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Section 4. Colombian consensus on the diagnosis and treatment of chronic, saprophytic and/or allergic syndromes associated with *Aspergillus* spp. in adult and pediatric patients*

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

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Abstract

Despite the ubiquity of *Aspergillus* species, and the fact that a person may inhale hundreds of conidia daily, only a small proportion of patients develop an infectious disease. *Aspergillus* spp. can cause a wide spectrum of diseases, depending on the patient's underlying immune function; these range from an allergic syndrome, (which does not represent a true infection), a hypersensitivity reaction (ABPA), a chronic process (CPA) or invasive aspergillosis (IA). All diseases associated with *Aspergillus* spp. have the potential to be misdiagnosed because symptoms and/or clinical findings overlap with each other, or with other non-fungal conditions. Greater clinical recognition of the different pulmonary syndromes is needed to identify those patients who could benefit from an appropriate therapeutic approach. Multidisciplinary management is required, where the role of antifungal therapy is only established for symptomatic and/or progressive disease management, taking into account the potential for azole resistance, which adds to the complexity of treatment and, in some cases, limits therapeutic options.

Keywords: aspergillosis; *Aspergillus;* guidelines; chronic pulmonary aspergillosis; non-invasive aspergillosis; aspergilloma; fungal ball; surgery; diagnosis; drug therapy; voriconazole; posaconazole; isavuconazole; caspofungin; micafungin; anidulafungin; amphotericin B.

Sección 4. Consenso colombiano para el diagnóstico y tratamiento de los síndromes crónicos, saprofíticos y/o alérgicos asociados a *Aspergillus* spp., en pacientes adultos y pediátricos*

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

Resumen

A pesar de la ubicuidad de las especies de *Aspergillus,* y el hecho que una persona pueda inhalar diariamente cientos de conidios, solo una pequeña proporción de pacientes desarrollan una enfermedad infecciosa. *Aspergillus* spp. puede causar un amplio espectro de enfermedades, que dependen de la función inmune subyacente del paciente, que incluyen desde un síndrome alérgico, (que no representa una verdadera infección), una reacción de hipersensibilidad (ABPA), un proceso crónico (APC) o una aspergilosis invasora (AI). Todas las enfermedades asociadas con *Aspergillus* spp., comparten el potencial de ser diagnosticadas erróneamente debido a que los síntomas y/o los hallazgos clínicos se superponen entre sí, o con otras afecciones no fúngicas. Es necesario un mayor reconocimiento clínico de los diferentes síndromes pulmonares, para lograr identificar aquellos pacientes que podrían beneficiarse de un enfoque terapéutico apropiado, lo que requiere de un manejo multidisciplinario, donde el papel del tratamiento antifúngico solo se encuentra establecido para el manejo sintomático y/o progresivo de una enfermedad, teniendo en cuenta el potencial de resistencia a los azoles, que se suma a la complejidad del tratamiento y que en algunos casos, limita las opciones terapéuticas.

Palabras claves: aspergilosis; *Aspergillus;* guias de práctica clínica; aspergilosis pulmonar crónica; aspergillosis no-invasiva; aspergiloma; bola fungica; cirugía; diagnostico; terapia medicamentosa; voriconazol; posaconazol; isavuconazol; caspofungina; micafungina; anidulafungina; anfotericina B.

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Introduction

Despite the ubiquity of *Aspergillus* species, and the fact that a person may inhale hundreds of conidia daily, only a small proportion of patients develop an infectious disease[1–11,14–27,36–89]. *Aspergillus* spp. can cause a wide spectrum of diseases, depending on the patient's underlying immune function; these range from an allergic syndrome, (which does not represent a true infection), a hypersensitivity reaction (ABPA), a chronic process (CPA) or invasive aspergillosis (IA)[4,9,49–51,54–56,16,18,19,42–45,48]. All diseases associated with *Aspergillus* spp. have the potential to be misdiagnosed because symptoms and/or clinical findings overlap with each other, or with other non-fungal conditions[4,9,60–63,14,16,49,52,53,57–59]. Greater clinical recognition of the different pulmonary syndromes is needed to identify those patients who could benefit from an appropriate therapeutic approach. Multidisciplinary management is required, where the role of antifungal therapy is only established for symptomatic and/or progressive disease management, taking into account the potential for azole resistance, which adds to the complexity of treatment and, in some cases, limits therapeutic options[4,16,66,42–47,64,65,81–89].

When a clinical syndrome associated with *Aspergillus* is not considered, this delay in diagnosis can lead to permanent lung damage[4,9,14,16,49]. Unlike allergic syndromes, a CPA, which often mimics other pulmonary diagnoses, is considered a progressive infection of the lung, comprising a broad clinical spectrum ranging from solid nodules, (which may mimic lung cancer), a single aspergilloma (usually occurring in a pre-existing cavity, classically considered a saprophytic infection), a CCPA (i.e., multiple cavities with or without aspergillomas), and a CFPA[9,16,18,19,51]. The diagnosis of *Aspergillus*-associated bronchitis is often delayed because the clinical presentation is similar to that of non-fungal bronchitis, where persistence of symptoms (> 1 month), lack of improvement with antibiotic treatment and persistent positive cultures strongly suggest its diagnosis[9,14,36,45]. The management of a patient with CPA remains a challenge, as it requires the prolonged use of systemic antifungal agents, whose assessment of response to treatment is complicated, and is generally based on the use of quality of life scoring systems, which evaluate weight gain and improvement in the patient's activity levels[3,19,51].

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]

The most severe form of aspergillosis among atopic patients is ABPA, which develops following sensitization to allergens, (especially *A. fumigatus*) in the airways, in a unique subset of individuals (CF patients or patients with corticosteroid-dependent asthma), which can be easily overlooked, at least initially, as persistent asthma and progressive pulmonary decline in the CF patient may be mistakenly attributed to other underlying diseases[3,51,57]. Early diagnosis, through specific clinical, radiographic and laboratory evaluations, is essential to prevent disease progression[51,57].

A detailed description of the background, methods and potential conflicts of interest can be found in the Section 1 of the guideline "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 chronic, saprophytic and/or allergic syndromes associated with *Aspergillus* spp. 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)[28–35].

SUB SECTION I. DIAGNOSIS AND THERAPEUTIC MANAGEMENT OF CHRONIC AND/OR SAPROPHYTIC SYNDROMS

QUESTIONS:

1. **In an adult patient with pulmonary involvement, how is the diagnostic approach for a non-invasive syndrome associated with *Aspergillus* spp. performed?**

Recommendation

1. *In an adult patient with pulmonary involvement, the consensus recommends performing the diagnostic approach of a non-invasive syndrome associated with* Aspergillus *spp. by: (a) patient without/mild immunocompromise, (b) positive cultures for* Aspergillus *spp. from sputum and/or bronchoalveolar lavage (BAL), on a recurrent basis, (c) persistently positive PCR test from sputum and/or BAL, and (d) detection of elevated* Aspergillus*-specific IgG Abs from serum.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Tables 2-4, Annex 1)[3,4,42,14,16,36–41].

a. **What is recommended in an adult patient diagnosed with a non-invasive syndrome associated with *Aspergillus* spp, in order to choose the type of drug, the dosage and the duration of antifungal treatment?**

Recommendation

2. *In a patient diagnosed with a non-invasive* Aspergillus *spp-associated syndrome associated with cough and recurrent pulmonary infections, the consensus recommends initiating antifungal treatment with ITZ (VO, 800 mg/8 h, day 1-2, then 200 mg/12 h), or with VCZ (PO, 6 mg/kg/12h, day 1, then 4 mg/kg/12h).* **(strong recommendation, low-quality evidence).** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [approach to the management of refractory or progressive aspergillosis]) (Table 5)[3,43–50].
3. *It is considered that in a patient diagnosed with a non-invasive syndrome associated with* Aspergillus *spp. the duration of antifungal treatment should be established on an individual basis, and will depend on the resolution of the lesions and the disappearance of pulmonary symptoms.* **(strong recommendation, low-quality evidence)**[3,39,43–45,48–50].

a. **In an adult patient diagnosed with a non-invasive syndrome associated with *Aspergillus* spp., what is recommended to choose the complementary measures to the antifungal treatment of the disease?**

Recommendation

4. *In a patient diagnosed with a non-invasive syndrome associated with* Aspergillus *spp. the consensus recommends reducing the fungal burden and associated inflammatory response.* **(strong recommendation, low-quality evidence)**[4,43].

2. **In a non-transplanted adult patient with pulmonary involvement, how is the diagnostic approach for *Aspergillus* spp. bronchitis performed?**

Recommendation

5. *In a non-transplanted adult patient with pulmonary involvement, the consensus recommends a diagnostic approach of* Aspergillus *spp. bronchitis by: (a) patient without/mild immunocompromise, (b) histopathology and/or culture positive for* Aspergillus *spp. from a respiratory tract specimen (induced sputum, tracheal aspirates, BAL, etc.), in a persistent manner, (c) positive PCR test from a respiratory tract specimen (induced sputum, tracheal aspirates, BAL, etc.), recurrently, and (d) detection of elevated* Aspergillus*-specific IgG Abs.* **(strong recommendation, high-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Tables 2-4, Annex 1)[4,14,53,36–41,51,52].

Table 2. *Aspergillus* species and antifungal susceptibility.

Species	AmB	VCZ	PCZ	ITZ	CAS
Fumigati					
A. lentulus	**R**	**R**	V	**R**	S/V
A. viridinutans	**R**	**R**	S	**R**	S
A. felis	S	V	V	V	S
A. pseudofischeri	S	**R**	S	**R**	S
A. fumigatiaffinis	**R**	**R**	S	**R**	S
A. udagawae	V	V	S	S	S
A. fumisynnematus	S	S	S	S	S
A. hiratsukae	S	S	S	S	S
A. fischerianus	ND	ND	ND	ND	ND
A. novofumigatus	S	**R**	**R**	**R**	S
Flavi					
A. flavus	**R**	S	S	S	V
A. alliaceus	**R**	S	S	S	V
A. tamarii	V	S	S	S	S
A. nomius	**R**	S	S	S	S
Terrei					
A. terreus	**R**	S	S	S	V
A. alabamensis	**R**	S	S	S	ND
A. hortai	**R**	S	S	S	S
Nigri					
A. niger	S	S	S	V	S
A. tubingensis	S	S	S	V	S
A. awamori	S	ND	S	ND	ND
A. brasiliensis	S	S	S	**R**	ND
Nidulantes					
A. tetrazonus	S	S	S	S	**R**
A. nidulans	V	S	S	S	V
Versicolores					
A. versicolor	**R**	S	S	V	S
A. sydowii	**R**	S	S	V	S
Usti					
A. ustus	V	V	**R**	**R**	**R**
A. calidoustus	V	**R**	**R**	**R**	V
A. insuetus	**R**	**R**	**R**	**R**	ND
A. pseudodeflectus	V	**R**	**R**	**R**	V
A. keveii	**R**	**R**	**R**	**R**	ND
Circumdati					
A. persii	**R**	S	S	S	ND
A. ochraceus	**R**	S	S	S	S
A. westerdijkiae	**R**	S	S	S	S

⁺*For practical reasons, for PCZ, MIC: ≥0.25 mg/L is considered resistant; for AmB, ITZ and VCZ, MIC ≥ 2 mg/L is considered resistant.*

AmB: Amphotericin B; VCZ: Voriconazole; PCZ: Posaconazole; ITZ: Itraconazole; CAS: Caspofungin; S: Susceptible; R: Resistant; V: Variable; ND: No data.

Adapted from: Samson RA y col. (20), Gautier M y col.[26]

a. In a non-transplant patient diagnosed with *Aspergillus* spp. bronchitis, what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

6. *In a non-transplant patient diagnosed with* Aspergillus *spp. bronchitis due to possible fungal colonization of persistent and localized cavities, the consensus does not recommend initiating targeted antifungal therapy routinely.* **(strong recommendation, moderate-quality evidence)**[9,18,48,50,51,54–57].
7. *In a non-transplant patient diagnosed with* Aspergillus *spp. bronchitis requiring initiation of targeted antifungal therapy, the consensus recommends the use of VCZ (IV, 6 mg/kg/12h, day 1, then 4 mg/kg/12h), ITZ (IV, 200 mg/12h, day 2-3, then 200 mg/d), or PCZ (IV, 300 mg/12h, day 1, then 300 mg/d).* **(strong recommendation, high-quality evidence)** (Table 5)[4,9,18,50,55–58].
8. *It is considered that in a non-transplant patient diagnosed with* Aspergillus *spp. bronchitis, the duration of antifungal treatment should be established on an individual basis, and should last a minimum of 4-6 months.* **(weak recommendation, low-quality evidence)**[4,48,50].

b. In a non-transplant patient diagnosed with bronchitis due to *Aspergillus* spp, what is recommended to choose the complementary measures to the antifungal treatment of the disease?

Recommendation

9. *In a non-transplant patient diagnosed with* Aspergillus *spp. bronchitis, the consensus recommends performing a CBF with BAL sampling and removal of the mucoid impaction.* **(weak recommendation, moderate-quality evidence)**[4,49,52,53].
10. *In a non-transplant patient diagnosed with* Aspergillus *spp. bronchitis, pulmonary function and bronchoscopic evaluation is recommended. In the presence of mucoid impaction and/or a drop in lung function parameters (such as FEV1), consideration should be given to initiating targeted antifungal therapy.* **(weak recommendation, moderate-quality evidence)**[4,45,48,49].

3. In an adult patient with pulmonary involvement, how is the diagnostic approach for chronic pulmonary aspergillosis (CPA) performed?

Recommendation

11. *In an adult patient with pulmonary involvement, the consensus recommends making the diagnostic approach of a CPA (includes: chronic necrotizing pulmonary aspergillosis [CNPA], chronic cavitary pulmonary aspergillosis [CCPA], chronic fibrotic pulmonary aspergillosis [CFPA]), by: (a) patient with mild immunocompromise and/or very debilitated, (b) histological evidence of hyphal elements within the cavity, but without invasion of the pulmonary parenchyma, (c) positive cytology and/or culture for* Aspergillus *spp. from a respiratory tract specimen (induced sputum, tracheal aspirates, BAL, etc.) and/or pleural space, (d) positive PCR test from a respiratory tract specimen (induced sputum, tracheal aspirates, BAL, etc.) and/or pleural space, (e) detection of elevated* Aspergillus*-specific IgG Abs and/or positive serum* Aspergillus *precipitins, (f) abnormal findings on chest CT (e.g., ≥ 1 cavitated lesion, peri-cavitary opacities, progressive enlargement of new cavities, pleural thickening, and/or fibrosis [in CFPA]), and (g) symptoms and/or imaging findings for more than 3 months, and exclusion of other possible pathologies (including infectious diseases with similar behavior).* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Tables 2-4, Annex 1)[3,4,41–44,51,56,57,59–61,14,62,16,18,36–40].

a. In a patient diagnosed with CPA, what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

12. *In a patient diagnosed with CPA, the consensus recommends initiating long-term, targeted oral antifungal therapy to: (a) decrease clinical symptoms, (b) prevent progression to pulmonary destruction and/or fibrosis, and (c) lessen the magnitude and episodes of hemoptysis.* **(strong recommendation, moderate-quality evidence)**[3,4,16,42–45,51].
13. *In a patient diagnosed with CPA, the consensus recommends ITZ as a first choice of antifungal treatment (PO, 800 mg/8h, day 1-2, then 200 mg/12 h), or VCZ (PO, 6 mg/kg/12h, day 1, then 4 mg/kg/12h). 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 5 and 7)[3,4,63,16,42–47,50].
14. *PCZ (tablets [300 mg/12h, day 1, then 300 mg/d], or suspension [400 mg/12h]) is an alternative for antifungal treatment in a patient diagnosed with CPA when there is a risk of: (a) drug interactions and/or adverse effects, and (b) cases refractory to initial treatment and/or possible therapeutic failure.* **(weak recommendation, moderate-quality evidence)** (Table 5, Annexes 2 and 3)[3,4,16,42–45,58,64].
15. *An echinocandin (IV, CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), or AmB (AmB-D [0.7-1 mg/kg/d], L-AmB [3-5 mg/kg/d]), may be considered as salvage antifungal therapy in a patient diagnosed with CPA with suspected antifungal treatment failure associated with the development of azole resistance and/or adverse drug effect.* **(weak recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [therapeutic management approach to a refractory/progressive aspergillosis]) (Table 5) (Tabla 5)[3,4,16,42–45,65].

Table 3. Diseases caused by *Aspergillus* spp.

Chronic and/or saprophytic forms associated to *Aspergillus*	
CNPA (or SAIA)	It occurs in mildly immunocompromised or very weakened patients, with a duration of symptoms of about 1 to 3 months, and clinical and radiological features similar to CCPA, although it usually has no complications, can produce pneumothorax, aspergillomas or even an IPA. Its time course differs from IA, in which the rate of progression depends on the degree of immunosuppression. It occurs in the context of patients with: (a) advanced age with previous pulmonary disease, (b) COPD, (c) diabetes mellitus, (d) malnutrition, (e) alcoholism, (f) prolonged administration of corticosteroids or other immunosuppressive drugs, (g) connective tissue disorders, (h) radiation therapy, (i) NTMB, or (j) HIV.
CCPA	It occurs in subtly immunocompromised patients; symptoms last at least 3 months, in which fungal eradication is poor. It is characterized by the presence of multiple lung cavities, usually in the upper lobes, possibly containing one or more aspergillomas or irregular intraluminal material, which, if they progress, lead to CFPA. They occur in the setting of patients with: (a) TB, (b) ABPA, (c) resolved lung cancer, (d) pneumothorax with bullae formation, (e) COPD, and (f) fibrocavitary sarcoidosis.
CFPA	It is a complication of untreated CCPA, whose main characteristic is a significant loss of lung function due to severe fibrotic destruction.
Simple aspergilloma	Simple aspergilloma is a single immunologically protected fungus ball within a lung cavity; such a cavity may be pre-existing (from TB, sarcoidosis, histoplasmosis or bronchiectasis) or created by *Aspergillus* colonization; it may also involve the paranasal sinuses (in older persons with some pre-existing sinus abnormality, resulting in headache, rhinorrhea and post-nasal discharge). It is usually asymptomatic or presents mild symptoms that progress slowly for more than 3 months, and without radiological progression during the months of observation. Some may present with hemoptysis, bacterial superinfection or tissue invasion.
Aspergillus bronchitis	It is a rare disease characterized by the persistence of bronchitis symptoms for at least one month, with positive fungal cultures for *Aspergillus* spp. Respiratory symptoms include dyspnea, cough and expectoration, which may be copious. Although it can occur in immunocompetent patients, it is often associated with underlying pulmonary comorbidity or weakly attenuated immune states.
***Aspergillus*-associated allergic forms**	
ABPA	ABPA is caused by an exaggerated hypersensitivity reaction to antigens produced by *Aspergillus* species, most commonly *A. fumigatus*. The pathogenesis of the disease is complex, where several immunological and genetic factors are involved that predispose to the disease. It presents in the context of: (a) immunocompetent patients with healthy lungs, (b) adult patients with underlying steroid-dependent asthma, and (c) patients with CF. The clinical symptoms lead to recurrent episodes of bronchial obstruction in asthmatic patients, with fever, malaise, expectoration of dark mucous plugs, eosinophilia, and occasionally hemoptysis. In chronic cases, pulmonary fibrosis may develop, with gradual loss of lung function.
AFRS	AFRS is not considered a true fungal infection, but rather the result of an inflammatory reaction due to the fungal presence in the sinonasal tract. Fungi colonize the sinonasal tract during the first months of life; however, only a few immunocompetent asthmatic patients develop the disease, with sensitization to *Aspergillus* or other fungal allergens, in the absence of clinical and radiographic evidence of ABPA. The pathogenesis of the disease is not fully understood.

IA: invasive aspergillosis; IPA: Invasive pulmonary aspergillosis; IBA: Invasive bronchial aspergillosis; HSCT: Hematopoietic stem-cell transplantation; SOTR: Solid organ transplant recipient; HIV: Human Immunodeficiency Virus; COPD: Chronic obstructive pulmonary disease.; ICU: Intensive Care Unit; CNPA: Chronic necrotizing pulmonary aspergillosis; SAIA: subacute invasive/chronic necrotizing/semi-invasive aspergillosis; CCPA: Chronic cavitary pulmonary aspergillosis; CFPA: Chronic fibrosing pulmonary aspergillosis; TB: Pulmonary tuberculosis; NTMB: Non-tuberculous mycobacteria infection; CF: Cystic Fibrosis; ABPA: Allergic bronchopulmonary aspergillosis; AFRS: Allergic fungal rhinosinusitis.
Adapted from: Wilopo BAP y col.[9], Hope WW y col.[14], Denning DW y col.[16], Page ID y col.[39], Muldoon EG y col.[51], García-Vidal C y col.[58]

16. *It is considered that in a patient diagnosed with CPA, the antifungal treatment should last a minimum of 6 months, and will depend on the resolution of the lesions and/or the decrease in the patient's clinical symptoms.* **(strong recommendation, moderate-quality evidence)**[3,4,16,42–45,58].
17. *The consensus considers that in order to efficiently control the disease in a symptomatic patient diagnosed with CPA and progressive lung disease and/or immunosuppression, long-term antifungal treatment, even lifelong suppressive treatment, may be necessary. Continuous monitoring is recommended to assess for potential drug toxicity and/or the development of antifungal resistance.* **(strong recommendation, low-quality evidence)**[3,4,16,42–45,58].
18. *In a patient diagnosed with CPA, the consensus recommends performing a non-contrast multi-slice CT scan of the chest (low dose), every 3-6 months from the initiation of antifungal drug, to evaluate the response to treatment. Consideration is given to evaluating: (a) therapeutic failure, (b) azole intolerance, (c) drug toxicity and/or, (d) drug interactions.* **(strong recommendation, moderate-quality evidence)**[4,16,51,59–62].

a. In a patient diagnosed with CPA, what is recommended to choose the complementary measures to the antifungal treatment of the disease?

Recommendation

19. *The consensus considers that in a patient diagnosed with CPA, complementary surgical management with surgical debridement is an option to targeted antifungal therapy in a patient with: (a) localized disease, (b) intractable hemoptysis, (c) pulmonary destruction, and/or (d) unresponsive to antifungal therapy, including the patient with a clinically relevant isolate of azole-resistant* Aspergillus fumigatus *complex/section. The consensus also recommends careful evaluation of: (a) the patient's immune*

status, (b) the presence of comorbidities, (c) the confirmation of a single focus, and (d) the risks associated with the surgical intervention. **strong recommendation, moderate-quality evidence)** (Tables 2 and 6)[4,16,58].

4. How is the diagnostic approach for chronic cavitary pulmonary aspergillosis (CCPA) in an adult patient with pulmonary involvement performed?

Recommendation

20. *In an adult patient with pulmonary involvement, the consensus recommends making the diagnostic approach of a CCPA by: (a) patient without/minimal immunocompromise, (b) histological evidence of hyphal elements within the cavity, without evidence of tissue invasion, although frequently evidence of necrosis, (c) positive cytology and/or culture for* Aspergillus *spp. from sputum and/or BAL, (d) positive PCR test from sputum and/or BAL, (e) detection of elevated* Aspergillus*-specific IgG Abs and/or positive* Aspergillus *precipitins from serum, (f) findings of overt progressive disease on chest CT (e.g., new cavities, increased peri-cavitary infiltrates or increased fibrosis), and (g) chronic disease and/or chronic pulmonary symptoms and/or imaging findings of progressive disease for more than 3 months.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Tables 2-4, Annex 1)[3,4,40–45,51–53,56,9,57,59–61,14,16,18,36–39].

a. In a patient diagnosed with CCPA, ¿what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

21. *As an antifungal treatment option in a patient diagnosed with CCPA, the consensus recommends using ITZ (PO, 800 mg/8h, day 1-2, then 200 mg/12 h), or VCZ (PO, 6 mg/kg/12h, day 1, then 4 mg/kg/12h). 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 5 and 7)[3,4,63,16,42–47,55].
22. *PCZ (tablets [300 mg/12h, day 1, then 300 mg/d], or suspension [400 mg/12h]), is an alternative for antifungal treatment in a patient diagnosed with CCPA, when there is a risk of: (a) drug interactions and/or adverse effects, and (b) cases refractory to initial treatment and/or possible therapeutic failure.* **(weak recommendation, moderate-quality evidence)** (Table 5, Annexes 2 and 3)[3,4,16,42–45,58,64].
23. *An echinocandin (IV, CAS [70 mg, day 1, then 50 mg/d], MCF [100 mg/d]), or AmB (AmB-D [0.7-1 mg/kg/d], L-AmB [3-5 mg/kg/d]), may be considered as salvage antifungal treatment in a patient diagnosed with CCPA, with suspected antifungal treatment failure associated with the development of azole resistance and/or adverse drug effect.* **(weak recommendation, low-quality evidence)** (II Prophylaxis, Treatment and Prevention of IA in Adult and Pediatric Patients [therapeutic management approach to a refractory/progressive aspergillosis]) (Table 5)[3,4,16,42–45,58,65].
24. *It is considered that in a patient diagnosed with CCPA, the antifungal treatment should last a minimum of 6-12 months, and will depend on the resolution of the lesions and/or the decrease in the patient's clinical symptoms.* **(strong recommendation, moderate-quality evidence)**[3,4,16,42–45,58].
25. *The consensus considers that in order to efficiently control the disease in a symptomatic patient diagnosed with CCPA and progressive lung disease and/or immunosuppression, long-term antifungal treatment, including lifelong suppressive treatment, may be necessary. Continuous monitoring is recommended to assess for potential drug toxicity and/or the development of antifungal resistance.* **(strong recommendation, low-quality evidence)**[3,4,9,16,42–45,58].
26. *In a patient diagnosed with CCPA, the consensus recommends performing a non-contrast multi-slice chest CT (low dose) every 3-12 months from the initiation of the antifungal agent, to evaluate the response to treatment. Consideration is given to evaluating: (a) therapeutic failure, (b) azole intolerance, (c) drug toxicity, and/or (d) drug interactions.* **(strong recommendation, moderate-quality evidence)**[4,16,51,59–62].

b. In a patient diagnosed with CCPA, what is recommended to choose the complementary measures to the antifungal treatment of the disease?

Recommendation

27. *In a patient diagnosed with CCPA, the consensus does not recommend initiating targeted antifungal treatment without the presence of: (a) pulmonary symptoms, (b) weight loss, (c) fatigue, and (d) further deterioration and/or loss of lung function. Clinical and imaging follow-up is recommended every 3-6 months.* **(strong recommendation, moderate-quality evidence)**[4,51].
28. *In a patient diagnosed with CCPA, the consensus recommends initiating targeted antifungal treatment with the presence of: (a) pulmonary or general symptoms, (b) progressive loss of lung function, and (c) evidence of progressive disease on imaging.* **(strong recommendation, moderate-quality evidence)**[3,4,16,42–45,58,66].
29. *It is considered that in a patient diagnosed with CCPA, initiating antifungal treatment associated with bronchial artery embolization and/or oral treatment with tranexamic acid allows managing the manifestation of hemoptysis and preventing its recurrence.* **(strong recommendation, moderate-quality evidence)** (Table 6)[4,16,58,67].
30. *The consensus considers that in a patient diagnosed with CCPA, complementary surgical management with surgical debridement is an option to targeted antifungal therapy in a patient with: (a) localized disease, (b) persistent hemoptysis despite bronchial artery embolization, (c) pulmonary destruction, and/or (d) unresponsive*

Table 4. 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.
Chronic forms of pulmonary aspergillosis (CNPA, CCPA, CFPA)	Presence of hyphal elements within a cavity, without evidence of parenchymal invasion (occasionally, direct hyphal invasion of the tissue is observed, which defines a non-angioinvasive IPA). In *CNPA* there is colonization of pre-existing spaces by hyphal elements, often with dilated airways, mucosal invasion and necrotizing granulomatous inflammatory reaction. The airway lumen often has a mixture of hyphal elements and necrotic debris. In *CCPA*, a discrete mass is present, with the presence of intertwined hyphal elements, mucus, fibrin and cellular debris that colonize a cavity. There is no evidence of tissue invasion, although necrosis is common, and multiple cavities form and expand over time.	The most suggestive features of CPA are the presence of a cavitated lesion, with nodular opacities in the upper lobe, progressive enlargement of new cavities and/or adjacent pleural thickening. Associated involvement of bronchial or non-bronchial systemic arteries and, less frequently, the formation of pseudoaneurysms, can lead to hemoptysis, sometimes fatal. In a *CNPA* there may not be a previous cavitated lesion. Generally, an area of consolidation is found in an upper lobe, progressing over days or weeks. The predominant characteristic is the presence of a thin-walled cavity, which expands during 1-3 months. It may present pleural thickening, presence of aspergillomas, pneumothorax and pleural effusion. The presence of the "air-crescent sign" is a sign of necrosis, indicative of worsening disease. In *CCPA*, unilateral or bilateral areas of consolidation are typically seen, associated with multiple thick-walled, usually expandable cavities, which may contain one or more aspergillomas, with variable pleural thickening. Thickened pleura is often associated with more evident extrapleural fat than normal, indicating chronicity. These findings are frequently asymmetric and predominantly located in areas with pre-existing abnormalities due to underlying lung disease. Radiologic evolution is usually slower and may take years. *CFPA* is the terminal fibrosing evolution of *CCPA*, and occurs when it remains untreated, resulting in extensive pulmonary fibrosis. Fibrosis may be limited to one or both upper lobes, but may also affect the entire hemithorax. There is no distinguishing feature of a *CPA*-related fibrosis other than the presence of cavitation and aspergillomas. Progression over time may provide a clue to the etiology of the fibrosis.
Aspergilloma	A conglomerate of intertwined hyphal elements is observed, mixed with fibrin, mucus, cellular debris and other blood products. There is no evidence of parenchymal invasion by hyphal elements.	An aspergilloma usually presents as a solid, round or oval upper lobe intracavitary mass, partially surrounded by a crescent of air, the mobile "air-crescent" sign. This finding can be demonstrated by acquiring the images in the supine and prone position (the aspergilloma often moves within the cavity). Calcification can be seen in the aspergilloma either extensively or as dense nodules. Adjacent pleural thickening is often seen, which may be the first radiographic sign, before visible mass-forming changes within a cavity.

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.
***Aspergillus*-associated allergic forms**		
	Pathological findings	**Imaging findings**
ABPA	Macroscopically, lung specimens usually show airways filled with thick, tough sputum, with fibrous material consisting of scattered, typically fragmented, hyphal elements. *Charcot-Leyden* crystals (a by-product of eosinophil breakdown), Curschmann spirals (desquamated epithelium associated with eosinophilic infiltration) and inflammatory cells (macrophages, eosinophils and lymphocytes) are often seen.	Imaging findings consist of recurrent pneumonic consolidation (80%), mucoid airway impaction (30%), and atelectasis (20%). Chronic (permanent) findings consist of increased lung volume, tubular or annular shadows and lobar contraction. Multislice CT findings include bronchiectasis (cylindrical or cystic), mucus plugging, atelectasis, peripheral consolidation or ground-glass opacity, mosaic attenuation due to air trapping evident on the expiration sequence.
RAF	This entity occurs in patients with a history of chronic allergic rhinitis, often with hyperplastic nasal mucosa, which forms nasal polyps. Sinus contents evidence a thick, clayey, green, brown or grayish mucus. Microscopically there is evidence of eosinophilic ("allergic") mucin, containing mucin mixed with sloughed epithelial cells, eosinophils, *Charcot-Leyden* crystals, eosinophilic debris and other inflammatory cells arranged in a lamellar pattern, and associated with sparse and scattered hyphal elements.	In contrast to ABPA, there are no radiographic criteria or characteristic findings in an AFRS. On the CT scan, almost complete opacification of some cavities can be seen, with heterogeneous density resembling soft tissues within the affected sinus, and thinning of the bony walls of the affected sinus.

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; CPA: Chronic pulmonary aspergillosis; CNPA: Chronic necrotizing pulmonary aspergillosis; CFPA: Chronic fibrosing pulmonary aspergillosis; CCPA: Chronic cavitary pulmonary aspergillosis; CNS: Central nervous system; CSF: Cerebrospinal fluid; ABPA: Allergic bronchopulmonary aspergillosis; AFRS: Allergic fungal rhinosinusitis.

Adapted from: Hope WW y col.[14], Muldoon EG y col.[51], Riscili BP y col.[57], Orlowski HLP y col.[59], Chong S y col.[68], Aribandi M y col.[120], Hage CA y col.[121].

to antifungal therapy, including patients with a clinically relevant isolate of azole-resistant A. fumigatus *complex/section. It is recommended to carefully evaluate: (a) the patient's immunological status, (b) the presence of co-morbidities, (c) confirmation of a single focus, and (d) the risks associated with the surgical intervention.* **(strong recommendation, moderate-quality evidence)** (Tables 2 and 6)[4,16,58].

31. *In a patient diagnosed with CCPA refractory to antifungal therapy (including manifestation of multi-azole resistance) and/or with life-threatening hemoptysis, the consensus recommends careful evaluation of the patient's clinical context, followed by lobectomy or pneumonectomy.* **(strong recommendation, moderate-quality evidence)** (Tables 2 and 6)[4,16,58].

5. In an adult patient with pulmonary/sinus involvement, how is the diagnostic approach of a fungus ball (aspergilloma) performed?

Recommendation

32. *In an adult patient with pulmonary involvement, the consensus recommends making the diagnostic approach of a pulmonary fungus ball (aspergilloma) by: (a) patient without/mild immunocompromise, (b) histological evidence of hyphal elements within the cavity, but without invasion of the pulmonary parenchyma, (c) positive culture for* Aspergillus *spp. from respiratory tract specimen (induced sputum, tracheal aspirates, BAL, etc.), occasionally, (d) detection of elevated* Aspergillus*-specific IgG Abs and/or positive* Aspergillus *precipitins from serum,*

Table 5. 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.
	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.

AZOLES	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.
	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 y col.[122], Gilbert D y col.[123], Jenks JD y col.[124], Ghannoum M y Perfect J (eds).[125], Ruiz-Camps I y col.[126], Bellmann R y col.[127], Cuenca-Estrella M[128], Lewis RE[129], Nett JE y col.[130], Autmizguine J y col.[131].

(e) chest CT findings of a single cavity with an imaging stable (or slowly progressive) fungus ball (aspergilloma) and pleural thickening, and (f) imaging findings for more than 3 months. **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/ *Aspergillus* Disease) (Tables 2-4, Annex 1)[3,14,68,36,39–41,59–62].

33. *In an adult patient with sinus involvement, the consensus recommends making the diagnostic approach of a sinus fungus ball (aspergilloma) by: (a) patient with pre-existing sinus abnormality, (b) histopathology and/or culture positive for* Aspergillus *spp. from sinus aspirate and/or surgically removed material, (c) positive PCR test from sinus aspirate and/or surgically removed material, (d) detection of positive* Aspergillus *precipitins from serum, and (e) findings of maxillary sinus opacification with soft tissue density and punctate calcifications or anthroliths on non-contrast CT scan.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease) (Tables 2-4, Annex 1)[4,14,62,36–39,42,59–61].

a. In a patient diagnosed with a pulmonary/sinus fungal ball (aspergilloma), what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

34. *In an asymptomatic patient diagnosed with a single, stable pulmonary/sinus fungus ball (aspergilloma) without progression of cavity size (for at least 6-24 months), the consensus does not recommend initiating targeted antifungal therapy.* **(strong recommendation, moderate-quality evidence)**[3,4,9,16,42–45,58].
35. *In a symptomatic patient diagnosed with a pulmonary/ sinus fungus ball (aspergilloma), according to the clinical context of the patient, and in whom complementary surgical management with surgical debridement is contraindicated, the consensus recommends initiating long-term antifungal treatment with: (a) ITZ (PO, 800 mg/8h, day 1-2, then 200 mg/12h), (b) VCZ (PO, 6 mg/kg/12h, day 1, then 4 mg/kg/12h), or (c) PCZ (tablets [400 mg/12h], or suspension [400mg/12h]).* **(strong recommendation, low-quality evidence)**[3,4,64,16,42–47,58].
36. *In a symptomatic patient diagnosed with a pulmonary fungus ball (aspergilloma) and recurrent hemoptysis, according to the clinical context of the patient, it is recommended to instill the antifungal drug in the cavity with a fungus ball (aspergilloma).* **(strong recommendation, moderate-quality evidence)**[3,4,64,16,42–47,58].
37. *In a patient diagnosed with a pulmonary fungus ball (aspergilloma) in the context of a CCPA, it is recommended to initiate a long-term antifungal treatment with: (a) ITZ (PO, 800 mg/8h, day 1-2, then 200 mg/12 h), (b) VCZ (PO, 6 mg/kg/12h, day 1, then 4 mg/kg/12h), or (c) PCZ (tablets [400 mg/12h], or suspension [400mg/12h]).* **(strong recommendation, low-quality evidence)**[3,4,64,16,42–47,58].

b. In a patient diagnosed with a pulmonary/sinus fungus ball (aspergilloma), what is recommended to choose the complementary measures to the antifungal treatment of the disease?

Recommendation

38. *Surgical management by video-assisted thoracoscopy with surgical debridement is recommended in a symptomatic patient diagnosed with a pulmonary/simple sinus/ single fungus ball (aspergilloma), if not contraindicated. It is recommended to carefully evaluate: (a) the patient's immunological status, (b) the presence of comorbidities, (c) confirmation of a single focus, and (d) the risks associated with surgical intervention.* **(strong recommendation, moderate-quality evidence)**[3,4,16,42–45,58].
39. *To prevent and/or cure life-threatening hemoptysis in a patient diagnosed with a simple/single pulmonary fungus ball (aspergilloma), the consensus recommends careful evaluation of the patient's clinical context, followed by lobectomy or pneumonectomy.* **(strong recommendation, moderate-quality evidence)** (Table 6)[3,4,9,16,42–45,58].
40. *In a patient diagnosed with a pulmonary/simple sinus/ single fungus ball (aspergilloma) and surgical effusion of aspergilloma with moderate risk (related to the location and morphology of the cavity), it is recommended to initiate peri/post-operative antifungal treatment with an azole or an echinocandin (at standard doses).* **(strong recommendation, low-quality evidence)** *In a patient diagnosed with a pulmonary/simple sinus/single fungus ball (aspergilloma) and surgical effusion of aspergilloma with moderate risk (related to the location and morphology of the cavity), it is recommended to initiate peri/ post-operative antifungal treatment with an azole or an echinocandin (at standard doses).* **(strong recommendation, low-quality evidence)**[3,4,16,42–46,58,65].

SUB SECTION II: DIAGNOSIS AND THERAPEUTIC MANAGEMENT OF ALLERGIC SYNDROMES ASSOCIATED WITH *Aspergillus* spp.

QUESTIONS:

1. In an adult patient with pulmonary involvement, how is the diagnostic approach for allergic bronchopulmonary aspergillosis (ABPA)?

Recommendation

41. *In a patient with pulmonary involvement, the consensus recommends making the diagnostic approach of ABPA by: (a) patient with an underlying predisposing condition of asthma or cystic fibrosis (CF), (b) clinical and/or pulmonary function deterioration from baseline, (c) detection of elevated total IgE Abs (> 1000 IU/mL) and/or elevated serum* Aspergillus*-specific IgE Abs (and/or positive skin test for* Aspergillus *Ags), and (d) at least 2 of the following*

Table 6. 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 y col.[56], García-Vidal C y col.[58], Walsh TJ y col.[97].

Table 7. 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: Ullmann AJ y col.[42], Fortún J y col.[56], Ashbee HR y col.[63], Cendejas-Bueno E y col.[132].

criteria: (i) detection of elevated Aspergillus*-specific IgG Abs and/or positive* A. fumigatus *precipitins from serum, (ii) elevated total eosinophil count (>500 cells/mm^3) and, (iii) abnormal chest imaging findings and/or a change in baseline abnormalities.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease [value of Abs detection in IA/*Aspergillus* disease]) (Tables 2-4, Annex 2)[39–41,51,69].

42. *In a patient with suspected ABPA, the consensus recommends performing a chest CT and/or chest X-ray to detect possible pulmonary abnormalities. The presence of transient opacifications or evidence of bronchiectasis (+/- mucus plugging and budding tree changes) is considered highly suggestive of ABPA.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease [imaging approach to chronic and allergic forms associated with *Aspergillus* spp.]) (Tables 3 and 4, Annex 2)[39,51,59–62].
43. *In a patient diagnosed with ABPA, it is recommended to perform measurement of total IgE Abs from serum every 1-2 months, to evaluate the response to treatment.* **(strong recommendation, moderate-quality evidence))** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease [value of Abs detection in IA/*Aspergillus* disease][40,41,70].

a. In a patient diagnosed with ABPA in the context of asthma or CF, what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

44. *In a patient diagnosed with ABPA in the context of asthma or CF, the consensus recommends as first treatment option the administration of systemic corticosteroids (prednisolone or prednisone [0.5mg/k/d for 14 days, then 0.5mg/k every other day]), with a minimum duration of 6-8 weeks and dose tapering until completing 3 months of treatment.* **(strong recommendation, high-quality evidence)**[70].
45. *In a patient diagnosed with ABPA in the context of asthma or CF, the consensus recommends initiating antifungal therapy if exacerbation of the disease occurs and/or to allow reduction in long-term corticosteroid dose, and/or when prednisolone dose cannot be reduced.* **(strong recommendation, moderate-quality evidence)**[4].
46. *In a patient diagnosed with ABPA, persistent asthma and imaging evidence of bronchiectasis (+/- mucus plugging and budding tree changes) in whom reduction of the corticosteroid dose has not been possible, it is recommended to initiate antifungal treatment with ITZ (PO, children 5 mg/kg/d, one dose, or, if the total dose exceeds 200 mg/d, two doses per day). It is considered that the duration of antifungal treatment should be established on an individual basis, and should last a maximum of 16 weeks.* **(strong recommendation, moderate-quality evidence)** (Table 5)[4,47,70].
47. *In a patient diagnosed with ABPA and CF and/or with progressive pulmonary decline (which may be permanent), it is recommended to initiate antifungal treatment with ITZ (PO, children 5 mg/kg/d, one dose, or, if the total dose exceeds 200 mg/d, two doses per day). It is considered that the duration of antifungal treatment should be established on an individual basis, and should last a maximum of 16 weeks.* **(strong recommendation, moderate-quality evidence)** (Table 5)[4,47,70].
48. *VCZ (children: [IV <50 kg, 9 mg/kg/12h, day 1, then 8 mg/kg/12h; ≥50 kg, 6 mg/kg/12h, day 1, then 4 mg/kg/12h], or [PO <50 kg, 9 mg/kg/12h (maximum dose 350 mg/12h); ≥50 kg, 200-300 mg/12h]), is an alternative for antifungal treatment in a patient diagnosed with ABPA in the context of asthma or CF.* **(weak recommendation, moderate-quality evidence)** (Table 5)[4,46].
49. *PCZ (suspension [200 mg/8h] or tablets [300 mg/12h, day 1, then 300 mg/d]) is an alternative for antifungal treatment in a patient older than 13 years diagnosed with ABPA in the context of CF.* **(weak recommendation, moderate-quality evidence)** (Table 5)[4,64].
50. *In a patient diagnosed with ABPA in the context of asthma or CF, the consensus recommends performing TDM of the azoles (VCZ, ITZ, PCZ) of choice, to improve antifungal efficacy, evaluate therapeutic failure and reduce pharmacological toxicity. Liver function monitoring is considered to evaluate toxicity related to azole use.* **(strong recommendation, moderate-quality evidence)** (I Diagnosis and Follow-up of IA/*Aspergillus* Disease [TDM in the therapeutic management of an IA/*Aspergillus* disease]) (Table 7, Annex 4)[63,71].
51. *In a patient diagnosed with ABPA in the context of asthma or CF, the consensus does not recommend initiating antifungal treatment with nebulized AmB.* **(weak recommendation, low-quality evidence)**[71,72].

b. In a patient diagnosed with ABPA in the context of asthma or CF, what is recommended for choosing complementary measures to the treatment of the disease?

Recommendation

52. *In a patient diagnosed with ABPA in the context of asthma or CF, presenting high titers of total IgE Abs without clinical control of the disease despite treatment with systemic corticosteroids and/or antifungal agents, the consensus recommends initiating treatment with omalizumab (375 mg, subcutaneously, twice a month).* **(weak recommendation, moderate-quality evidence)**[4,40,41,51,73].
53. *In a patient diagnosed with ABPA in the context of asthma or CF, it is recommended to use nebulized hypertonic solution (7%, 4-5 ml) to reduce sputum viscosity and facilitate expectoration of mucus plugs.* **(weak recommendation, moderate-quality evidence)**[4,71,74].
54. *In a patient diagnosed with ABPA in the context of asthma or CF, with frequent exacerbations and imaging evidence of bronchiectasis, long-term use of azithromycin is recommended to decrease cough and expectoration.* **(strong recommendation, moderate-quality evidence)**[4,75,76].

55. *In a patient diagnosed with ABPA in the context of asthma or CF, on treatment with oral corticosteroids and compliant with treatment, with proximal bronchial collapse persisting after 3-4 weeks, therapeutic bronchoscopy is recommended.* **(strong recommendation, moderate-quality evidence)**[74,77].
56. *In a patient with a high suspicion of developing ABPA in the context of asthma or CF, it is recommended to implement environmental control measures to minimize environmental exposure to* Aspergillus *conidia.* **(strong recommendation, low-quality evidence)**[74,77].

2. In an adult patient with sinus involvement, how is the diagnostic approach for fungal allergic rhinosinusitis (FAR)?

Recommendation

57. *The diagnostic approach of FAR is considered to be based on: (a) clinical picture of a chronic rhinosinusitis with nasal polyposis, (b) presence of very thick, eosinophil-rich mucus, (c) visualization of hyphal elements from mucus, (d) detection of very high total IgE Abs from serum (and/or immediate positive skin test to fungal Ags, not necessarily* A. fumigatus*), and (e) abnormal findings on CT scan of paranasal sinuses (e.g., almost complete opacification of some cavities).* **(strong recommendation, moderate-quality evidence)** (Tables 2-4, Annex 2)[40,41,59–62,78,79].

a. In a patient diagnosed with FAR, what is recommended in order to choose the type of drug, the dosage and the duration of antifungal treatment?

Recommendation

58. *In a patient diagnosed with FAR with a refractory infection and/or very early relapses, the consensus recommends oral ITZ, at standard doses, as a first antifungal treatment option.* **(weak recommendation, low-quality evidence)**[4,47,79].

a. In a patient diagnosed with FAR, what is recommended for choosing complementary measures to the treatment of the disease?

Recommendation

59. *In a patient diagnosed with a moderate to severe form of FAR, the consensus recommends surgical management with polypectomy and sinus lavage. Surgical management is not recommended in a patient diagnosed with a mild form of FAR.* **(strong recommendation, moderate-quality evidence)**[4,79].
60. *In a patient diagnosed with FAR, it is recommended to initiate complementary treatment with oral and topical nasal corticosteroid after the surgical procedure, to reduce symptoms and/or possible relapse of the disease.* **(strong recommendation, moderate-quality evidence)**[4,80].

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

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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.

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