In this registry, 10% of VAP are of fungal origin, mainly caused by Aspergillus sp. which accounts for 8% in ICU patients [1]. The role of other molds is anecdotal: zygomycosis infections are currently restricted to patients with hematological malignancies, primarily with prolonged neutropenia and solid organ transplanted patients with a degree of immunosuppression. In contrast, there has been a significant decrease in recent years in diabetic ketoacidosis as a zygomycosis risk, associated with improved management of diabetes in the general population [2]. Infections from agents such as Fusarium, Scedosporium, and Lomentosphora, while other molds are limited to prolonged neutropenias and similar behavior to invasive aspergillosis. Pneumocystis jirovecci pneumonia, restricted to patients with cellular immunosuppression and endemic fungal infections (Histoplasma spp. and others) are in certain geographical areas, and need special consideration.

Candida spp. as a causative agent of VAP is controversial. Some authors exclude it as an etiological agent and others estimate its incidence below 1%, related to risk factors such as severe immunosuppression, malnutrition, high fungal load (e.g., diabetes, alcoholism, gastroesophageal reflux, presence of esophageal diverticula), or broad-spectrum antibiotic therapy [3]. Regardless of causality, a recent meta-analysis associated airway colonization by Candida spp. in ICU patients with a longer duration of intubation, higher ICU mortality, and a higher 28-day mortality rate [4].

RISK FACTORS FOR INVASIVE PULMONARY ASPERGILLOSION (IPA) IN ADMISSIONS TO THE ICU

By the number of patients, ICU admission alone is the largest risk factor for IPA, above classic factors such as the onc-hematologic patient or transplant recipients, as they comprise most IPA diagnoses in a general hospital [5]. Bassetti et al. categorized patients in the ICU according to IPA risk (Table 1) [6]. Isolation of Aspergillus spp. in respiratory
specimens is associated with high mortality in the critically ill patient. Invasive forms can be associated with mortality between 69–77%, but colonization in the absence of infection is also associated with a mortality of 38%, as demonstrated in a recent study on 563 patients from 30 ICUs in eight countries [7]. The following independent mortality factors were observed: age, hematopoietic progenitor transplantation, mechanical ventilation, high SOFA score ( Sequential Organ Failure Assessment) and dialysis at diagnosis – which are associated with invasion vs. colonization in cancer patients (including hematologic) or solid organ transplantation [7].

Patients with severe chronic obstructive pulmonary disease (COPD) receiving broad-spectrum antibiotics and corticosteroids are becoming one of the main risk groups for IPA in ICU [8]. Guinea et al. analyzed the risk of IPA in COPD patients and confirmed the following: admission to the ICU, chronic heart failure, antibiotic treatment in the 3 months prior to admission, accumulated dosage of corticosteroids equivalent to > 700 mg prednisone in the 3 months prior to admission, and a similar accumulated dosage of corticosteroids from admission to the first clinical isolation of Aspergillus [8].

Table 1

| Risk Factors for IPA in ICU Patients |
|------------------------------------|
| **1. High risk**                   |
| Neutropenia (500/mm³)              |
| Hematological malignancy           |
| Allogeneic HSCT                    |
| **2. Intermediate risk**           |
| Prolonged treatment with corticosteroids before admission to the ICU |
| Autologous HSCT                    |
| COPD                               |
| Liver cirrhosis                    |
| Solid organ cancer                 |
| HIV infection                      |
| Lung transplantation               |
| Systemic immunosuppressive therapy |
| **3. Low risk**                    |
| Severe burns                       |
| Solid organ transplant             |
| Steroid treatment for > 7 days     |
| Prolonged stay in ICU (> 21 days)  |
| Malnutrition                       |
| Post cardiac surgery               |
| Near drowning                      |

COPD chronic obstructive pulmonary disease, HIV human immunodeficiency virus, HSCT hematopoietic stem cell transplantation, ICU intensive care unit, and IPA invasive pulmonary aspergillosis. Modified from reference [6].

The use of certain biologics is associated with an increased risk of IPA in clinical practice; in recent years, this includes ibritinib –used to treat chronic lymphocytic leukemia, mantle lymphoma, and Waldenstrom’s disease; an elevated risk of IPA was observed when used in combination or after other immunosuppressive treatment, especially Janus kinase inhibitors (JAK) (ruxolitinib) or idelalisib [9].

Controversy exists about ECMO (extracorporeal membrane oxygenation) as a risk factor for IPA in ICU patients. Some studies attribute a 7% risk of IPA to ECMO patients [10]. However, a study conducted in over 20,000 patients in 300 centers in the American Extracorporeal Life Support Organization Registry found that 1.4% was the risk of IPA among ECMO patients, higher in onco-hematology, solid organ transplantation, or influenza [11].

In recent years, certain respiratory viral infections, such as influenza or SARS-CoV-2, appear as important risk factors for IPA. A study performed in 7 ICUs in Belgium and the Netherlands, confirmed an incidence of IPA in 19% of those admitted with influenza to the ICU; this reached 32% in immunocompromised patients, with an associated overall mortality of 51% [12]. Coinciding with the SARS-CoV-2 pandemic, an increased incidence of IPA is described, especially in patients admitted to the ICU, estimated at 20–35% in certain national series [13].

**DIAGNOSIS OF ASPERGILLUS PNEUMONIA: PECULIARITIES OF THE CRITICALLY ILL PATIENT**

Regardless of the type of clinical form or baseline condition, documentation of hyphae on biopsy, or isolation of Aspergillus spp. in a culture of a sterile specimen constitutes a diagnosis of proved infection. However, this can only be confirmed in a minority of patients.

The positive predictive value of Aspergillus isolation in sputum is generally low, depending on patient type and risk; it may not exceed 10% in COPD patients, or even reach 50% in liver transplant recipients, or exceed 80% in hematopoietic stem cell transplant patients. The EORTC and Mycoses study groups (MSGs) developed well-validated criteria in onco-hematological patients [14,15]. As such, a diagnosis of probable aspergillosis includes the intersection of 3 factors: a) host at risk (e.g., prolonged neutropenia, GVHD, or solid organ transplantation), b) image: the presence of at least one of the following four patterns: dense, well-circumscribed lesions with or without a halo sign, air crescent sign cavity, wedge-shaped and segmental, or a lobar consolidation, and c) microbiologic: Aspergillus spp. isolation in respiratory samples, a positive galactomannan (GM) in serum or bronchoalveolar lavage (BAL), or a positive direct test (cytology, direct microscopy). Positive PCR was not considered diagnostic of IPA in previous consensus criteria [14] but was incorporated in the last version [15]. The presence of only 2 factors: a) host and b) image, in the absence of a microbiological confirmation, can only be considered possible invasive fungal infection.

Application of these criteria to a patient admitted to the
ICU is challenging. Different studies confirmed that the sensitivity of these criteria decreases significantly in non-onco-hematological patients; in these patients, according with a bronchopulmonary origin, the most frequent radiological infiltrates are peribronchial consolidation or a tree-in-bud pattern, differing from the typical signs observed in onco-hematological patients (re: halo sign or air crescent sign cavity) [16].

In addition to low specificity of IPA infiltrates in the non-onco-hematologic patient is the lower cost-effectiveness of serum GM with bronchopulmonary forms of IPA, the case with most ICU patients. Serum GM has a lower sensitivity in patients with immunosuppressive conditions and in COPD patients vs. hematological patients. We previously confirmed a sensitivity of only 56% in the diagnosis of IPA in liver recipients [17], with a sensitivity < 50% reported in a systematic review of the literature for non-hematology–oncology patients [18]. The value of serum GM in patients with COPD, and risk of IPA, was evaluated in several studies, with sensitivity ranging between 30% and 60% [18]. Reduced sensitivity has been linked to two factors: increased clearance of GM by circulating neutrophils and lower angio-invasiveness of Aspergillus spp. [18].

To overcome these problems in ICU patients, new criteria for probable or putative aspergillosis are proposed (AspICU) and extensively validated in prospective cohorts [19] (Table 2). These criteria require a 'sine qua non' condition or isolation of Aspergillus spp. in respiratory samples (sputum or broncho-aspirated sample). Thereafter, for AspICU criteria, the following combination was required: a) compatible signs and symptoms, b) abnormal medical imaging by portable chest X-ray or CT scan of the lungs (not limited to accepted in onco-hematologic patients), and c) host risk factors or positive cytological smear. For diagnosis of tracheobronchitis, the presence of tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar on a bronchoscopic analysis with visualization of hyphae in biopsy or isolation of Aspergillus in culture, is required [19].

These discrepancies in diagnostic criteria led to considerable confusion in ICU patients. The description in recent years of IPA in patients with influenza, and more recently in patients infected by SARS-CoV-2, allowed these diagnostic criteria to be reevaluated. Table 3 shows criteria applied for diagnosis of IPA with influenza (IAPA) for patients admitted to the ICU [20]. These criteria, as in AspICU criteria, accept the presence of "pulmonary infiltrates" without specificity of EORTC/MSG infiltrates (halo sign, air crescent sign cavity...). To acquire specificity, it is compensated with a more demanding microbiological criterion, such as isolation of Aspergillus spp. or a GM > 1.0 in BAL, or the presence of positive GM in blood (> 0.5); yet, as already mentioned, this technique is not sensitive in non-onco-hematological patients [20]. In the absence of BAL, the iso-
lateralization of *Aspergillus* in sputum, tracheal aspirate, or bronchial aspirate (sample with a higher risk of colonization) is compensated by a pulmonary infiltrate of IPA, such as cavity infiltrate, which would not be justified with any other cause [20].

In the absence of characteristic radiological images, most diagnostic criteria in the ICU and non-onco-hematological patients employs the bronchoalveolar lavage, primarily GM in BAL, as the principal tool for IPA diagnosis. In a recent multicenter study to analyze the role of GM in bronchoalveolar lavage fluid for diagnosis of IPA in non-hematological patients including ICU and COPD patients a global sensitivity of BALF GM (optical density index [ODI] ≥ 1.0) of 77.4% was confirmed; sensitivity was higher in patients with immunosuppressive conditions than those with COPD (81.8% vs 66.7%; p: 0.38) [16]. In COPD patients, the best performance was obtained for BALF GM (ODI ≥ 0.5). The sensitivity of GM in serum was very poor in both populations (36.4% and 11.6%, respectively) [16].

The recently published criteria for IPA in patients with SARS-CoV-2 infection (CAPA) include the same criteria as IAPA for proven and probable aspergillosis, although for probable aspergillosis, they also consider diagnostic criteria as the visualization of hyphae on BAL cytology (or fungal stain) and PCR amplification of *Aspergillus* spp. in blood (x2) or BAL, provided that such amplification occurs in advance of cycle 36 [21]. In addition, the CAPA criteria also include a category of possible aspergillosis that maintains the same clinical and imaging criteria as probable aspergillosis, but it allows for a microbiological "non-bronchoscopic lavage" specimen [21]. The visualization of hyphae in non-bronchoscopic lavage, or in isolation in culture or a high titer (> 4 GM), or > 2 for a determination when accompanied by isolation in culture – are all considered diagnostic. Detection of GM in non-bronchoscopic lavage is seen as evidence of CAPA; on the other hand, proposed cutoff values are based on a single study and need further validation [22]. Authors propose that although classification of possible CAPlA will likely be sufficient to initiate antifungal therapy, in line with other consensus statements, it is not recommended for enrolling patients in clinical trials [21].

Lateral flow devices (LFD) to detect fungal antigens are not novel [23,24]. The first LFD for IA was described in 2008 but generated pooled sensitivity and specificity [23]. The recent release of the IMMY Sona Aspergillus GM lateral flow assay (LFA) incorporates two monoclonal antibodies (Mab), one novel Mab and one targeting a similar GM epitope to the Bio-Rad Platelia Aspergillus Antigen Assay (Hercules, CA, USA), has the potential to improve performance as demonstrated with cryptococcal LFD [23]. Comparison to the OLM LFD when testing BAL fluid showed the LFA as providing significantly better sensitivity (83% vs. 69%, p = 0.008), while maintaining specificity (87%) for proven or probable IPA [23]. An automated digital cube reader for quantification of results was recently added to the test kits. Diagnostic performance of the LFA is improved when utilizing a higher cutoff of 1.0 or 1.5 ODI, vs. the currently recommended cutoff of 0.5 ODI, which showed limited specificity [24].

**IPA THERAPY IN ICU**

We recommend either voriconazole or isavuconazole as first-line treatment for possible, probable, or proven aspergillosis in the ICU patient. Since Herbrecht’s study [25], all guidelines include voriconazole as the first option; however, the critically ill patient has some characteristics that may limit its use, or the possibility of interactions with other drugs metab-
In clinical practice, isavuconazole is metabolized at the cytochrome p450 level, despite the need to have levels available, given the frequency with which voriconazole cannot reach therapeutic levels. This makes isavuconazole or liposomal amphotericin B important alternatives in many patients in ICU. Voriconazole levels below 1 mg/L are associated with therapeutic failure in up to 46% of cases; response improves when this level is reached [26]. However, several studies, especially in the ICU, confirmed that approximately half the patients do not achieve serum therapeutic levels [27]. This difficulty with voriconazole occurs even with its intravenous formulation, as related to the individual-dependent bioavailability characteristic of this drug. Yet, the therapeutic range of voriconazole is narrow and serum levels > 5 mg/L are associated with hepatic and encephalopathic toxicity [26]. The presence of high levels has been documented in the ICU in up to 10% of patients.

The SECURE study conducted mainly in onco-hematological patients, but not including critically ill patients, confirmed the non-inferiority of isavuconazole vs. voriconazole in IPA, but with a significant reduction in hepatic, cutaneous, and ocular toxicity [28]. A recently published randomized, double-blind study also confirmed the non-inferiority of posaconazole to voriconazole, mainly in onco-hematological patients [29]. In the case of posaconazole, in addition to intravenous administration, the oral tablet formulation also significantly improved the pharmacokinetics and absorption of the oral solution formulation [29]. Among the three azole drugs mentioned, isavuconazole has a lower degree of interactions, conferring a substantial advantage in the critically ill patient [30]. Isavuconazole is a moderate CYP3A4 inhibitor, while other azoles, especially voriconazole, in addition to inhibiting CYP3A4, also inhibit CYP2C8, CYP2C9, and CYP2C19 (Table 4). This indicates that the use of certain drugs, such as lopinavir, prednisone, estradiol, atorvastatin, or midazolam, do not require adjustment when administered with isavuconazole, only with voriconazole; others, such as cyclosporine, tacrolimus or sirolimus, where use may be contraindicated in the presence of voriconazole, they can be used with caution with isavuconazole [30]. Unlike other QT-prolonging azoles (voriconazole, posaconazole), isavuconazole reduces QT, favoring isavuconazole in the ICU. In favor of their use are post hoc results of the SECURE study, in which > 95% of patients receiving isavuconazole had levels > 1.5 mg/L, and determinations > 7 mg/L occurring in < 10%: these were not associated with increased toxicity, so except under special conditions, level monitoring was not required.

These arguments were also used by other authors to justify the use of liposomal amphotericin B to the detriment of voriconazole. Garnacho et al. in a consensus of ICUs in Spain, justified the use of amphotericin B to the detriment of voriconazole in the management of aspergillosis in ICU patients, if the following circumstances were present: a) concomitant treatment with drugs metabolized by CYP3A4 or 2C9, b) treatment with drugs that can prolong QT, c) severe liver failure (Child C), or d) glomerular filtration rate < 50 mL/min [31].

Most guidelines advise against the use of combination therapy to treat invasive aspergillosis, due to lack of scientific evidence in published studies. In addition to in vitro and experimental studies, with diverse and contradictory results, the only prospective randomized clinical trial for a mainly onco-hematological population, analyzing the superiority of voriconazole and anidulafungin over voriconazole monotherapy did not confirm a significant reduction in mortality at 12 weeks, except in some subgroups [32]. In general, echinocandins are not recommended for use as monotherapy in primary invasive aspergillosis [20,21]. Despite this study, with some methodological limitations (long recruitment period and large number of losses, among others), many experts still consider the use of combination therapy in severe patients, especially given high expected mortality, such as ICU patients.

Optimal duration of therapy is unknown, as radiological lung imaging may not be a helpful tool, but the expert panel suggests 6–12 weeks as a treatment course. It seems reasonable to include follow-up lung CT imaging to document the resolution of infiltrates before termination of treatment. In patients who are immunocompromised, longer treatment might be necessary. Following the GM-index in serum as a measure of therapeutic response may be limited by its poor sensitivity if testing serum in non-neutropenic patients. However, follow-up respiratory samples, such as GM testing, could be useful in determining efficacy in patients who are GM-positive, which may similarly help determine treatment duration [20,21].

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### Table 4

| Azole        | CYP2C8 | CYP2C9 | CYP2C19 | CYP3A4 |
|--------------|--------|--------|---------|--------|
| Fluconazole  | +      | ++     | +       | ++     |
| Itraconazole | ++     | +      | -       | +++    |
| Voriconazole | ++     | ++     | +++     | +      |
| Posaconazole | -      | -      | -       | +++    |
| Isavuconazole| -      | -      | -       | +/++   |

Notes: -, no inhibition; +, mild inhibition; ++, moderate inhibition; ++++, strong inhibition. Modified from reference [30].

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CONFLICTS OF INTEREST

Author declares no conflicts of interest

REFERENCES

1. Estudio Nacional de Vigilancia de Infección Nosocomial en Servicios de Medicina Intensiva (ENVIN/ELICS). Informe 2020. Sociedad Española de Medicina intensiva Crítica y Unidades Coronarias (SEMICUC). http://hws.vhebron.net/envin-eliccs/.

2. Vallabhaneni S, Benedict K, Derado G, Mody RK. Trends in Hospitalizations Related to Invasive Aspergillosis and Mucormycosis in the United States, 2000–2013. Open Forum Infect Dis. 2017 Jan 13;4(1):ofw268. doi: 10.1093/ofid/ofw268.

3. Schnabel RM, Linssen CF, Guion N, van Mook WN, Bergmans DC. Candida pneumonia in intensive care unit? Open Forum Infect Dis. 2014 May 27;1(1):ofu026. doi: 10.1093/ofid/ofu026.

4. Huang D, Qi M, Hu Y, Yu M, Liang Z. The impact of Candida spp airway colonization on clinical outcomes in patients with ventilator-associated pneumonia: A systematic review and meta-analysis. Am J Infect Control 2020;48(6):695–701.

5. Zilberberg MD, Nathanson BH, Harrington R, Spalding JR, Shorr AF. Epidemiology and Outcomes of Hospitalizations With Invasive Aspergillosis in the United States, 2009–2013. Clin Infect Dis 2018;67(5):727–735.

6. Bassetti M, Garnacho-Montero J, Calandra T, Kullberg B, Dimopoulos G, Azoulay E, et al. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. Intensive Care Med 2017;43(9):1225–1238.

7. Taccone FS, Van den Abeele AM, Bulpa P, Misser W, Meersseman W, Cardoso T, et al. AspICU Study Investigators. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care 2015;19(1):7.

8. Guinea J, Torres-Narbona M, Gijón P, Muñoz P, Pozo F, Peláez T, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect 2010;16(7):870–7.

9. Chamilos G, Loinakis MS, Kontoyiannis DP. Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways. Clin Infect Dis 2018;66(1):140–148.

10. Rodriguez-Goncer I, Thomas S, Foden P, Richardson MD, Ashworth A, Barker J, et al. Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. Eur J Clin Microbiol Infect Dis 2018;37(7):1251–1257.

11. Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care 2018;22(1):98.

12. Schauwlieghae AFAD, Rijnders BJA, Philips N, Verwijr S, Vanderbeke L, Van Tienen C, et al. Dutch-Belgian Mycosis study group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6(10):782–792.

13. Armstrong-James D, Youngs J, Bicanic T, Abdolrasouli A, Denning DW, Johnson E, et al. Confronting and mitigating the risk of COVID-19 associated pulmonary aspergillosis. Eur Respir J 2020;56(4):2002554.

14. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46(12):1813–21.

15. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Badley 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):1367–1376.

16. Fortún J, Martín-Dávila P, Gomez Garcia de la Pedrosa E, Silva JT, García-Rodríguez J, Benito D, et al. Galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive aspergillosis in non-hematological patients. J Infect 2016;72(6):738–744.

17. Fortun J, Martín-Dávila P, Alvarez ME, Sanchez-Sousa A, Quereda C, Nasv E, et al. Aspergillus antigennemia sandwich-enzyme immunoassay test as a serodiagnostic method for invasive aspergillosis in liver transplant recipients. Transplantation 2001 Jan 15;71(1):145e9.

18. Leeflang MM, Debepts-Ossenkopp YL, Visser CE, Scholten RJ, Hooft L, Blijmer HA, et al. Galactomannan detection for invasive pulmonary aspergillosis in immunocompromized patients. Cochrane Database Syst Rev 2008 Oct 8;(4). CD007394.

19. Blot SJ, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186(1):56–64.

20. Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med 2020;46(8):1524–1535.

21. Koehler P, Bassetti M, Chakrabarti A, Chen SC, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMJ/SHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021;21(6):e149–e162.

22. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A National Strategy to Diagnose Coronavirus Disease 2019–Associated Invasive Fungal Disease in the Intensive Care Unit. Clin Infect Dis. 2021 Oct 5;73(7):e1634–e1644. doi: 10.1093/cid/ciaa1298.

23. White, LP.; Price, J.S. Recent Advances and Novel Approaches in Laboratory-Based Diagnostic Mycology. J Fungi 2021,7,41.

24. Jenks JD, Prattes J, Frank J, Spiess B, Mehta SR, Boch T, et al. Performance of the Bronchoalveolar Lavage Fluid Aspergillus Galactomannan Lateral Flow Assay With Cube Reader for Diagnosis of Invasive Pulmonary Aspergillosis: A Multicenter Cohort Study. Clin Infect Dis 2021;73(7):e1737–e1744.
25. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347(6):408-15.

26. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, Marchetti O. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 2012;55(3):381-90.

27. Hoenigl M, Duettmann W, Raggam RB, Seeber K, Troppan K, Fruhwald S, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. Antimicrob Agents Chemother 2013;57(7):3262-7.

28. 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.

29. Maertens JA, Rahav G, Lee DG, Ponce-de-León A, Ramírez Sánchez IC, Klimko N, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet 2021;397(10273):499-509.

30. Wu X, Clancy CJ, Rivosecchi RM, Zhao W, Shields RK, Marini RV, et al. Pharmacokinetics of Intravenous Isavuconazole in Solid-Organ Transplant Recipients. Antimicrob Agents Chemother 2018;62(12):e01643-18.

31. Garnacho-Montero J, Olaechea P, Alvarez-Lerma F, Alvarez-Rocha L, Blanquer J, Galván B, et al. Epidemiology, diagnosis and treatment of fungal respiratory infections in the critically ill patient. Rev Esp Quimioter 2013;26(2):173-88.

32. 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.