/0000-0002-8491-6686
20 Department of Pediatrics, Universidad del Valle. Center for the Study of Pediatric Infectious Diseases, Centro Médico Imbanaco. Cali, Colombia. https://orcid.org/0000-0003-3066-5938
21 Clínica Centro, Mi Red IPS. Postgraduate course in Internal Medicine, Universidad Libre de Colombia, Barranquilla Heaquarters. Critical Care Postgraduate Course, Universidad Simón Bolívar. Barranquilla, Colombia. https://orcid.org/0000-0001-7921-0307
22 Fundación Valle del Lili. Universidad ICESI. Cali, Colombia. https://orcid.org/0000-0001-7947-5436
23 Committee on Infections and Epidemiological Surveillance, Centro Médico Imbanaco. Research Vice-Rectory, Universidad El Bosque. Bogotá, Colombia. https://orcid.org/0000-0002-6093-7845
+ Correspondence: Pilar Rivas-Pinedo, jprivasp@unal.edu.co
Associate Professor, Head-Group Coordinator, Department of Microbiology, School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia.

Recibido: 11/06/2021; Aceptado: 22/01/2022

Cómo citar este artículo: J.M. Oñate, *et al.* Section 3. Colombian consensus on the diagnosis and treatment of extrapulmonary aspergillosis in adult patients. Infectio 2022; 26(3): 340-359

Introduction

The clinical manifestations of *Aspergillus* spp. associated diseases are variable and depend on the interaction between the inoculating dose (which is not known and probably varies widely), the patient's ability to resist infection at both local and systemic level, and the virulence of the etiologic agent. The major difficulty in establishing a clinical classification scheme lies in the existence of a broad and continuous spectrum of disease, associated with a complicated diagnosis and clinical management[1–11,14–49,58–118]. An invasive aspergillosis (IA) can present as a localized infection in one organ, or as part of a disseminated infection, which presents itself in a varied spectrum of clinical pictures. However, no clinical trials have been completed to evaluate the different specific therapeutic approaches according to the type of involvement in these patients[3,21,76]. The most common clinical forms of IA occur in the lung and paranasal sinuses[62,64,116–118], chronic pulmonary aspergillosis (CPA) can be complicated by spreading to contiguous structures such as the pleural space, pericardium, chest wall and mediastinal structures such as the esophagus and great vessels[3,49,69]. It frequently spreads beyond the respiratory tract, and can affect the skin, CNS, eyes, liver, kidneys and other structures[20,61,62,90,118–120].

Most definitions covering disseminated aspergillosis require the demonstration of *Aspergillus* spp. in two or more non-contiguous compromised sites, with the assumption of endovascular or bloodstream infection implicated in the pathogenesis[20,49,65,119–123], which must be differentiated from local dissemination or extension through tissue planes (e.g., sinus aspergillosis with direct extension to the meninges and brain)[61,63,90], from multifocal disease within an organ, and from situations where there is more than one site of infection within the organ (e.g., IPA and tracheobronchial aspergillosis)[20,49]. However, infection at two primary sites where it is assumed that infection is initiated simultaneously (e.g., concomitant acute invasive sinusitis and IPA) should probably not be considered as disseminated disease[3,20,21,49].

Table 1. Scale for measuring the quality of evidence and strength of recommendations.

Quality of evidence	
High (i)	The probability that the results will change is minimal.
Moderate (ii)	Results may change over time, but will not change dramatically.
Low (i)	The results can definitely change over time.
Strength of recommendation	
Strong	It is recommended to implement this recommendation in daily clinical practice.
Weak	It is recommended that before implementing this recommendation, the risks and benefits to the patient, as well as the costs or utilization of health resources, be evaluated.

Adapted from: Andrews JC et al.[12]

From a practical point of view, the diagnosis of extrapulmonary aspergillosis poses a number of difficulties related to the use of diagnostic tools, since the revised EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) criteria[65], specifically state that, in the case of suspected disease, the site from which clinical samples should be taken should be related to the region of tissue damage (defined clinically and radiologically), but that this is not feasible in many cases (e.g., CNS aspergillosis)[21,69,76]. Finally, proven disseminated aspergillosis has been defined as proven/probable IA at two noncontiguous involved sites (e.g., pulmonary and cutaneous disease), and probable disseminated aspergillosis has been defined as a proven/probable IA at one involved site, but with evidence of tissue damage at a noncontiguous (usually sterile) site, that is compatible with an IA (with evidence of invasive disease), but without diagnostic evidence for the involved site[3,21,45,49,58–99].

A detailed description of the background, methods and potential conflicts of interest can be found in the Section 1 "Colombian Consensus on the Diagnosis and Follow-Up of Invasive Aspergillosis and *Aspergillus* Disease in Adult and Pediatric Patients". Summarized below are the recommendations for the diagnosis and treatment of extrapulmonary aspergillosis. To assess the quality of the evidence and the strength of the recommendations, the modified GRADE methodology[12,13] was used. It assigns each recommendation with separate ratings for the underlying quality of the evidence supporting the recommendation, and for the strength with which the recommendation is made, establishing the following levels of evidence: LOW (III): results may definitely change over time; MODERATE (II): results may change over time, but will not change dramatically; HIGH (I): the likelihood that the results will change is minimal. The strength of the recommendation (STRONG OR WEAK) was evaluated taking into account the balance between benefits and risks, quality of evidence, patient values and preferences, and cost or resource utilization (Table 1)[50–57]

QUESTIONS:

1. In an adult patient with sinus involvement, how is the diagnostic approach for acute/chronic invasive *Aspergillus* spp. sinusitis?

Recommendation

1. *In an adult patient with sinus involvement, the consensus recommends performing the diagnostic approach for acute/chronic invasive* Aspergillus *spp. sinusitis by (a) histopathology and/or culture positive for* Aspergillus *spp. from sinus biopsy and/or sinus aspirate material, and/or contiguous site (e.g., orbit, brain) (b) positive PCR-DNA detection test from sinus biopsy, (c) positive* Aspergillus *galactomannan antigen (AGA) test from serum (x2), and (d) abnormal computed tomography (CT) findings (e.g., sinus opacification, evidence of erosion of bone structures, and/or destruction of contiguous structures).* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58–73].

a. In an adult patient diagnosed with acute/chronic invasive *Aspergillus* spp. sinusitis, what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

2. *In a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis the consensus recommends evaluating the degree of invasion and/or dissemination.* **(strong recommendation, high-quality evidence)**[3,49,65].
3. *In an immunocompromised patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis it is recommended to initiate primary targeted antifungal therapy.* **(strong recommendation, high-quality evidence)**[3].
4. *In a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis the consensus recommends VCZ (intravenously [IV.], 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. Therapeutic monitoring of antifungal drugs (TMD) is recommended to improve antifungal efficacy, evaluate therapeutic failure and decrease drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease [TDM in the therapeutic management of IA/*Aspergillus* Disease]) (Tables 3 and 4)[3,21,59,60,62,74–76].
5. *L-AmB (IV., 3-5 mg/kg/d), and ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d), are an alternative antifungal treatment in a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitiss.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,62,74,77–79].
6. *An echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.) may be considered for salvage antifungal therapy in a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients) [approach to the therapeutic management of refractory/progressive aspergillosis]) (Table 4)[3,80–85].
7. *The consensus does not recommend in a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis the initiation of antifungal treatment by washing with topical AmB solutions.* **(strong recommendation, high-quality evidence)**[3].
8. *It is considered that in a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 6-8 weeks.* **(strong recommendation, moderate-quality evidence)**[3,21].

Table 2. Pathological and imaging findings in diseases caused by *Aspergillus* spp.

***Aspergillosis* of the lower respiratory tract**		
	Pathological findings	**Imaging findings**
IPA (angioinvasive)	Evidence of tissue plane disruption and vascular invasion by adhesion of surface components of fungal structures (including vascular wall components, basement membrane, extracellular matrix, and cellular constituents), associated with coagulative necrosis and hemorrhagic infarction. Fungal lesion (or fungal sequestration) and areas of distal wedge-shaped pulmonary infarction are manifestations of angioinvasion.	Imaging findings depend on the patient's characteristics, and a wide variety of nonspecific radiographic patterns may be present. X-ray may show peripheral opacities (ill-defined, 1-3 cm, gradually merging into larger opacities) with or without cavitation. The opacities may increase in size and become necrotic in their central part, which reduces their density and favors air trapping, producing the "air-crescent sign"; such cavitation occurs after neutrophil recovery, which is a sign of good prognosis. An early but non-specific finding on CT is the presence of nodular opacities with a ground-glass border "halo sign" (reflecting hemorrhage and edema surrounding the lesion), also the presence of peripheral opacities by complete alveolar occupation, wedge-shaped with a base towards the pleura which, in the appropriate clinical setting, are highly suggestive of angioinvasive aspergillosis. On multislice CT, a budding tree pattern can be seen. Pleural effusion and mediastinal adenopathies are rare. Invasion of the chest wall or mediastinal pleura may occur.
IPA (non-angioinvasive)	There is no evidence of vascular invasion by the fungal structures, with the presence of a pyogranulomatous inflammatory infiltrate, inflammatory necrosis or cavitation (occasionally a mixed histologic picture may be observed).	Almost any radiologic pattern may be present. Nonspecific abnormalities may be evident, including airspace disease, single or multiple nodular infiltrates (with or without halo sign), segmental or subsegmental consolidation, diffuse ground-glass opacities or cavitation. CT allows a better definition of halo and crescent signs.
ABI	It is an invasive disease that mainly affects the large airways, (bronchoscopically accessible). It is classified as: *Aspergillus tracheobronchitis*, in which there is tracheobronchial inflammation, with a mucus exudate containing hyphal elements of *Aspergillus* spp. with no other identifiable pathogen. The inflammation is superficial, the mucosa is intact, without pseudomembrane formation, deep focal ulceration or other focal endobronchial abnormalities. *Pseudomembranous tracheobronchitis*, in which there is necrosis and detachment of the bronchial epithelium, together with formation of a pseudomembrane containing necrotic debris and hyphal elements. The depth of infection is variable and there is superficial invasion, which does not extend beyond the bronchial cartilage. *Ulcerative tracheobronchitis*, in which there are single or multiple, discretely abnormal focal areas with endobronchial plaques, nodules or areas of ulceration and necrosis. The depth of the ulcer varies, and may extend into the adjacent lung parenchyma and pulmonary vasculature.	Generally, imaging findings are normal, although X-ray and CT scan may show airway wall thickening, presence of patchy opacities or centrolobular nodules, atelectasis and/or lobar collapse.
***Aspergillosis* of the upper respiratory tract**		
	Pathological findings	**Imaging findings**
Acute invasive sinusitis	There is evidence of an acute and relatively sparse inflammatory infiltrate, with tissue infiltration by hyphal elements, angioinvasion and coagulative necrosis. It is locally more invasive, causes bone destruction, spreads to adjacent soft tissues and invades the pterygopalatine fossa, cavernous sinus and intracranial cavity. With vascular invasion and hematogenous dissemination.	Initially, noncontrast CT shows low-density mucosal thickening or soft tissue attenuation within the paranasal cavity, with a predilection for unilateral involvement of the ethmoid and the sphenoid cell. Aggressive bone destruction of the sinus walls can be rapid, and is associated with intracranial and intra-orbital extension. Bone erosion and mucosal thickening is sometimes subtle, as these fungi tend to extend along the vessels; extension beyond the sinuses may occur with intact bone walls. Intracranial extension of the disease from the sphenoid sinus leads to thrombosis of the cavernous sinus and even invasion Severe unilateral thickening of the soft tissues of the nasal cavity is the earliest finding and the most consistent, although nonspecific, sign seen on CT. More extensive changes, such as inflammation of the periantral fat, erosion, and orbital or intracranial invasion are more specific but late and infrequent features. *MRI* is the imaging of choice to evaluate intracranial and intra-orbital extension, as it better characterizes inflammatory changes in the orbital fat, extraocular muscles and proptosis resulting from intra-orbital invasion. Obliteration of periantral fat is a subtle sign of such extension, and should be looked for in patients at risk. Leptomeningeal enhancement with intracranial invasion may be seen, which is subtle in the early stages of infection. With the progression of infection there may be adjacent cerebritis, granulomas and brain abscess formation. Intracranial granulomas are hypointense in T1 and T2, with minimal enhancement in the contrasted T1 sequence.
Chronic invasive sinusitis	Presence of a mass composed of friable, necrotic or purulent material, associated with a mixed cellular infiltrate, inflammatory necrosis and invasion of contiguous structures, such as the skull base, orbit and brain.	Noncontrast *CT* shows a pseudomass with hyper-attenuated (dense) soft tissue in one or more of the paranasal sinuses, with an infiltrative appearance (mimicking cancer) and destruction of the sinus walls, with extension beyond the paranasal cavities. *MRI* is preferred to evaluate the associated intracranial extension, which behaves isointense on T1 and hypointense on T2 and FLAIR, without diffusion restriction, with mottled appearance in the bone tissue due to irregular bone destruction.
Sinus aspergilloma	Presence of a fungus ball composed of cheesy and friable material and a conglomerate of hyphal elements in concentric circles. The antral mucosa is well preserved, with chronic non-granulomatous inflammatory response, and no evidence of bone erosion.	There is evidence of sinus opacification with one or more oval or rounded soft tissue dense images, called foreign bodies, concretions or antroliths, found centrally or towards the orifice of the antrum, without evidence of tissue invasion; there may be thickening or sclerosis of the sinus wall due to pressure, which may lead to necrosis.

Cardiovascular *aspergillosis*		
	Pathological findings	**Imaging findings**
Native valve endocarditis	Presence of large friable vegetations, mural vegetations, extension to paravalvular structure and development of pancarditis. Embolic events in the main vessels, such as the aorta, iliac and femoral arteries, are characteristic.	Endocarditis may be occult or manifest as valvular vegetations on images. Right-sided vegetations on the tricuspid or pulmonary valves may indicate a venous source of the infection, which can cause pulmonary septic embolism. Vegetations on the mitral and aortic valves are symptomatic and can cause downstream arterial embolic effects such as stroke or visceral infarction. Despite their larger size (compared to that of bacterial origin), these vegetations are difficult to visualize at CT and MR imaging, unless gated cardiac examinations are performed, which improves the anatomical resolution of the images displayed in 4 Ch, 3 Ch and 2 Ch cine sequences. Approximately 78% of patients with *Aspergillus* endocarditis have demonstrable vegetations on transthoracic echocardiography.
Prosthetic valve endocarditis	Probably associated with direct inoculation of fungal elements during surgery, or by seeding of the endocardium from the lungs in the perioperative period. There is evidence of vegetation causing prosthetic malfunction and valvular dehiscence.	Echocardiographic findings are non-specific, and include compromised mechanical valve function and seating, paravalvular leak and paravalvular abscess formation.
Pericardial aspergillosis	It may arise by contiguous dissemination from the pleura or myocardium. There is evidence of fibrinous or exudative pericarditis, or contiguous IPA, or myocardial aspergillosis. *Postmortem* findings demonstrate patchy, diffuse pericarditis, or the presence of multiple raised nodules or plaques on one or both pericardial surfaces.	Pericardial aspergillosis is not a frequent *ante mortem* diagnosis, but should be suspected when a patient with IPA develops pericardial effusion (suspected clinically or seen on imaging), or there is other evidence of pericardial disease. There is echocardiographic evidence of pericardial disease, including pericardial effusion and signs of pericardial tamponade, with a widened cardiac silhouette on chest X-ray.
CNS *Aspergillosis*		
	Pathological findings	**Imaging findings**
Cerebrovascular aspergillosis	Evidence of vessel invasion by scarce hyphal elements, cerebral infarction in vascular territory, necrosis and hemorrhagic transformation with little inflammatory response, without evidence of abscess or granuloma formation, and with contiguous involvement of the meninges.	The radiologic appearance is non-specific, and may be normal or near normal in the early stages of infection. CT and MRI features in a specific clinical setting may support the diagnosis. Imaging features include intraparenchymal and extraparenchymal (skull base) lesions with perilesional edema, basal meningeal enhancement, hydrocephalus and infarcts, with or without hemorrhage. In addition, imaging may provide evidence of concomitant pulmonary, sinus, orbital or mastoid involvement. Massive lesions may have a homogeneous enhancement (granuloma) or a peripheral ring (abscess). The presence of lesions at the base of the skull, with homogeneous enhancement associated with intrasinusal, orbital or mastoid lesions, suggest the diagnostic possibility of *Aspergillus* infection.
Brain abscess	It may be the result of hematogenous seeding in the context of significant immunologic impairment. There is evidence of abscess formation, consisting of an area of central liquefactive necrosis in which hyphal elements are scarce or absent, and surrounded by an area of hemorrhagic necrosis with an acute inflammatory infiltrate interspersed with multiple hyphal elements.	*CT* or *MRI* shows single or multiple space-occupying lesions showing ring enhancement, mass effect or cerebral edema.
Brain granuloma	There is evidence of a firm, rubbery or gritty mass, without suppuration, with florid granulomatous inflammation and fibrinous tissue interspersed with hyphal elements.	CT shows a space-occupying lesion. The MRI characteristic of *Aspergillus* granulomas, shows to be extremely hypointense on T2, and hypointense or isointense on T1.
Fungal cerebral aneurysm	There is evidence of aneurysm formation in the intracranial artery, and invasion of the vessel wall by hyphal elements. The aneurysm may rupture or leak, which usually manifests as hemorrhage into the subarachnoid space.	In catheter angiographies and CT and MRI angiographies, aneurysms are usually fusiform, most often involving the proximal vasculature, such as internal carotid arteries and vessels forming the polygon of Willis. Intracranial hemorrhage may be a complication of vasculitis or fungal aneurysm formation, which appears hyperdense on non-contrast CT.
Meningitis	Presence of a thick grayish-white membrane covering the brain, in cases of dissemination from sinuses; or of focal and contiguous meningitis in cases of cerebrovascular aspergillosis, with the formation of a cerebral abscess, meninges infiltrated by hyphal elements and inflammatory infiltrate. CSF shows neutrophil pleocytosis, elevated protein and low to normal glucose.	Radiologic abnormalities within the meninges are usually absent. MRI shows thick meningeal enhancement on T1-weighted images, particularly at the skull base. The presence of leptomeningeal enhancement is nonspecific, but nodularity may be more specific of a fungal infection.
Ocular *aspergillosis*		
	Pathological findings	**Imaging findings**
Endogenous endophthalmitis	There is evidence of hyphal elements within the retinal and subretinal structures, with chorioretinal abscess formation, secondary vitritis, thrombosis and retinal vessel rupture, with retinal detachment. A fundus examination shows white, spongy preretinal lesions with deep creamy-white retinal lesions and intraretinal hemorrhages, with large wedge-shaped quadrants of pigmented and scarred chorioretinal atrophy.	A *fluorescein angiogram* shows hyperfluorescence of the preretinal granuloma and surrounding deep retinal lesions, with staining of the chorioretinal scars, focal vasculitis and leakage of the involved vessels. *Ocular ultrasound* shows dense opacities in the vitreous chamber for vitritis, thickening of the retinochoroidal layer due to subretinal exudative lesions, pre and intraretinal hemorrhages, preretinal layering of exudates that lead to epiretinal membranes and retinal detachment.
Exogenous endophthalmitis	It is due to direct inoculation of viable organisms, which may be accidental or iatrogenic, after penetrating ocular wounds or cataract surgery. Ocular abnormalities are not necessarily limited to the posterior globe.	Ocular ultrasound may reveal intraocular abnormalities.

Scleritis	Infiltration of the sclera by hyphal elements is more common in the setting of recent surgery, accidental or traumatic injury, or may be due to hematogenous seeding.	Diagnostic imaging is not usually performed.
Keratitis	Situations in which the integrity of the cornea is altered, such as surgery, trauma or use of contact lenses. It presents with stromal infiltrate, stromal abscess formation, invasion by hyphal elements and coagulative necrosis.	Diagnostic imaging is not usually performed.
Cutaneous *aspergillosis*		
	Pathological findings	**Imaging findings**
Primary cutaneous aspergillosis	There is evidence of significant local tissue destruction, spread to contiguous structures and disseminated infection, where it may be difficult to determine whether hyphal elements are found on the surface, or involve deeper structures.	Diagnostic imaging is not usually performed. Diagnosis is made by histopathology and culture.
Secondary cutaneous aspergillosis	There is evidence that cutaneous involvement is due to hematogenous seeding.	Diagnostic imaging is not usually performed. Diagnosis is made by histopathology and culture.
Osteoarticular *aspergillosis*		
	Pathological findings	**Imaging findings**
Osteomyelitis	It can occur by direct traumatic or iatrogenic inoculation, dissemination from contiguous structures or hematogenous seeding.	Fungal lesions can be seen on simple X-ray, CT and MRI, and may be helpful in stratifying and guiding needle biopsy of the lesion. The imaging features of infections are often nonspecific and difficult to differentiate from findings due to pyogenic infections or other causes of inflammatory arthropathy. CT findings include bone destruction, mixed lytic and sclerotic foci, cortical thickening and joint space narrowing.
Septic arthritis	It may be the result of hematogenous seeding, or direct inoculation after joint instrumentation.	CT and MRI findings are nonspecific. The most common findings are bone erosion, joint space narrowing, synovitis and joint effusions.
Renal *aspergillosis*		
	Pathological findings	**Imaging findings**
Renal aspergillosis	This entity is the result of hematogenous seeding, and is usually an incidental finding in the context of disseminated disease. Several different pathological processes are observed, ranging from vascular involvement with tissue infarction to renal abscess formation. Involvement of the renal vasculature results in multiple areas of renal infarction and ischemic and papillary necrosis. The renal vein may also be involved with complications including renal vein thrombosis and renal infarction.	CT reveals typically heterogeneous focal abscesses; these appear as hypoattenuating collections, which replace the renal parenchyma, with or without associated hydronephrosis. Advanced infection can lead to renal infarction and necrosis, which appears on contrast-enhanced MRI and on CT as a hypointense image, rarely progressing to emphysematous pyelonephritis.
Renal aspergilloma	Similar to formation of aspergillomas of pulmonary or sinus origin; the renal pelvis is the most common site of involvement. Aspergilloma is composed of gray or brown cheesy material that completely fills and occludes the pelvis and other components of the collecting system. The renal parenchyma is not involved, although there may be an ascending infection.	The presence of an aspergilloma occupying the renal collecting system, appearing as a heterogeneous hypoechoic mass within the dilated calyces, can be seen by ultrasound. On CT they appear as soft tissue dense masses within the collecting system. MRI often shows isointense masses on T1 and hyperintense on T2. They may cause local vascular inflammation resulting in thrombosis. More indolent chronic infections may cause parenchymal calcifications.
Gastrointestinal *aspergillosis*		
	Pathological findings	**Imaging findings**
Intestinal aspergillosis	An upper and lower intestinal aspergillosis arises from hematogenous seeding, and occurs as part of a disseminated infection. Focal areas of ulceration with variable depth and abscess formation are observed. Infiltration of hyphal elements in the intestinal wall, arteritis and thrombus formation within intramural vessels are seen.	Imaging findings of abdominal infections are variable and include nonspecific lesions, organomegaly and lymphadenopathy. Intestinal aspergillosis can manifest itself in a variety of ways, with intestinal obstruction, perforation or toxic megacolon, as a result of ischemia or tissue infarction.
Various gastrointestinal syndromes	Several rare syndromes are related to *Aspergillus* infection: stomatitis (with purplish discoloration of the gingiva, necrotic ulceration with an overlying gray membrane, and subsequent invasion of the alveolar bone), hepatosplenic disease (with formation of a hepatosplenic abscess) and peritonitis secondary to chronic ambulatory peritonitis.	CT shows a wide range of findings; the angioinvasive characteristic of *Aspergillus* can help predict its diagnosis. Fungal vascular invasion can cause vascular thrombosis, occlusion or pseudoaneurysm with or without rupture, ischemic or hemorrhagic tissue necrosis.

IPA: Invasive pulmonary aspergillosis; IBA: Invasive bronchial aspergillosis; CT: Computed tomography; MRI: Magnetic resonance imaging; HSCT: Hematopoietic stem-cell transplantation; GVHD: Graft-versus-host disease; HIV: human immunodeficiency virus; CGD: Chronic granulomatous disease; SOT: Solid organ transplant; CNS: Central nervous system; CSF: Cerebrospinal fluid.

Adapted from: Gregg KS et al. (11), Hope WW et al. (49), Orlowski HL et al. (69), Murthy JM et al. (90), Spadea L et al. (91), Bariteau JT et al. (106), Yeom SK et al. (111), Aribandi M et al. (154), Chong S et al. (155), Hage CA et al. (156), Payne SJ et al. (157).

b. In an adult patient diagnosed with acute/chronic invasive *Aspergillus* spp. sinusitis, what is the role of the surgical procedure?

Recommendation

9. *In a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis with paranasal sinus involvement and no mucosal involvement, the consensus recommends careful surgical evaluation and consideration of surgical debridement.* **(strong recommendation, high-quality evidence)**[3].
10. *In a patient diagnosed with acute/chronic invasive* Aspergillus *spp. sinusitis with paranasal sinus involvement and with mucosal invasion or sphenoidal involvement, the consensus recommends initiating primary targeted antifungal therapy associated with adjunctive surgical management with surgical debridement.* **(strong recommendation, high-quality evidence)** (Table 5)[3,21,74].

2. In an adult patient with cardiovascular involvement, how is the diagnostic approach for endocarditis or pericarditis due to *Aspergillus* spp. performed?

Recommendation

11. *In a patient with cardiovascular involvement, the consensus recommends a diagnostic approach for native valve endocarditis due to* Aspergillus *spp. by: (a) histopathology and/or culture positive for* Aspergillus *spp. from retrieved embolus and/or resected valve, (b) positive PCR test from blood or from retrieved embolus and/or resected valve, (c) positive AGA test from serum (x2), and (d) echocardiographic evidence of endocardial abnormalities.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58–60,65–73,86].
12. *In a patient with cardiovascular involvement, the consensus recommends a diagnostic approach for prosthetic valve endocarditis by: (a) histopathology and/or culture positive for* Aspergillus *spp. from retrieved embolus and/or resected valve, (b) positive PCR test from blood, retrieved embolus and/or resected valve, (c) positive AGA test from serum (x2), and (d) echocardiographic evidence of abnormalities (e.g., prosthetic valve malfunction, paravalvular leak, paravalvular collection, or vegetations larger than 10 mm).* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of AI/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58–60,65–73,86].
13. *In a patient with cardiovascular involvement, the consensus recommends a diagnostic approach for pericarditis, by: (a) histopathology and/or culture positive for* Aspergillus *spp. from biopsy and/or pericardial aspiration, (b) positive PCR test from blood and/or pericardial fluid, (c) positive AGA test from serum (x2) and/or pericardial fluid (x1), and (d) echocardiographic evidence of pericardial disease, (e.g., pericardial effusion, signs of pericardial tamponade, widened cardiac silhouette [on chest X-ray]).* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58–60,65–73,86].

a. In an adult patient diagnosed with *Aspergillus* spp. endocarditis or pericarditis, what is recommended in choosing the type of drug, dosage, and duration of antifungal treatment?

Recommendation

14. *In a patient diagnosed with native/prosthetic valve endocarditis due to* Aspergillus *spp. the consensus recommends multidisciplinary medical-surgical therapeutic management. Early surgical management (valve replacement, abscess drainage, endocardial lesions) with aggressive surgical debridement is considered.* **(strong recommendation, moderate-quality evidence)** (Table 5)[21,76].
15. *In a patient diagnosed with* Aspergillus *spp. pericarditis, initiation of targeted antifungal treatment associated with complementary management with pericardiocentesis is recommended.* **(strong recommendation, moderate-quality evidence)** (Table 5)[21,76].
16. *In a patient diagnosed with* Aspergillus *spp. endocarditis/pericarditis, the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,21,59,60,74–76].
17. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with* Aspergillus *spp. endocarditis/pericarditis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,21,76–79].
18. *An echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.) may be considered for salvage antifungal therapy in a patient diagnosed with* Aspergillus *spp. endocarditis/pericarditis.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 4)[3,21,76,80–85].
19. *In a patient diagnosed with* Aspergillus *spp. endocarditis/pericarditis, L-AmB (IV., 3-5 mg/kg/d) and VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) may be considered as an option for combination antifungal therapy.* **(strong recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [combined antifungal treatment according to the at-risk population]) (Annex 2)[3,21,76–78,87–89].
20. *It is considered that in a patient diagnosed with* Aspergillus *spp. endocarditis/pericarditis, the duration of antifungal therapy should be established on an individual basis, and lifelong suppressive antifungal therapy should be considered.* **(weak recommendation, low-quality evidence)**[3,21,76].

Table 3. Recommendations for TDM.

Drug	Indications	Time to TDM after treatment initiation	Effective plasma concentration	Toxicity plasma concentration
ITZ	• To improve efficacy in patients (immunocompromised or not) receiving ITZ, in prophylaxis or for treatment of an IFD or an allergic fungal disease: • When there are drug interactions, when starting or stopping therapy (either by inhibiting absorption or affecting its metabolism) • In co-medications (with Cytochrome P450 inducers). • In case of suspicion of non-adherence to oral therapy. • In the absence of pharmacological response. • Concern about gastrointestinal absorption, especially over prolonged periods. • Possible clinical or laboratory manifestations of toxicity.	Measure from day 4-7, after the start of treatment.	In prophylaxis: 0.5 mg/L, (HPLC), or; > 3 mg/L (bioassay) For treatment: > 1-4 mg/, (HPLC)	Toxicity is associated with serum levels of ITZ > 17.1 mg/L (bioassay), or ~4 mg/L, (HPLC).
VCZ	• To improve efficacy in patients (immunocompromised or not) receiving VCZ, in prophylaxis or for treatment of an IFD: • When drug interactions are present, when starting or stopping therapy. • In case of suspicion of non-adherence to oral therapy. • Concern about gastrointestinal absorption, especially over prolonged periods. • In the absence of pharmacological response. • In interactions with drugs administered simultaneously. • When changing from oral to intravenous administration or vice versa. • In case of hepatic insufficiency. • In its administration in pediatric patients.	Measure from day 4-7, after initiation of treatment, or on day 4 after dose adjustment.	In prophylaxis: > 1 mg/L. For treatment: 1-5.5 mg/L Repeat TDM during week 2 of treatment.	< 4.5-5.5 mg/L, (HPLC)
PCZ	• To improve efficacy in patients (immunocompromised or not) receiving PCZ, in prophylaxis or for salvage treatment of an IFD: • When drug interactions are present, when starting or stopping therapy. • In case of suspicion of non-adherence to oral therapy. • Concern about gastrointestinal absorption, especially over prolonged periods. • In the absence of pharmacological response. • In co-medications, including H_2 antagonists and proton pump inhibitors. • In mucositis and other types of gastrointestinal disorders.	Measure from day 4-7, after the start of treatment.	In prophylaxis: > 0.7 mg/L at steady state, or, 0.35 mg/L after 48 hours from the start of treatment. For treatment: > 1 mg/L.	Serum PCZ levels of, 0.5-3.75 mg/L are considered safe and effective in all three formulations. Serum PCZ levels above this exposure range may be associated with toxicity.
ISZ	• To improve efficacy, safety and treatment adherence in patients receiving ISZ	Measure serum concentration on day 5, after initiation of treatment, and then regularly thereafter.	Data are limited to support routine TDM, but may be indicated in case of treatment failure, drug interactions or if toxicity is suspected.	

TDM: Therapeutic drug monitoring of antifungal agents; ITZ: Itraconazole; VCZ: Voriconazole; PCZ: Posaconazole; ISZ: Isavuconazole; IFD: Invasive fungal disease; HPLC: High-performance liquid chromatography.
Adapted from: Fortún J et al.[20], Ullmann AJ et al.[21], Ashbee HR et al.[59], Cendejas-Bueno E. et al.[158].

3. In an adult patient with CNS involvement, how is the diagnostic approach for CNS (brain, spinal cord and/or meninges) aspergillosis performed?

Recommendation

21. *In a patient with CNS involvement, the consensus recommends making the diagnostic approach for cerebrovascular aspergillosis by: (a) histopathology and/or culture positive for* Aspergillus *spp. from biopsy and/or from brain aspirate, and/or from contiguous site (e.g., paranasal sinus), (b) positive PCR test from cerebrospinal fluid (CSF) and/or from biopsy and/or brain aspirate, (c) positive AGA test from serum (x2) and/or CSF (x1), and (d) abnormal CT findings (e.g., one or more non-enhancing hypodense regions consistent with cerebral infarction, and/or hyperdense regions consistent with hemorrhage or hemorrhagic transformation).* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58,60,65–73,86].
22. *In a patient with CNS involvement, the consensus recommends making the diagnostic approach for an* Aspergillus *spp. brain abscess by: (a) histopathology and/or culture positive for* Aspergillus *spp. from abscess biopsy and/or aspirate, and/or from contiguous site (e.g., paranasal sinus), (b) positive PCR test from CSF or brain biopsy and/or aspirate, (c) positive AGA test from*

serum (x2) and/or CSF (x1), and (d) abnormal findings on contrast-enhanced magnetic resonance imaging (MRI) (e.g., evidence of single or multiple space-occupying lesions showing ring enhancement, mass effect and/or cerebral edema). **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58,60,65–73,86].

23. *In a patient with CNS involvement, the consensus recommends making the diagnostic approach for* Aspergillus *spp. meningitis by: (a) histopathology and/or culture positive for* Aspergillus *spp. from meningeal biopsy and/or CSF and/or contiguous site (e.g., paranasal sinus), (b) positive PCR test from CSF and/or blood, and (c) positive AGA test from serum (x2) and/or CSF (x1).* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58,60,65–73,86].

a. In an adult patient diagnosed with CNS (brain, spinal cord and/or meninges) aspergillosis, what is recommended in choosing the type of drug, dosage and duration of antifungal therapy?

Recommendation

24. *In a patient diagnosed with CNS aspergillosis (brain, spinal cord and/or meninges), the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,21,59,60,75,76].
25. *High-dose L-AmB (IV., 10 mg/kg/d), or ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) is an alternative for antifungal treatment in a patient diagnosed with CNS aspergillosis (brain, spinal cord and/or meninges), when there is a risk of: (a) hepatotoxicity due to VCZ use, (b) drug interactions, (c) intolerance to azole treatment.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,21,76–79].
26. *LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.) may be considered for salvage antifungal therapy in a patient diagnosed with CNS (brain, spinal cord and/or meninges) aspergillosis.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 4)[3,21,76,80–85].
27. *In a patient diagnosed with CNS aspergillosis (brain, spinal cord and/or meninges) with evidence of single lesions, the consensus recommends that, if feasible, adjunctive surgical management with surgical debridement be performed.* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,21,76].
28. *In a patient diagnosed with CNS aspergillosis (brain, spinal cord and/or meninges), a surgical approach is recommended according to the size of the lesion, its location and characteristics, and/or the impact on intracranial pressure and visual acuity. Surgical options considered are: (a) surgical decompression, (b) stereotactic drainage, (c) external ventricular drain (EVD) catheter placement, and (d) hemicraniectomy.* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,76].
29. *In a patient diagnosed with CNS (brain, spinal cord and/or meninges) aspergillosis, the consensus does not recommend initiating antifungal combination therapy.* **(weak recommendation, low-quality evidence)**[3,76].
30. *In a patient diagnosed with CNS (brain, spinal cord and/or meninges) aspergillosis, the consensus does not recommend initiating intrathecal or intralesional antifungal therapy and/or administration of corticosteroid therapy.* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,76].
31. *It is considered that in a patient diagnosed with CNS (brain, spinal cord and/or meninges) aspergillosis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 12 months.* **(strong recommendation, moderate-quality evidence)**[3,21,76,90].

4. In an adult patient with ocular involvement, how is the diagnostic approach for endogenous/exogenous *Aspergillus* spp. endophthalmitis performed?

Recommendation

32. *In a patient with ocular involvement, the consensus recommends making the diagnostic approach for endogenous/exogenous* Aspergillus *spp. endophthalmitis by (a) histopathology and/or culture positive for* Aspergillus *spp. from aqueous humor and vitreous humor specimen, (b) positive PCR test from aqueous humor and vitreous humor specimen, and (c) ocular ultrasound evidence of abnormalities.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,66–69].

a. In an adult patient diagnosed with endogenous/exogenous *Aspergillus* spp. endophthalmitis, what is recommended for choosing the type of drug, dosage and duration of antifungal treatment?

Recommendation

33. *In a patient diagnosed with endogenous/exogenous* Aspergillus *spp. endophthalmitis, the consensus recommends as a first choice of antifungal treatment to use IV. (6 mg/kg/12h, day 1, then 4 mg/kg/12h) or orally (PO.) VCZ (> 40 kg, 400 mg/12h, day 1, then 200 mg/12h).* **(strong recommendation, high-quality evidence)** (Table 4)[3,75,91–95].
34. *VCZ (100 µg/ 0.1ml) and D-AmB (5-10 µg) for intravitreal use, alone or in combination with VCZ, IV. or PO., are an alternative for antifungal treatment in a patient diagnosed with endogenous/exogenous* Aspergillus *spp. endophthalmitis.* **(strong recommendation, low-quality evidence)**[21,87–89,91–96].

35. *ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) or L-AmB (IV., 3-5 mg/kg/d) are an alternative for antifungal treatment in a patient diagnosed with endogenous/exogenous* Aspergillus *spp. endophthalmitis* **(strong recommendation, low-quality evidence)** (Table 4)[3,76–79].
36. *PCZ (IV., 300 mg/12h, day 1, then 300 mg/d) or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d), may be considered for salvage antifungal therapy in a patient diagnosed with endogenous/exogenous* Aspergillus *spp. endophthalmitis.* **(strong recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the therapeutic management of refractory/progressive aspergillosis]) (Table 4)[3,80–82,84,85,91].
37. *In a patient diagnosed with endogenous/exogenous endophthalmitis due to* Aspergillus *spp. the consensus recommends multidisciplinary medical-surgical management and close consultation with ophthalmology. In case of clinical suspicion of an IFI/IA, early initiation of antifungal treatment associated with vitrectomy is considered.* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,91].
38. *It is considered that in a patient diagnosed with endogenous/exogenous* Aspergillus *spp. endophthalmitis, the duration of systemic and/or intravitreal antifungal treatment should be established on an individual basis, and should last a minimum of 4-6 weeks.* **(strong recommendation, low-quality evidence)**[3,91].

5. In an adult patient with ocular involvement, how is the diagnostic approach for *Aspergillus* spp. keratitis performed?

Recommendation

39. *In a patient with ocular involvement, the consensus recommends a diagnostic approach for* Aspergillus *spp. keratitis by: (a) positive culture for* Aspergillus *spp. from corneal specimen.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2)[45,49,66,68].

a. In an adult patient diagnosed with *Aspergillus* spp. keratitis, what is recommended in choosing the type of drug, dosage, and duration of antifungal treatment?

Recommendation

40. *In a patient diagnosed with* Aspergillus *spp. keratitis, the consensus recommends 5% natamycin ophthalmic suspension as the first antifungal treatment option.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,97].
41. *VCZ (1-2%) or AmB (0.15-0.3%) topically are an alternative for antifungal treatment in a patient diagnosed with* Aspergillus *spp. keratitis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,98–102].
42. *In a patient diagnosed with* Aspergillus *spp. keratitis presenting with giant ulcers in the anterior chamber or hypopyon, the consensus recommends using IV. VCZ (400 mg/d) as adjuvant antifungal therapy.* **(strong recommendation, moderate-quality evidence)**[3,97].
43. *In a patient diagnosed with* Aspergillus *spp. keratitis who does not respond to topical antifungal treatment, the consensus recommends penetrating keratoplasty.* **(weak recommendation, moderate-quality evidence)** (Table 5)[3,97].
44. *It is considered that in a patient diagnosed with* Aspergillus *spp. keratitis, the duration of systemic and/or intravitreal antifungal treatment should be established on an individual basis, and should last a minimum of 3-4 weeks.* **(strong recommendation, low-quality evidence)**[3,97].

6. In an adult patient with otic involvement, how is the diagnostic approach for *Aspergillus* spp. external otitis performed?

Recommendation

45. *In a patient with otic involvement, the consensus recommends a diagnostic approach for* Aspergillus *spp. external otiti by: (a) direct microscopy positive for* Aspergillus *spp. from a specimen of the external auditory canal.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease)[49,66].

a. In an adult patient diagnosed with *Aspergillus* spp. external otitis, what is the recommendation for choosing the type of drug, dosage and duration of antifungal treatment?

Recommendation

46. *In an immunocompetent patient diagnosed with non-invasive* Aspergillus *spp. external otitis, the consensus recommends a complete mechanical cleaning of the external auditory canal and initiation of treatment with boric acid or a topical antifungal agent. It is not recommended to use potentially ototoxic drugs, creams, gels or ointments in a patient with a perforated tympanic membrane.* **(strong recommendation, moderate-quality evidence)**[3].
47. *The consensus considers that in an immunocompromised patient diagnosed with* Aspergillus *spp. external otitis, the infection may be associated with bacterial otitis, and may extend and involve deeper structures (e.g., mastoids).* **(strong recommendation, moderate-quality evidence)**[3,103–105].
48. *The consensus considers that in an immunocompromised patient diagnosed with invasive* Aspergillus *spp. external otitis, it may be necessary to initiate a prolonged course of targeted antifungal therapy with: (a) VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h), (b) ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d), (c) PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or (d) L-AmB (IV., 3-5 mg/kg/d).* **(strong recommendation, moderate-quality evidence)**[3,77–80,103–105].

Table 4. Systemic antifungal agents for treatment of IA. ADME, Doses.

POLYENES	ANPHOTERICIN B	A	It is not absorbed PO.		
		D	It has little CNS penetration.		
		M	Degradation in tissue.		
		E	Renal (<10% unmodified); Biliary (15%)		
		Adjustment	Kidney failure: no changes, no dose adjustment required. On HD or CAPD it dialyzes <5%. Liver failure: no changes, no dose adjustment required.		
		Pregnancy	It can be used in cases of strict necessity.		
		Lactation	Contraindicated		
		Formulations	D-AmB	L-AmB	LC-AmB
		Dosage for adults	IV. 0,4-1 mg/kg/d	IV. 3-5 mg/kg/d	IV. 3-5 mg/kg/d
		Dosage for children	IV. 0,4-1 mg/kg/d	IV. 3-5 mg/kg/d	IV. 3-5 mg/kg/d
ECHINOCANDINS	CASPOFUNGIN	A	IV only.		
		D	Widespread, although it decreases in CNS.		
		M	Hepatic and spontaneous chemical degradation.		
		E	Renal (41% inactive metabolites); Fecal (35% inactive metabolites).		
		Adjustment	Kidney failure: No changes. On HD: does not dialyze. Liver failure: *Child-Pugh* A: no changes, no dose adjustment required, *Child-Pugh* B: 70 mg 1st d, then 35 mg/d, *Child-Pugh* C: no studies available in this population.		
		Pregnancy	Avoid it if there is an alternative.		
		Lactation	Should be avoided.		
		Dosage for adults	IV, 70 mg 1st dose, then 50 mg/d (70 mg/d if >80 kg), perfuse the doses in 60 min.		
		Dosage for children	IV, <3 months of age, 25 mg/m2/d, one dose. > 3 months 70 mg/m2, then 50 mg/m2/d, one dose, not to exceed the adult dose.		
	ANIDULAFUNGIN	A	IV only.		
		D	Widespread, although it decreases in CNS.		
		M	Spontaneous chemical degradation.		
		E	Renal (<1%); Fecal (>90% inactive metabolites).		
		Adjustment	Kidney failure: no changes. On HD: does not dialyze. Liver failure: no changes, no dose adjustment required.		
		Pregnancy	Avoid it if there is an alternative.		
		Lactation	Should be avoided.		
		Dosage for adults	IV, 200 mg 1st dose (in 3h), then 100 mg/d (in 1.5h).		
		Dosage for children	IV, 3 mg/kg 1st dose, then 1.5 mg/kg/d.		
	MICAFUNGIN	A	IV only.		
		D	Widespread, although it decreases in CNS.		
		M	Hepatic (via catechol-O-methyltransferase), CYP3A *in vitro*.		
		E	Renal [10-30% (<1% unmodified)]; Fecal (70% as metabolites).		
		Adjustment	Kidney failure: no changes. On HD: does not dialyze. Liver failure: *Child-Pugh* A and B: no changes, no dose adjustment required, *Child-Pugh* C: no data.		
		Pregnancy	Avoid it if there is an alternative.		
		Lactation	Should be avoided.		
		Dosage for adults	IV. 100-150 mg/d (in perfusion for 1 h).		
		Dosage for children	Newborn: 4 to 10 mg/kg/d in one dose. > 4 months (<40 kg): 2-4 mg/kg/d in one dose. > 40 kg: 100 mg/d.		
AZOLES	FLUCONAZOLE	A	IV and PO (high).		
		D	Very wide. High CNS penetration		
		M	Hepatic. [10% (CYP34A4)].		
		E	Renal [70-80% (glomerular filtration and tubular reabsorption)].		
		Adjustment	Kidney failure: GF > 50: 100-400 mg/kg/d; GF 10-50: 50% of dose; GF <10: 50% of dose. In HD, it dialyzes 50%: 100-400 mg/kg/d (post-HD); In CAPD: 50-200 mg/kg/d; In CRRT: 200-400 mg/kg/d. Liver failure: *Child-Pugh* A: no dose adjustment required. *Child-Pugh* B, *Child-Pugh* C: use it as a last option, monitor liver function and assess dosage adjustment.		
		Pregnancy	Avoid it if there is an alternative.		
		Lactation	It can be used.		
		Dosage for adults	PO 50-800 mg/d; IV. 50-800 mg/d. Requires loading dose in severe shock/sepsis: 800 mg (12 mg/kg).		
		Dosage for children	> 1 year, 3-12 mg/kg/d; neonates 6-12 mg/kg/d.		

AZOLES	ITRACONAZOLE	A	IV and PO.
		D	Low. Does not penetrate CNS.
		M	Hepatic, extensive via CYP34A4, CYP3A5, hydroxy-itraconazole metabolite (fluconazole-like activity).
		E	Renal (< 1% unmodified, 40% metabolites); Biliary (55% metabolites).
		Adjustment	Kidney failure: IV formulation contains cyclodextrin, which accumulates in kidney failure (not +2 weeks). GF > 10: no changes (IV formulation should not be used if GF < 30, use oral formulation, 50-100 mg/d), GF < 10: 50% of PO formulation. On HD: it dialyzes < 5%, 100 mg/12-24h PO formulation; In CAPD it dialyzes < 5%, 100 mg/12-24h PO formulation; In CRRT: 100-200 mg/12-24h of PO formulation. Liver failure: there are few data available for PO use. Caution should be exercised when administering it, and should be monitored in patients with hepatic dysfunction. In patients with increased liver enzymes or active liver disease, or in those who have experienced liver toxicity with other drugs, do not administer unless the expected benefits outweigh the risk of liver injury.
		Pregnancy	Avoid it if there is an alternative.
		Lactation	Should be avoided.
		Dosage for children	> 5 years, 2.5 mg/kg/12h.
		Dosage for children	> 5 years, 2.5 mg/kg/12h.
	VORICONAZOLE	A	IV and PO (high).
		D	Very wide. High CNS penetration
		M	Hepatic. They are P-450 inhibitors. IV. CYP2C19, CYP3A4, CYP2C9; P.O. CYP3A4
		E	Renal (85% inactive metabolites, 2% unmodified); Fecal (20% inactive metabolites).
		Adjustment	Kidney failure: PO, no changes. With IV use, the diluent (cyclodextrin) may accumulate; GF > 50: 4 mg/kg/12h; GF 10-50: Do not use the IV formulation; GF < 50 (accumulation of cyclodextrin with IV formulation), use the PO formulation 200 mg/12h; GF < 10: use the PO formulation 200 mg/12h. On HD: does not dialyze, use the PO formulation 200 mg/12h; CAPD: does not dialyze, use the PO formulation 200 mg/12h; CRRT: use the PO formulation: 200 mg/12h. Liver failure: IV: *Child-Pugh* A and B: 6 mg/kg/12h for 2 doses, then 2 mg/kg/12h (50% dose reduction). PO: *Child-Pugh* A and B: 400 mg/kg /12h for 2 doses (> 40 kg weight), then 100 mg/12h (50% dose reduction). *Child-Pugh* C: avoid it, no studies are available in this population.
		Pregnancy	Avoid it if there is an alternative.
		Lactation	Should be avoided.
		Dosage for adults	IV. 6 mg/kg/12h 1st dose, then 4 mg/kg/12h. PO > 40 kg, 400 mg/12h 1st dose, then 200 mg/12h; < 40 kg, 200 mg/12h 1st dose, then 100 mg/12h. Bioavailability of 95%, administration with food decreases it by 20-30% (administer it on an empty stomach).
		Dosage for children	IV. 2-12 years or 12-14 years and weight < 50 kg, 9 mg/kg/12h. 1st dose, then 8 mg/kg/12h. PO. 9 mg/kg/12h (maximum dose 350 mg/12h). Child > 12 years and weight ≥ 50 kg or > 15 years, same as adult.
	POSACONAZOLE	A	IV and PO.
		D	Widespread.
		M	Hepatic (glucuronoconjugation); Inactive metabolisms, CYP3A4.
		E	Renal (14% inactive metabolites); Fecal (77%, 66% unmodified).
		Adjustment	Kidney failure: GF > 50: 300 mg/d; GF 10-50: 300 mg/d; GF <10: 300 mg/d. On HD: does not dialyze, 300 mg/d; In CAPD: 300 mg/d; In CRRT: 300 mg/d. Liver failure: no changes, no dose adjustment required.
		Pregnancy	Avoid it if there is an alternative.
		Lactation	Contraindicated.
		Dosage for adults	PO suspension (40 mg/mL): 400 mg/12h, with meals (if no meals are taken, 200 mg/6h). PO. 200 mg/8h (with food), for prophylaxis. Delayed-release tablets ([DRT] 100 mg): 300 mg/12h 1st dose, then 300 mg/d, for prophylaxis. IV: 300 mg/12h 1st dose, then 300 mg/d (prophylaxis). It takes 7-10 d to achieve steady state. It takes 7-10 d to reach steady state. No IV formulation. Administration with food (preferably fatty) significantly increases absorption. On the other hand, an increase in gastric pH (antacids, H antagonists, proton pump inhibitors) and grade I-II mucositis decrease it.
		Dosage for children	Children > 13 years old, same as in adults. Children < 13 years, there are no specific recommendations. Children 2-16 years with CGD for 30 d: 10-14 kg: 120 mg/12h; 15-19 kg: 160 mg/12h; 20-24 kg: 200 mg/12h; 25-29 kg: 220 mg/12h; 30-34 kg: 260 mg/12h; 35-39kg: 280 mg/12h; ≥40 kg: 300 mg/12h.

AZOLES	ISAVUCONAZOLE	A	IV and PO.
		D	Widespread, although it decreases in CNS.
		M	Hepatic. CYP 3A4. CYP3A4 - CYP3A5.
		E	<1% urine. Degradation products in urine.
		Adjustment	Kidney failure: no changes. IV. GF > 50: 200 mg/d; GF 10-50: 200 mg/d; GF <10: 200 mg/d. On HD: 200 mg/d; In CAPD: 200 mg/d; In CRRT: 200 mg/d. Liver failure: No dose adjustment is required in patients with mild or moderate liver failure (*Child-Pugh* A and B). There is no experience in severe liver failure (*Child-Pugh* C).
		Pregnancy	Teratogenic.
		Lactation	Contraindicated.
		Dosage for adults	IV and PO: 200 mg/8h, first 48 h (6 doses), then 200 mg/d, started 12-24h after loading dose.
		Dosage for children	No data available.

IA: invasive aspergillosis; A: Administration; D: Distribution; M: Metabolism; E: Excretion; D-AmB: Amphotericin B deoxycholate; L-AmB: Liposomal amphotericin B; LC-AmB: Amphotericin B lipid complex; GF: Glomerular filtration; IV: Intravenous route; PO: Oral route; d: Day/days; h: Hour/hours; g: Grams; mg: Milligrams; kg: Kilograms; HD: Hemodialysis; CAPD: Continuous Ambulatory Peritoneal Dialysis; CRRT: Continuous Renal Replacement Therapy; CGD: Chronic Granulomatous Disease; CNS: Central Nervous System.

Adapted from: Mensa-Pueyo J, et al.[159], Gilbert D, et al.[160], Jenks JD. et al.[161], Ghannoum MA, Perfect JR (eds).[162], Ruiz-Camps I et al.[163], Bellmann R et al.[164], Cuenca-Estrella M[165], Lewis RE[166], Nett JE et al. (167), Autmizguine J et al.[168].

49. *In an immunocompromised patient diagnosed with invasive* Aspergillus *spp. external otitis, the consensus recommends initiating targeted antifungal therapy, associated with complementary surgical management with surgical debridement, according to the clinical situation and the extent of the infection.* **(strong recommendation, low-quality evidence)** (Tables 4 and 5)[3,103–105].
50. *It is considered that in a patient diagnosed with invasive* Aspergillus *spp. external otitis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 6-8 weeks.* **(strong recommendation, moderate-quality evidence)**[3,21,76].

7. In an adult patient with skin involvement, how is the diagnostic approach for primary/secondary cutaneous aspergillosis performed?

Recommendation

51. *In a patient with skin involvement, the consensus recommends performing the diagnostic approach for a primary/secondary aspergillosis: (a) patient with proven/probable pulmonary and/or disseminated involvement and/or history of trauma, and (b) histopathology and/or culture positive for* Aspergillus *spp. from a skin and/or contiguous site specimen.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2)[45,49,66–68].

a. In an adult patient diagnosed with primary/secondary cutaneous aspergillosis, what is recommended in choosing the drug type, dosage, and duration of antifungal therapy?

Recommendation

52. *In a patient diagnosed with primary/secondary cutaneous aspergillosis, the consensus recommends evaluating a possible hematogenous source and/or dissemination from contiguous structures and/or the primary focus and/or association with trauma.* **(strong recommendation, moderate-quality evidence)**[3,86].
53. *In a patient diagnosed with primary/secondary cutaneous aspergillosis, the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[21,59,60,75,76].
54. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with primary/secondary cutaneous aspergillosis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,21,76–79].
55. *In a patient diagnosed with primary/secondary cutaneous aspergillosis, the consensus recommends initiating targeted antifungal therapy associated with adjunctive surgical management with surgical debridement (e.g., for burns and/or massive soft tissue wounds or lesions).* **(strong recommendation, high-quality evidence)** (Table 5)[3,76].
56. *It is considered that in a patient diagnosed with primary/secondary cutaneous aspergillosis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 6-8 weeks.* **(Strong recommendation, moderate-quality evidence)**[3,76].

8. In an adult patient with osteoarticular involvement, how is the diagnostic approach for osteomyelitis and/or *Aspergillus* spp. bone infection performed?

Recommendation

57. *In a patient with osteoarticular involvement, the consensus recommends a diagnostic approach for osteomyelitis and/or* Aspergillus *spp. bone infection by: (a) histopatho-*

logy and/or culture positive for Aspergillus *spp. from percutaneous biopsy of the affected bone and/or contiguous soft tissue structures.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2)[45,49,65–69,106,107].

a. In an adult patient diagnosed with osteomyelitis and/or *Aspergillus* spp. bone infection, what is recommended in choosing the type of drug, dosage and duration of antifungal treatment?

Recommendation

58. *In a patient diagnosed with osteomyelitis and/or* Aspergillus *spp. bone infection, the consensus recommends prolonged use of IV. (6 mg/kg/12h, day 1, then 4 mg/kg/12h), or PO. (200mg/12h) VCZ as a first choice of antifungal treatment. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,21,59,60,75,76,106].
59. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with osteomyelitis and/or* Aspergillus *spp. bone infection.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,21,76–79].
60. *An echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.), may be considered for salvage antifungal treatment in a patient diagnosed with osteomyelitis and/or* Aspergillus *spp. bone infection.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 4)[3,76,80–85,106].
61. *In a patient diagnosed with osteomyelitis and/or* Aspergillus *spp. bone infection, L-AmB (IV., 3-5 mg/kg/d) and VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) may be considered as an option for combination antifungal therapy.* **(strong recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [combined antifungal treatment according to the at-risk population]) (Annex 2)[3,21,76–78,87–89].
62. *In a patient with osteomyelitis and/or* Aspergillus *spp. bone infection, it is recommended to initiate primary targeted antifungal therapy associated with adjunctive surgical management with surgical debridement of devitalized bone.* **(strong recommendation, high-quality evidence)** (Table 5)[3,76,106].
63. *It is considered that in a patient diagnosed with osteomyelitis and/or* Aspergillus *spp. bone infection, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 90 days, with the possibility of long courses (> 6 months).* **(strong recommendation, moderate-quality evidence)**[3,21,76].

9. In an adult patient with peritoneal involvement, how is the diagnostic approach for *Aspergillus* spp. peritonitis performed?

Recommendation

64. *In a patient with peritoneal involvement, the consensus recommends making the diagnostic approach for* Aspergillus *spp. peritonitis by: (a) histopathology and/or culture positive for* Aspergillus *spp. from peritoneal fluid, (b) positive PCR test from peritoneal fluid, (c) positive AGA test from serum (x2) and/or peritoneal fluid (x1), and (d) positive (1,3)-β-D-glucan (BDG) test from serum.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,58,66–73,86,108–110].

Table 5. Adjuvant surgery for the management of an IA.

Involved organ	Recommended approach
Lesions close to great vessels and/or pericardium.	Resection of the lesion
Pericardial involvement	Pericardiectomy
Chest wall invasion due to pulmonary lesion	Resection of thoracic lung and wall lesion (possibility of subsequent reconstruction).
Empyema	Chest tube drainage, consider surgical drainage and thoracotomy (in case of fibrinopurulent or organized empyema).
Hemoptysis secondary to lung injury	Cavity resection or embolization
Skin and soft tissue involvement	Debridement and resection with wide margins
Infected vascular catheters and prostheses	Removal of devices
Endocarditis	Removal of the device, excision of the vegetation and resection of the infected valves.
Osteomyelitis	Debridement and cleaning of the affected tissue, if possible, with subsequent reconstruction (musculoskeletal grafts, bone grafts).
Sinusitis	Cleaning, curettage and resection of affected tissues
CNS involvement	Resection and removal of affected tissue and space-occupying lesions.
Endophthalmitis or panophthalmitis	Vitrectomy, evisceration or enucleation. Consider intravitreal administration of antifungal agents.
Extrahepatic or perihepatic bile duct obstruction	Resection, excision and clearance, or intraluminal drainage or stent placement

CNS: Central nervous system.

Adapted from: Fortún J et al.[20], García-Vidal C et al.[76], Walsh TJ et al.[169].

10. In the adult patient diagnosed with *Aspergillus* spp. peritonitis, what is recommended in choosing the type of drug, dosage, and duration of antifungal therapy?

Recommendation

65. *In a patient diagnosed with* Aspergillus *spp. peritonitis, the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,21,59,60,75,76].
66. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with* Aspergillus *spp. peritonitis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,21,76–79].
67. *In a patient diagnosed with* Aspergillus *spp. peritonitis, the consensus recommends initiating primary targeted antifungal therapy, associated with evaluating the removal of the peritoneal dialysis catheter.* **(weak recommendation, moderate-quality evidence)**[3,76].
68. *It is considered that in a patient diagnosed with* Aspergillus *spp. peritonitis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 2 weeks IV., followed by PO., until completing 12 weeks.* **(weak recommendation, moderate-quality evidence)**[3,76].

10. In an adult patient with gastrointestinal and/or hepatic involvement, how is the diagnostic approach for gastrointestinal and/or hepatic aspergillosis performed?

Recommendation

69. *In a patient with gastrointestinal and/or hepatic involvement, the consensus recommends making the diagnostic approach for gastrointestinal and/or hepatic aspergillosis by: (a) patient with proven/probable pulmonary and/or sinus involvement, (b) histopathology and/or culture positive for* Aspergillus *spp. from gastrointestinal and/or liver and/or contiguous site biopsy (b) positive PCR test from gastrointestinal and/or liver biopsy, and (c) positive AGA test from serum (x2).* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58,65–73,86,111].

a. In an adult patient diagnosed with gastrointestinal and/or hepatic aspergillosis, what is recommended in choosing the type of drug, dosage, and duration of antifungal therapy?

Recommendation

70. *In a patient diagnosed with gastrointestinal and/or hepatic aspergillosis, the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,21,59,60,74–76].
71. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then, 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with gastrointestinal and/or hepatic aspergillosis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,74,77–79].
72. *An echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.) may be considered for salvage antifungal therapy in a patient diagnosed with gastrointestinal and/or hepatic aspergillosis.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 4)[3,80–85].
73 *In a patient diagnosed with gastrointestinal and/or hepatic aspergillosis, multidisciplinary medical-surgical management and close consultation with surgery is recommended. In the clinical suspicion of an IFI/IA, antifungal treatment associated with early complementary surgical management is considered to prevent possible complications (perforation, hemorrhage, infarction or obstruction).* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,21,76].
74. *It is recommended that in a patient diagnosed with hepatic aspergillosis and extrahepatic or perihepatic biliary obstruction, and/or localized lesions refractory to antifungal therapy, adjunctive surgical management be considered.* **(weak recommendation, low-quality evidence)** (Table 5)[3,21,76].
75. *In a patient diagnosed with hepatic aspergillosis, an echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), and VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h), may be considered as an option for combination antifungal therapy.* **(strong recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [combined antifungal treatment according to the at-risk population]) (Annex 2)[3,21,76,81,85,87–89].
76. *It is considered that in a patient diagnosed with gastrointestinal and/or hepatic aspergillosis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 6-8 weeks.* **(strong recommendation, moderate-quality evidence)**[3,21].

11. In an adult patient with renal involvement, how is the diagnostic approach for renal aspergillosis performed?

Recommendation

77. *In a patient with renal involvement, the consensus recommends making the diagnostic approach for renal aspergillosis by: (a) histopathology and/or culture positive*

for Aspergillus spp. from renal biopsy and/or from parenchymal and/or contiguous site abscesses, (b) positive PCR test from renal biopsy, and (c) positive AGA test from serum (x2). **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease) (Table 2, Annex 1)[45,49,58,65–73,86,112].

a. In an adult patient diagnosed with renal aspergillosis, what is recommended in choosing the type of drug, dosage, and duration of antifungal therapy?

Recommendation

78. *In a patient diagnosed with renal aspergillosis, the consensus recommends VCZ (IV., 6 mg/kg/12h, day 1, then 4 mg/kg/12h) as the first antifungal treatment option. TDM is recommended to improve antifungal efficacy, evaluate therapeutic failure and reduce drug toxicity.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-Up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Tables 3 and 4)[3,59,60,75,112–115].
79. *L-AmB (IV., 3-5 mg/kg/d) or ISZ (IV., 200 mg/8h, day 1-2, then, 200 mg/d) are an alternative for antifungal treatment in a patient diagnosed with renal aspergillosis.* **(strong recommendation, moderate-quality evidence)** (Table 4)[3,77–79].
80. *In a patient diagnosed with renal aspergillosis, an echinocandin (IV., CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), LC-AmB (IV., 5 mg/kg/d), PCZ (IV., 300 mg/12h, day 1, then 300 mg/d), or ITZ (IV., 200 mg/12h, day 1-2, then 200 mg/d.) may be considered for salvage antifungal therapy.* **(strong recommendation, moderate-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 4)[3,80–85].
81. *The use of local D-AmB through nephrostomy irrigation is an alternative antifungal treatment in a patient diagnosed with renal aspergillosis.* **(strong recommendation, moderate-quality evidence)** (Tables 3 and 4)[3,115].
82. *In a patient diagnosed with renal aspergillosis, multidisciplinary medical-surgical therapeutic management and close consultation with urology is recommended. Upon clinical suspicion of IFI/IA, initiation of antifungal therapy associated with early adjunctive surgical management is considered.* **(strong recommendation, moderate-quality evidence)** (Table 5)[3,21,76].
83. *It is considered that in a patient diagnosed with renal aspergillosis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 12 weeks, and will depend on the clinical evolution of the patient.* **(weak recommendation, low-quality evidence)**[3,76,114,115].

Ethical disclosures

Financial support. Support for this guideline was provided by Pfizer Colombia, Merck Colombia, Stendhal Colombia, Biotoscana Colombia.

Confidentiality of data. In this consensus there are not data from patients.

Right to privacy and informed consent. No data from patients is published.

Conflict of interest and Funding. The authors have presented a list of potential conflicts of interest in one dedicated section to this topic. The funders do not intervened in the manuscript writing or approval.

Protection of human and animal subjects. There are not experimental data from humans and animals in this work.

Supplementary material online

The tables that are described as annex on the text, are available at the link for supplementary material online, of this manuscript, at the website of journal.

References

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi. 2017;3(4).
2. Global Action Fund for Fungal Infections (GAFFI). Priority Fungal Infections. 2017.
3. Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;63(4):e1–60.
4. Latgé JP, Chamilos G. *Aspergillus fumigatus* and aspergillosis in 2019. Clin Microbiol Rev. 2020;33(1):e00140-18.
5. Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect. 2012;65(5):453–64.
6. Kontoyiannis DP., Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: Overview of the transplant-associated infection surveillance network (TRANSNET) database. Clin Infect Dis. 2010;50(8):1091–100.
7. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (Transnet). Clin Infect Dis. 2010;50(8):1101–11.
8. Husain S, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):1–24.
9. Wilopo BAP, Richardson MD, Denning DW. Diagnostic Aspects of Chronic Pulmonary Aspergillosis: Present and New Directions. Curr Fungal Infect Rep. 2019;13(4):292–300.
10. Alvarez-Moreno CA, Cortes JA, Denning DW. Burden of fungal infections in Colombia. J Fungi. 2018;4(2):1–13.
11. Gregg KS, Kauffman CA. Invasive Aspergillosis: Epidemiology, Clinical Aspects, and Treatment. Semin Respir Crit Care Med. 2015;36(5):662-72.
12. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation - Determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726–35.
13. Alonso-Coello P, Rigau D, Sanabria AJ, Plaza V, Miravitlles M,

Martinez L. Calidad y fuerza: el sistema GRADE para la formulación de recomendaciones en las guías de práctica clínica. Arch Bronconeumol. 2013;49(6):261–7.
14. Chamilos G, Luna M, Lewis RE, Bodey GP, Chemaly R, Tarrand JJ, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). Haematologica. 2006;91(7):986–9.
15. Antinori S, Nebuloni M, Magni C, Fasan M, Adorni F, Viola A, et al. Trends in the postmortem diagnosis of opportunistic invasive fungal infections in patients with AIDS: A retrospective study of 1,630 autopsies performed between 1984 and 2002. Am J Clin Pathol. 2009;132(2):221–7.
16. Cornillet A, Camus C, Nimubona S, Gandemer V, Tattevin P, Belleguic C, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: A 6-year survey. Clin Infect Dis. 2006;43(5):577–84.
17. Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of Direct Healthcare Costs of Fungal Diseases in the United States. Clin Infect Dis. 2019;68(11):1791–7.
18. Houšť J, Spížek J, Havlíček V. Antifungal Drugs. Metabolites. 2020;10(3):106.
19. Pemán J, Salavert M. Epidemiología y prevención de las infecciones nosocomiales causadas por especies de hongos filamentosos y levaduras. Enferm Infecc Microbiol Clin. 2013;31(5):328–41.
20. Fortún J, Meije Y, Fresco G, Moreno S. Aspergilosis. Formas clínicas y tratamiento. Enferm Infecc Microbiol Clin. 2012;30(4):201–8.
21. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24:e1–38.
22. Aguilar CA, Hamandi B, Fegbeutel C, Silveira FP, Verschuuren EA, Ussetti P, et al. Clinical risk factors for invasive aspergillosis in lung transplant recipients: Results of an international cohort study. J Hear Lung Transplant. 2018;37(10):1226–34.
23. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics. 2006;117(4).
24. Singh N, Paterson DL. *Aspergillus* Infections in Transplant Recipients. Clin Microbiol Rev. 2005;18(1):44–69.
25. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. Vol. 78, Medicine. 1999. p. 123–38.
26. Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, et al. Epidemiological trends in invasive aspergillosis in France: The SAIF network (2005-2007). Clin Microbiol Infect. 2011;17(12):1882–9.
27. Husain S, Silveira FP, Azie N, Franks B, Horn D. Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance® registry analysis. Med Mycol. 2017;55(3):269–77.
28. Neofytos D, Chatzis O, Nasioudis D, Boely Janke E, Doco Lecompte T, Garzoni C, et al. Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study. Transpl Infect Dis. 2018;20(4):0–1.
29. Muñoz P, Cerón I, Valerio M, Palomo J, Villa A, Eworo A, et al. Invasive aspergillosis among heart transplant recipients: A 24-year perspective. J Hear Lung Transplant. 2014;33(3):278–88.
30. Fortún J, Carratalá J, Gavaldá J, Lizasoain M, Salavert M, De La Cámara R, et al. Guidelines for the treatment of invasive fungal disease by *Aspergillus* spp. and other fungi issued by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2011 Update. Enferm Infecc Microbiol Clin. 2011;29(6):435–54.
31. Vandewoude K, Blot S, Benoit D, Depuydt P, Vogelaers D, Colardyn F. Invasive aspergillosis in critically ill patients: Analysis of risk factors for acquisition and mortality. Acta Clin Belg. 2004;59(5):251–7.
32. Herbrecht R, Bories P, Moulin JC, Ledoux MP, Letscher-Bru V. Risk stratification for invasive aspergillosis in immunocompromised patients. Ann N Y Acad Sci. 2012;1272(1):23–30.
33. Pemán J, Quindós G. Aspectos actuales de las enfermedades invasivas por hongos filamentosos. Rev Iberoam Micol. 2014;31(4):213–8.
34. Gavalda J, Len O, San Juan R, Aguado JM, Fortun J, Lumbreras C, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: A case-control study. Clin Infect Dis. 2005;41(1):52–9.
35. Saliba F, Delvart V, Ichaï P, Kassis N, Botterel F, Mihaila L, et al. Fungal infections after liver transplantation: Outcomes and risk factors revisited in the MELD era. Clin Transplant. 2013;27(4):454–61.
36. Fortún J, Martín-Dávila P, Moreno S, De Vicente E, Nuño J, Candelas A, et al. Risk factors for invasive aspergillosis in liver transplant recipients. Liver Transpl. 2002;8(11):1065–70.
37. Osawa M, Ito Y, Hirai T, Isozumi R, Takakura S, Fujimoto Y, et al. Risk Factors for Invasive Aspergillosis in Living Donor Liver Transplant Recipients. Liver Transpl. 2007;13(4):566–70.
38. Cook JC, Cook A, Tran RH, Chang PP, Rodgers JE. A case-control study of the risk factors for developing aspergillosis following cardiac transplant. Clin Transplant. 2018;32(9):0–1.
39. Altiparmak MR, Apaydin S, Trablus S, Serdengecti K, Ataman R, Ozturk R, et al. Systemic fungal infections after renal transplantation. Scand J Infect Dis. 2002;34(4):284–8.
40. Dimopoulos G, Frantzeskaki F, Poulakou G, Armaganidis A. Invasive aspergillosis in the intensive care unit. Ann N Y Acad Sci. 2012;1272(1):31–9.
41. Groll AH, Schrey D, Tragiannidis A, Bochennek K, Lehrnbecher T. Invasive Aspergillosis in Children and Adolescents. Curr Pharm Des. 2013;19(20):3545–68.
42. Tragiannidis A, Roilides E, Walsh TJ, Groll AH. Invasive aspergillosis in children with acquired immunodeficiencies. Clin Infect Dis. 2012;54(2):258–67.
43. Samson RA, Visagie CM, Houbraken J, Hong SB, Hubka V, Klaassen CHW, et al. Phylogeny, identification and nomenclature of the genus *Aspergillus*. Stud Mycol. 2014;78(1):141–73.
44. Balajee SA, Marr KA. Phenotypic and genotypic identification of human pathogenic aspergilli. Future Microbiol. 2006;1:435–45.
45. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17(12):e383–92.
46. Schwartz IS, Patterson TF. The Emerging Threat of Antifungal Resistance in Transplant Infectious Diseases. Curr Infect Dis Rep. 2018;20(3).
47. Gautier M, Normand AC, Ranque S. Previously unknown species of *Aspergillus*. Clin Microbiol Infect. 2016;22(8):662–9.
48. van der Linden JWM, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, et al. Prospective multicenter international surveillance of azole resistance in *Aspergillus fumigatus*. Emerg Infect Dis. 2015;21(6):1041–4.
49. Hope WW, Walsh TJ, Denning DW. The invasive and saprophytic syndromes due to *Aspergillus* spp. Med Mycol. 2005;43(SUPPL.1).
50. Martínez-Sahuquillo Amuedo M, Echevarría Ruiz De Vargas M. Métodos de consenso. Uso adecuado de la evidencia en la toma de decisiones. «Método RAND/UCLA». Rehabilitación. 2001;35(6):388–92.
51. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. Br Med J. 2008;336(7654):1170.
52. Cluzeau F, Burgers J, Brouwers M, Grol R, Mäkelä M, Littlejohns P, et al. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: The AGREE project. Qual Saf Heal Care. 2003;12(1):18–23.
53. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: Performance, usefulness and areas for improvement. Cmaj. 2010;182(10):1045–52.
54. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: Assessment of validity of items and tools to support application. Cmaj. 2010;182(10).
55. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol. 2010;63(12):1308–11.
56. Flórez Gómez ID, Montoya DC. Las guías de práctica clínica y el instrumento AGREE II. Rev Colomb Psiquiatr. 2011;563–76.
57. Varela-Ruiz M, Díaz-Bravo L, García-Durán R. Descripción y usos del método Delphi en investigaciones del área de la salud. Investig en Educ Médica. 2012;1(2):90–5.
58. Amsden JR. Fungal biomarkers, antifungal susceptibility testing, and therapeutic drug monitoring-practical applications for the clinician in a tertiary care center. Curr Fungal Infect Rep. 2015;9(2):111–21.
59. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: Guidelines from the british society for medical mycology. J Antimicrob Chemother. 2014;69(5):1162–76.
60. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: A randomized controlled trial. Clin Infect Dis. 2012;55(8):1080–7.
61. Fadda GL, Succo G, Moretto P, Veltri A, Castelnuovo P, Bignami M, et al. Endoscopic endonasal surgery for sinus fungus balls: Clinical, radiological, histopathological, and microbiological analysis of 40 cases and review of the literature. Iran J Otorhinolaryngol. 2019;31(1):35–44.
62. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. BMC Infect Dis. 2011;11(1):250.

63. Chang YS, Chen PL, Hung JH, Chen HY, Lai CC, Ou CY, et al. Orbital complications of paranasal sinusitis in Taiwan, 1988 through 2015: Acute ophthalmological manifestations, diagnosis, and management. PLoS One. 2017;12(10):1–14.
64. Humphrey JM, Walsh TJ, Gulick RM. Invasive *Aspergillus* sinusitis in human immunodeficiency virus infection: Case report and review of the literature. Open Forum Infect Dis. 2016;3(3).
65. Donnelly PJ, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–76.
66. Borman AM, Johnson EM. Interpretation of Fungal Culture Results. Curr Fungal Infect Rep. 2014;8(4):312–21.
67. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev. 2011;24(2):247–80.
68. Alastruey-Izquierdo A, Alcazar-Fuoli L, Cuenca-Estrella M. Antifungal susceptibility profile of cryptic species of *Aspergillus*. Mycopathologia. 2014;178(5–6):427–33.
69. Orlowski HLP, McWilliams S, Mellnick VM, Bhalla S, Lubner MG, Pickhardt PJ, et al. Imaging spectrum of invasive fungal and fungal-like infections. Radiographics. 2017;37(4):1119–34.
70. Maertens JA, Blennow O, Duarte RF, Muñoz P. The current management landscape: Aspergillosis. J Antimicrob Chemother. 2016;71(v):ii23–9.
71. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother. 2017;72:i19–28.
72. Patterson TF, Donnelly JP. New concepts in diagnostics for invasive mycoses: Non-culture-based methodologies. J Fungi. 2019;5(1):1–9.
73. Cruciani M, Mengoli C, Barnes R, Peter Donnelly J, Loeffler J, Jones BL, et al. Polymerase chain reaction blood tests for the diagnosis of invasive aspergillosis in immunocompromised people. Cochrane Database Syst Rev. 2019;2019(9).
74. Anselmo-Lima WT, Lopes RP, Valera FCP, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. Rhinology. 2004;42(3):141–4.
75. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann J-W, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408–15.
76. Garcia-Vidal C, Alastruey-Izquierdo A, Aguilar-Guisado M, Carratalà J, Castro C, Fernández-Ruiz M, et al. Executive summary of clinical practice guideline for the management of invasive diseases caused by *Aspergillus*: 2018 Update by the GEMICOMED-SEIMC/REIPI. Enferm Infecc Microbiol Clin. 2019;37(8):535–41.
77. Cordonnier C, Bresnik M, Ebrahimi R. Liposomal amphotericin B (AmBisome®) efficacy in confirmed invasive aspergillosis and other filamentous fungal infections in immunocompromised hosts: A pooled analysis. Mycoses. 2007;50(3):205–9.
78. Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad Trial). Clin Infect Dis. 2007;44(10):1289–97.
79. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760–9.
80. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: An externally controlled trial. Clin Infect Dis. 2007;44(1):2–12.
81. Candoni A, Mestroni R, Damiani D, Tiribelli M, Michelutti A, Silvestri F, et al. Caspofungin as first line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. Eur J Haematol. 2005;75(3):227–33.
82. Caillot D. Intravenous itraconazole followed by oral itraconazole for the treatment of amphotericin-B-refractory invasive pulmonary aspergillosis. Acta Haematol. 2003;109(3):111–8.
83. Dockrell DH. Salvage therapy for invasive aspergillosis. J Antimicrob Chemother. 2008;61(SUPPL. 1):41–4.
84. Panackal AA, Parisini E, Proschan M. Salvage combination antifungal therapy for acute invasive aspergillosis may improve outcomes: a systematic review and meta-analysis. Int J Infect Dis. 2014;28:80–94.
85. Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: An European Organisation for Research and Treatment of Cancer study. Bone Marrow Transplant. 2010;45(7):1227–33.
86. Powers-Fletcher M, Hanson KE. Nonculture Diagnostics in Fungal Disease. Infect Dis Clin North Am. 2016;30(1):37–49.
87. Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. Ann Intern Med. 2015;162(2):81–9.
88. Martín-Peña A, Aguilar-Guisado M, Espigado I, Cisneros JM. Antifungal combination therapy for invasive aspergillosis. Clin Infect Dis. 2014;59(10):1437–45.
89. Garbati MA, Alasmari FA, Al-Tannir MA, Tleyjeh IM. The role of combination antifungal therapy in the treatment of invasive aspergillosis: A systematic review. Int J Infect Dis. 2012;16(2):e76–81.
90. Murthy JMK, Sundaram C. Fungal infections of the central nervous system. 1st ed. Vol. 121, Handbook of Clinical Neurology. Elsevier B.V.; 2014. 1383–1401 p.
91. Spadea L, Giannico MI. Diagnostic and management strategies of *Aspergillus* endophthalmitis: Current insights. Clin Ophthalmol. 2019;13:2573–82.
92. Hoenigl M, Krause R. Antifungal Therapy of Aspergillosis of the Central Nervous System and *Aspergillus* Endophthalmitis. Curr Pharm Des. 2013;19(20):3648–68.
93. Shen YC, Wang CY, Tsai HY, Lee HN. Intracameral Voriconazole Injection in the Treatment of Fungal Endophthalmitis Resulting From Keratitis. Am J Ophthalmol. 2010;149(6):916–21.
94. Fuentes-Irigoyen R, De Rosales Cabrera AMM, Riestra AC, Vila MN, Dávila-Pousa C, Alonso Herreros JM, et al. Consensus SEO-SEFH of recommendations for use and compounding of ophthalmic preparations. Farm Hosp. 2018;42(2):82–8.
95. Payne JF, Keenum DG, Sternberg PJ, Thliveris A, Kala A, Olsen TW. Concentrated intravitreal amphotericin B in fungal endophthalmitis. Arch Ophthalmol. 2010;128(12):1546–50.
96. Behera UC, Budhwani M, Das T, Basu S, Padhi TR, Barik MR, et al. Role of early vitrectomy in the treatment of fungal endophthalmitis. Retina. 2018;38(7):1385–92.
97. Thomas PA, Kaliamurthy J. Mycotic keratitis: Epidemiology, diagnosis and management. Clin Microbiol Infect. 2013;19(3):210–20.
98. Prajna VN, Lalitha PS, Mascarenhas J, Krishnan T, Srinivasan M, Vaitilingam CM, et al. Natamycin and voriconazole in *Fusarium* and *Aspergillus* keratitis: Subgroup analysis of a randomised controlled trial. Br J Ophthalmol. 2012;96(11):1440–1.
99. Kaushik S, Ram J, Brar GS, Jain AK, Chakraborti A, Gupta A. Intracameral amphotericin B: Initial experience in severe keratomycosis. Cornea. 2001;20(7):715–9.
100. O' Day DM, Head SW, Robinson RD, Clanton JA. Corneal penetration of topical amphotericin B and natamycin. Curr Eye Res. 1986;5(11):877–82.
101. Jurkunas U V, Langston DP, Colby K. Use of Voriconazole in the Treatment of Fungal Keratitis. Int Ophthalmol Clin. 2007;47(2):47–59.
102. Parchand S, Gupta A, Ram J, Gupta N, Chakrabarty A. Voriconazole for fungal corneal ulcers. Ophthalmology. 2012;119(5).
103. Ho T, Vrabec JT, Yoo D, Coker NJ. Otomycosis: Clinical features and treatment implications. Otolaryngol - Head Neck Surg. 2006;135(5):787–91.
104. Anwar K, Gohar MS. Otomycosis; Clinical features, predisposing factors and treatment implications. Pakistan J Med Sci. 2014;30(3):2–5.
105. Gordon G, Giddings NA. Invasive otitis externa due to *Aspergillus* species: Case report and review. Clin Infect Dis. 1994;19(5):866–70.
106. Bariteau JT, Waryasz GR, McDonnell M, Fischer SA, Hayda RA, Born CT. Fungal osteomyelitis and septic arthritis. J Am Acad Orthop Surg. 2014;22(6):390–401.
107. Kohli R, Hadley S. Fungal arthritis and osteomyelitis. Infect Dis Clin North Am. 2005;19(4):831–51.
108. Manzano-Gayosso P, Hernández-Hernández F, Méndez-Tovar LJ, González-Monroy J, López-Martínez R. Fungal peritonitis in 15 patients on continuous ambulatory peritoneal dialysis (CAPD). Mycoses. 2003;46(9–10):425–9.
109. Nannini EC, Paphitou NI, Ostrosky-Zeichner L. Peritonitis due to *Aspergillus* and zygomycetes in patients undergoing peritoneal dialysis: Report of 2 cases and review of the literature. Diagn Microbiol Infect Dis. 2003;46(1):49–54.
110. García-Agudo R, García-Martos P. Aspectos clínicos y microbiológicos de la peritonitis fúngica en diálisis peritoneal. Nefrologia. 2009;29(6):506–17.
111. Yeom SK, Kim HJ, Byun JH, Kim AY, Lee MG, Ha HK. Abdominal aspergillosis: CT findings. Eur J Radiol. 2011;77(3):478–82.
112. Flechner SM, McAninch JW. Aspergillosis of the urinary tract: Ascending route of infection and evolving patterns of disease. J Urol. 1981;125(4):598–601.

113. Waller S, Raglow Z, Lemons S, Johnson P, Eid A, Schmitt T, et al. Microwave ablation of a large renal aspergilloma. Transpl Infect Dis. 2014;16(3):496–500.
114. Lisson SW, Hellinger WC, Parra RO. Primary bilateral parenchymal renal *Aspergillus* infection. Urology. 2002;60(2):345.
115. Kauffman CA. Diagnosis and management of fungal urinary tract infection. Infect Dis Clin North Am. 2014;28(1):61–74.
116. Grosjean P, Weber R. Fungus balls of the paranasal sinuses: A review. Eur Arch Oto-Rhino-Laryngology. 2007;264(5):461–70.
117. Karkas A, Rtail R, Reyt E, Timi N, Righini CA. Sphenoid sinus fungus ball. Eur Arch Oto-Rhino-Laryngology. 2013;270(3):893–8.
118. Turner JH, Soudry E, Nayak J V., Hwang PH. Survival outcomes in acute invasive fungal sinusitis: A systematic review and quantitative synthesis of published evidence. Laryngoscope. 2013;123(5):1112–8.
119. Ammannaya GKK, Sripad N. Fungal endocarditis: What do we know in 2019? Kardiol Pol. 2019;77(7–8):670–3.
120. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. Linee guida ESC 2015 per il trattamento dell'endocardite infettiva: Task Force per il Trattamento dell'Endocardite Infettiva della Società Europea di Cardiologia (ESC): Con il patrocinio dell'Associazione Europea di Chirurgia Cardiotoracica (EACTS) e dell. G Ital Cardiol. 2016;17(4):277–319.
121. Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis. 2002;35(4):359–66.
122. Kalokhe AS, Rouphael N, El Chami MF, Workowski KA, Ganesh G, Jacob JT. *Aspergillus* endocarditis: A review of the literature. Int J Infect Dis. 2010;14(12):21036091.
123. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev Infect Dis. 1990;12(6):1147–201.
124. Gumbo T, Taege AJ, Mawhorter S, McHenry MC, Lytle BH, Cosgrove DM, et al. *Aspergillus* valve endocarditis in patients without prior cardiac surgery. Medicine (Baltimore). 2000;79(4):261–8.
125. McCormack J, Pollard J. *Aspergillus* endocarditis 2003-2009. Med Mycol. 2011;49(SUPPL. 1):30–4.
126. Le Moing V, Lortholary O, Timsit JF, Couvelard A, Bouges-Michel C, Wolff M, et al. *Aspergillus* pericarditis with tamponade: report of a successfully treated case and review. Clin Infect Dis. 1998;26(2):451–60.
127. Sundaram C, Umabala P, Laxmi V, Purohit AK, Prasad VSSV, Panigrahi M, et al. Pathology of fungal infections of the central nervous system: 17 Years' experience from Southern India. Histopathology. 2006;49(4):396–405.
128. Murthy JMK. Fungal infections of the central nervous system: The clinical syndromes. Neurol India. 2007;55(3):221–5.
129. Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. Ther Adv Infect Dis. 2013;1(3):85–105.
130. Sahin SZ, Akalin H, Ersoy A, Yildiz A, Ocakoglu G, Cetinoglu ED, et al. Invasive Fungal Infections in Renal Transplant Recipients: Epidemiology and Risk Factors. Mycopathologia. 2015;180(1–2):43–50.
131. Schwartz S, Thiel E. Cerebral aspergillosis: Tissue penetration is the key. Med Mycol. 2009;47(SUPPL. 1):387–93.
132. Rivas González AM, Cardona Castro NM. Antimicóticos de uso sistémico: ¿Con qué opciones terapéuticas contamos? Rev CES Med. 2009;23(1):61–76.
133. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: A retrospective analysis. Infection. 2011;39(3):201–10.
134. Schwartz S, Cornely OA, Hamed K, Marty FM, Maertens J, Rahav G, et al. Isavuconazole for the treatment of patients with invasive fungal diseases involving the central nervous system. Med Mycol. 2020;58(4):417–24.
135. Rouzaud C, Jullien V, Herbrecht A, Palmier B, Lapusan S, Morgand M, et al. Isavuconazole diffusion in infected human brain. Antimicrob Agents Chemother. 2019;63(10):2018–20.
136. Kovanda LL, Giamberardino C, McEntee L, Toffaletti DL, Franke KS, Bartuska A, et al. Pharmacodynamics of isavuconazole in a rabbit model of cryptococcal meningoencephalitis. Antimicrob Agents Chemother. 2019;63(9):1–10.
137. Lee A, Prideaux B, Lee MH, Zimmerman M, Dolgov E, Perlin DS, et al. Tissue distribution and penetration of isavuconazole at the site of infection in experimental invasive aspergillosis in mice with underlying chronic granulomatous disease. Antimicrob Agents Chemother. 2019;63(6).
138. Schwartz S, Ruhnke M, Ribaud P, Corey L, Driscoll T, Cornely OA, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood. 2005;106(8):2641–5.
139. Gao H, Pennesi ME, Shah K, Qiao X, Hariprasad SM, Mieler WF, et al. Intravitreal voriconazole: An electroretinographic and histopathologic study. Arch Ophthalmol. 2004;122(11):1687–92.
140. Riddell Iv J, McNeil SA, Johnson TM, Bradley SF, Kazanjian PH, Kauffman CA. Endogenous *Aspergillus* endophthalmitis: report of 3 cases and review of the literature. Med. 2002;81(4):311–20.
141. Parize P, Chandesris MO, Lanternier F, Poirée S, Viard JP, Bienvenu B, et al. Antifungal therapy of *Aspergillus* invasive otitis externa: Efficacy of voriconazole and review. Antimicrob Agents Chemother. 2009;53(3):1048–53.
142. Vennewald I, Klemm, E. Otomycosis: Diagnosis and treatment. Clin Dermatol. 2010;28(2):202–11.
143. Liu X, Yang J, Ma W. Primary cutaneous aspergillosis caused by *Aspergillus fumigatus* in an immunocompetent patient. Med. 2017;96(48):e8916.
144. Tatara AM, Mikos AG, Kontoyiannis DP. Factors affecting patient outcome in primary cutaneous aspergillosis. Med. 2016;95(26):e3747.
145. Gamaletsou MN, Rammaert B, Bueno MA, Moriyama B, Sipsas N V., Kontoyiannis DP, et al. *Aspergillus* osteomyelitis: Epidemiology, clinical manifestations, management, and outcome. J Infect. 2014;68(5):478–93.
146. Gabrielli E, Fothergill AW, Brescini L, Sutton DA, Marchionni E, Orsetti E, et al. Osteomyelitis caused by *Aspergillus* species: A review of 310 reported cases. Clin Microbiol Infect. 2014;20(6):559–65.
147. Gamaletsou MN, Rammaert B, Bueno MA, Sipsas N V., Moriyama B, Kontoyiannis DP, et al. *Aspergillus* arthritis: analysis of clinical manifestations, diagnosis, and treatment of 31 reported cases. Med Mycol. 2017;55(3):246–54.
148. Stratov I, Korman TM, Johnson PDR. Management of *Aspergillus* osteomyelitis: Report of failure of liposomal amphotericin B and response to voriconazole in an immunocompetent host and literature review. Eur J Clin Microbiol Infect Dis. 2003;22(5):277–83.
149. Yilmaz F, Uslu HB, Bora F, Suleymanlar G, Sanli T, Ersoy F. *Aspergillus* peritonitis in chronic peritoneal dialysis patients: Review of the literature and report of two cases. BANTAO J. 2014;12(1):52–5.
150. Tanis BC, Verburgh CA, Van der Pijl JW, Van't Wout JW. *Aspergillus* peritonitis in peritoneal dialysis. Nephrol Dial Transplant. 1995;10(7):1240–3.
151. Wang AYM, Yu AWY, Li PKT, Lam PKW, Leung CB, Lai KN, et al. Factors predicting outcome of fungal peritonitis in peritoneal dialysis: Analysis of a 9-year experience of fungal peritonitis in a single center. Am J Kidney Dis. 2000;36(6):1183–92.
152. Kazan E, Maertens J, Herbrecht R, Weisser M, Gachot B, Vekhoff A, et al. A retrospective series of gut aspergillosis in haematology patients. Clin Microbiol Infect. 2011;17(4):588–94.
153. Eggimann P, Chevrolet JC, Starobinski M, Majno P, Totsch M, Chapuis B, et al. Primary invasive aspergillosis of the digestive tract: Report of two cases and review of the literature. Infection. 2006;34(6):333–8.
154. Aribandi M, McCoy VA, Bazan C. Imaging features of invasive and noninvasive fungal sinusitis: A review. Radiographics. 2007;27(5):1283–96.
155. Chong S, Lee KS, Yi CA, Chung MJ, Kim TS, Han J. Pulmonary fungal infection: Imaging findings in immunocompetent and immunocompromised patients. Eur J Radiol. 2006;59(3):371–83.
156. Hage CA, Carmona EM, Epelbaum O, Evans SE, Gabe LM, Haydour Q, et al. Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice: An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2019;200(5):535–50.
157. Payne SJ, Mitzner R, Kunchala S, Roland L, McGinn JD. Acute Invasive Fungal Rhinosinusitis: A15-Year Experience with 41 Patients. Otolaryngol - Head Neck Surg (United States). 2016;154(4):759–64.
158. Cendejas-Bueno E, Cuenca-Estrella M, Gómez-López A. Indicaciones clínicas de la monitorización de azoles de uso sistémico. Hacia la optimización del tratamiento de la infección fúngica. Rev Esp Quimioter. 2014;27(1):1–16.
159. Mensa-Pueyo J, Gatell-Artigas J, Garcìa-Sànchez JE. Guía De Terapéutica Antimicrobiana. Barcelona, España: Antares; 2016.
160. Gilbert D, Chambers H, Eliopoulos G, Chambers H, Saag M, Pavia A. The Sanford Guide. To Antimicrobial Therapy 2017. 47th Editi. USA: Antimicrobial Therapy, INC; 2017.
161. Jenks JD, Salzer HJF, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: Design, development, and place in therapy. Drug Des Devel Ther. 2018;12:1033–44.
162. Ghannoum M, Perfect J. Antifungal Therapy, 2nd Edition. New York. CRC Press. 2019. 2nd ed. Ghannoum M, Perfect J, editors. New York: CRC Press; 2019.
163. Ruiz-Camps I, Cuenca-Estrella M. Antifungals for systemic use. Enferm Infecc Microbiol Clin. 2009;27(6):353–62.

164. Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. Infection. 2017;45(6):737–79.
165. Cuenca-Estrella M. Antifúngicos en el tratamiento de las infecciones sistémicas: importancia del mecanismo de acción, espectro de actividad y resistencias. Rev Esp Quim. 2010;23(4):169–76.
166. Lewis RE. Current concepts in antifungal pharmacology. Mayo Clin Proc. 2011;86(8):805–17.
167. Nett JE, Andes DR. Antifungal Agents: Spectrum of Activity, Pharmacology, and Clinical Indications. Infect Dis Clin North Am. 2016;30(1):51–83.
168. Autmizguine J, Guptill JT, Cohen-Wolkowiez M, Benjamin DK, Capparelli E V. Pharmacokinetics and pharmacodynamics of antifungals in children: Clinical implications. Drugs. 2014;74(8):891–909.
169. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: Clinical practice guidelines of the infectious diseases society of America. Clin Infect Dis. 2008;46(3):327–60.
170. Blyth CC, Gilroy NM, Guy SD, Chambers ST, Cheong EY, Gottlieb T, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J. 2014;44(12):1333–49.
171. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. Eur Respir J. 2016;47(1):45–68.
172. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433–44.
173. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20(S3):5–26.
174. Warris A, Lehrnbecher T, Roilides E, Castagnola E, Brüggemann RJM, Groll AH. ESCMID-ECMM guideline: diagnosis and management of invasive aspergillosis in neonates and children. Clin Microbiol Infect. 2019;25(9):1096–113.
175. Ruhnke M, Behre G, Buchheidt D, Christopeit M, Hamprecht A, Heinz W, et al. Diagnosis of invasive fungal diseases in haematology and oncology: 2018 update of the recommendations of the infectious diseases working party of the German society for hematology and medical oncology (AGIHO). Mycoses. 2018;61(11):796–813.
176. Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. Clin Microbiol Infect. 2014;20(S3):27–46.
177. Klein CN, Pfeiffer CD. Diagnosis of Invasive Aspergillosis: Use of the Galactomannan Assay. Curr Treat Options Infect Dis. 2015;7(3):163–75.
178. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev. 2014;27(3):490–526.
179. Ruiz-Camps I, Jarque I. Enfermedad fúngica invasora por hongos filamentosos en pacientes hematológicos. Rev Iberoam Micol. 2014;31(4):249–54.