Update in Micology

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Comments on practice guidelines for the diagnosis and management of aspergillosis made by the IDSA in 2016

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ABSTRACT

We sought to review the most important updates in the treatment of aspergillosis after the publication of the clinical practice guidelines for the diagnosis and management of invasive aspergillosis (IA) by the Infectious Diseases Society of America. Our aim is to discuss some of the key aspects concerning the following topics: early initiation of antifungal therapy, antifungal agent of choice, follow-up of patients with IA, and breakthrough aspergillosis.

Comentarios sobre las guías IDSA 2016 de diagnóstico y tratamiento de la aspergilosis

RESUMEN

Tras la publicación de la nueva guía de práctica clínica sobre el diagnóstico y manejo de la aspergilosis invasora (AI) de la Infectious Diseases Society of America, se ha realizado una revisión de los puntos más importantes de la actualización del tratamiento de la aspergilosis. Por dicho motivo, a continuación se discutirán los siguientes aspectos claves de interés: tratamiento precoz, tratamiento antifúngico de elección, seguimiento de los pacientes con AI y aspergilosis de brecha.

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INTRODUCTION

Previous clinical practice guidelines for the diagnosis and management of invasive aspergillosis (IA) published in 2008 by the Infectious Diseases Society of America (IDSA) were updated in 2016[1]. In this context, we hereby review the most important novelties in the treatment of aspergillosis. Our aim is to discuss some of the key aspects concerning the following topics: early initiation of antifungal therapy, recommended antifungal agent, follow-up of patients with IA, and management of breakthrough aspergillosis.

EARLY INITIATION OF ANTIFUNGAL THERAPY

Two of the essential tools to successfully manage these infections are to know the physiopathogenesis of the filamentous fungi, and to identify the host immune response to the aggression.

The spores participate in the earliest stage of the aspergillus pathogenesis. After being inhaled by the host, the spores are recognised as foreign and are subsequently destroyed by the immune system. However, in some hosts spores find it easier to reach the lower respiratory tract, where they are deposited in the alveoli. In the neutropenic host, spores turn into hyphae very easily, thus creating an angioinvasive aspergillosis. In other states of immunosuppression, such as patients with graft-versus-host disease and corticosteroid therapy, some spores turn into hyphae while others cause important polymorphonuclear granulocytes (PMN) recruitment and tissue damage[2].

For all these reasons, the length of time between inhalation of spores and the manifestations of the disease may vary largely. A recent paper describes a noticeable increase in the diagnosis of IA 28-42 days after a considerable build-up of ambient spores in the city of Barcelona[3]. In this context, the diagnosis of early forms of aspergillosis remains a challenge.

Recent investigations have revealed that the halo sign observed in the chest CT is an early sign of the infection. This radiologic image shows a macronodule (≥ 1 cm in diameter) surrounded by a perimeter of ground-glass opacity, without histopathological evidence of necrosis. Greene et al[4], documented that patients who start antifungal treatment on the basis of the identification of a halo sign by chest CT show a significantly better response to treatment and improved survival than those who initiate treatment after observing air crescent signs (suggestive of necrosis and characteristic of later-stage disease) in radiological assessments.

The latest guidelines recommend early initiation of antifungal therapy in patients with strongly suspected IA. In fact, they recommend that treatment should be warranted while a diagnostic evaluation is conducted.

RECOMMENDED ANTIFUNGAL REGIMEN

2016 IDSA guidelines establish voriconazole as the antifungal choice for IA treatment. This recommendation is mainly based on Herbercht's research and his comparison study between voriconazole and amphotericin B deoxycholate[5]. This study showed successful outcomes in 52.8% of the patients in the voriconazole group (complete responses in 20.8% and partial responses in 31.9%) and 31.6% of those in the amphotericin B group; and the survival rate at 12 weeks was also higher in patients treated with voriconazole (70.8 vs. 57.9; hazard ratio, 0.59; 95% confidence interval, 0.40-0.88). Other observational studies also support that voriconazole treatment is associated with better outcomes in patients with IA[6-9].

Voriconazole metabolism is highly variable between subjects. 2016 IDSA guidelines recommend and confirm the importance of therapeutic drug monitoring (TDM) when voriconazole, both po and iv, is used. A randomized controlled trial with 110 patients who were administered voriconazole for 12 weeks, revealed that patients submitted to routine TDM improved their treatment response in invasive fungal infections (IFI) (81% vs. 57%, p=0.04) and reduced drug discontinuations due to adverse events (4% vs. 17%, p=0.02)[10]. The first levels of voriconazole should be measured between days 5 and 7, when the most stable levels are most probably attained. The therapeutic aim is to reach levels between 1.5 and 5 mg/L. It is still unclear how voriconazole doses could be modified if monitored values prove to be too high or too low. The European Conference on Infections in Leukaemia (ECIL) published a guiding algorithm in December 2015 establishing patterns to be followed depending on administration method, usual dose, and blood levels of the antifungal drugs, which could be used as a valuable resource[11].

An important new aspect of these guidelines, is the positioning of isavuconazole as a treatment choice for IA with identical level of evidence as voriconazole. Maertens et al carried out a phase 3, randomised-controlled, non-inferiority trial with 527 patients to compare the use of isavuconazole vs. voriconazole for the primary treatment of invasive mold

disease, and proved the non-inferiority of isavuconazole in terms of clinical efficiency[12]. Mortality from first dose of study drug to day 84 was similar between treatment groups in both intention to treat populations (treatment difference -1.1%, 95% CI -8.9-6.7). The proportion of patients with serious treatment-emergent adverse events was similar between both groups. However, significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (109 [42%] vs. 155 [60%]; p<0.001), especially hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole (21 [8%] vs. 35 [14%]).

Another important topic is the positioning of a combined antifungal therapy with voriconazole and an echinocandin as a first-line option in selected patients with documented IA. Marr et al compared the administration of voriconazole-anidulafungin with voriconazole-placebo, in a randomized trial of 454 patients with haematologic malignancies and haematopoietic cell transplantation[13]. Mortality rates at week 6 were 19.3% for combination therapy and 27.5% for monotherapy (difference, -8.2 percentage points [95% CI -19.0-1.5]; p=0.087). In the subgroup of patients diagnosed of probable IA that was based on radiographic abnormalities and galactomannan antigen positivity in serum or BAL, the results were similar: mortality after 6 weeks was lower in combination therapy than monotherapy (15.7 vs. 27.3; p=0.037). This study was the first to use initial voriconazole doses of 300 mg/12h in a clinical setting. Compared with previous studies that had used 200 mg/12h, no increase in toxicity was documented.

In situations in which hepatic toxicities or drug interactions warrant non-azole alternatives, and when voriconazole-resistant molds remain of concern, the recommendation is to use liposomal amphotericin B (AmB). In highly immunocompromised patients, the effectiveness of AmB 3 mg/kg/day as first-line therapy for IA is demonstrated, with a response rate of 50% and a 12-week survival rate of 72%[14].

With regard to the duration of treatment, it is difficult to make recommendations. It depends on three key factors: the host, the clinical and microbiological response, and the evolution of CT findings.

FOLLOW-UP OF PATIENTS WITH INVASIVE ASPERGILLOSIS

The follow-up of invasive aspergillosis patients is difficult, as they are usually complex patients with abundant intercurrent processes. Patient's assessment is based on clinical evolution, performance of CT examinations, and monitoring of microbiological tests.

Repetition of a CT scan before 2 weeks after the start of treatment is not usually recommended, due to the paradoxical reaction that can sometimes be observed on the first 14 days

(a radiological worsening that does not necessarily mean a clinical deterioration of the patient).

With regard to microbiological tests, the key biomarker is galactomannan. Miceli et al[15], proved that the evolution of this biomarker over time is a good prognostic index. The correlation between the quantitative serum galactomannan index (within ≤1 week before outcome) and define outcomes was excellent, with k correlation coefficient of 0.87 (95% CI, 0.81-0.93; p<0.001) and 0.91 (95% CI, 0.86-0.96; p<0.001) for survival and global outcome, respectively.

WHAT THERAPEUTIC ACTIONS SHOULD BE TAKEN TO TREAT BREAKTHROUGH ASPERGILLOSIS?

Breakthrough IFI (bIFI) is defined as the IFI suffered by patients undergoing antifungal treatment, which appears 3-5 days after the initiation of such treatment, with prophylactic or therapeutic purpose.

As soon as a bIFI is suspected, examinations should be aimed at determining whether this bIFI is associated to a failure of previous antifungal therapy, to the host immunity, or to the presence of resistant fungi. On the basis of this concept, the guidelines recommend 4 actions: i) if the antifungal prophylaxis is with either voriconazole or posaconazole, pharmacological levels should be monitored; ii) to carry out a CT and a fibrobronchoscopy in order to rule out the presence of resistant fungi; iii) to change the antifungal agent family throughout the rest of the diagnostic process; iv) to reduce immunosuppression to the extent possible.

If TDM certificate low azole levels, bIFI will be probably related to prophylactic failure and adjusting the antifungal levels would arise as an appropriate strategy. Conversely, if TDM shows optimal drug levels, we should look at the possible presence of a resistant fungus, namely *Aspergillus* sp. or other filamentous fungi.

A recent study carried out by Biehl et al[16], compared the response presented by possible, probable, and proven bIFI cases in patients with acute myeloid leukaemia (AML) and allogeneic haematopoietic stem cell transplantation (HSCT). In this study, 250 AML patients with 329 hospitalizations and 409 HSCT patients with 496 hospitalizations were identified. In AML patients, there were 16 (6.4%) proven or probable bIFIs and 44 (17.6%) possible bIFIs. In HSCT patients, there were 14 (3.4%) proven or probable bIFIs and 37 (9.0%) possible bIFIs. A high variety of treatment approaches were observed. Switch from prophylaxis to liposomal amphotericin B was the most frequent approach in AML patients. Overall survival in this population did not differ between patients with or without bIFI (63.3% versus 70.0%; p=0.297). Conversely, the most frequent approach in HSCT patients was to keep the ongoing prophylaxis regimen. In this population, those patients with bIFI presented greater mortality than those patients without suspected infection (49.0% versus 66.8%; p=0.012).

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