Official journal of the Spanish Society of Chemotherapy

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Top-ten papers in fungal infection (2015-2017)

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ABSTRACT

We have clustered the published articles in fungal infection between 2016 and 2017 in four categories. First, the emergence of *Candida auris* as a nosocomial pathogen associated to high antifungal resistance and high mortality. Second, the growing importance of fungal infections associated to the use of biologic therapies. Third, the approval of isavuconazole for the treatment of filamentous fungi and dymorphic mycoses with positive results and less side effects. And finally, a mix of other important news regarding empiric therapy, fluconazole toxicity and difficult-to-treat fungal infections.

Key Words: Fungal infection; Treatment; Biologic therapies.

Los mejores artículos sobre infección fúngica

RESUMEN

Hemos agrupado los artículos publicados sobre infección fúngica entre 2016 y 2017 en cuatro categorías. Primero, la emergencia de *Candida auris* como un patógeno nosocomial asociado a alta resistencia a antifúngicos y alta mortalidad. Segundo, la creciente importancia de las infecciones fúngicas asociadas al uso de terapias biológicas. Tercero, la aprobación de isavuconazol para el tratamiento de los hongos filamentosos y las micosis por hongos dimórficos con buenos resultados y menos efectos adversos. Y por último, una combinación de otras noticias importantes en cuanto a terapia empírica, toxicidad del fluconazol e infecciones fúngicas difíciles de tratar.

Palabras clave: Infección fúngica; Tratamiento; Terapias biológicas

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INTRODUCTION

In order to inform of novelties in fungal infections, we have revised the published articles dating between 2016 and 2017 regarding this topic from clinical, bedside and treatment points-of-view. We have classified the most relevant articles into the following groups: i) Characteristics of *Candida auris* infection; ii) Fungal infections in patients treated with biologic therapies; iii) News in antifungal treatment; iv) Mix of interesting news.

CHARACTERISTICS OF *C. AURIS* INFECTION

C. auris is an emergent pathogen fungus that represents a big challenge for identification. Moreover, infection control measures when *C. auris* infection is diagnosed are mandatory.

First of all, we will comment on the article by Vallabhaneni et al [1], describing the first seven cases of *C. auris* infection reported in the United States. This paper shows us some important findings. First, whole genome sequencing showed that isolates from patients admitted to the same hospital were nearly identical, suggesting the possibility of a nosocomial outbreak. Additionally, the authors demonstrated that patients were colonized by *C. auris* for a long time after the initial infection and there existed multiple contaminated surfaces in the healthcare environment, potentially spreading throughout.

Later, Ruiz-Gaitán et al [2] reported the first four cases of one of the most important hospital outbreaks occurring in Europe (Valencia, Spain). Importantly, the authors showed how they initially misidentified the *C. auris* species. Investigation into the species continued due to the presence of a high-level resistance to fluconazole and voriconazole. The researchers characterized *C. auris* infection by genetic methods. The overall mortality was high (50%).

To finish this section, we will comment on the important paper of Lockhart et al [3], that describes 41 patients with *C.*

auris infection from 3 different continents. Whole-genome sequencing showed 4 different strains emerging simultaneously worldwide. High mortality rate (around 60%) and high antifungal resistance were found. All but four strains were highly resistant to fluconazole but very few were resistant to itraconazole and posaconazole (suggesting an efflux-pump mechanism related to fluconazole resistance); 7% were resistant to echinocandins and almost 50% were resistant to amphotericin B. Two strains were pan-fungal resistant.

FUNGAL INFECTIONS IN PATIENTS TREATED WITH BIOLOGIC THERAPIES

Patients receiving biologic therapies is a new, rising category of immunosuppressed hosts, about whom many questions about prophylaxis, treatment and general management are still unresolved.

Furthermore, an increasing evidence shows that different effects on the immune system could be associated with an increased risk of infections. For example, a randomized trial to evaluate the effectiveness of a monoclonal antibody against interleukin-17 demonstrated a huge efficacy of the therapy for psoriasis control, but noteworthily, the most important side effect of this drug was the *Candida* infection [4]. Also in this regard, different reports show an increased incidence of fungal infections in patients receiving tirosin kinase inhibitors and other biologic therapies [5–7] an antigen consistently expressed on B-lineage acute lymphoblastic leukaemia cells. We aimed to confirm the activity and safety profile of blinatumomab for acute lymphoblastic leukaemia. Methods: In a multicentre, single-arm, open-label phase 2 study, we enrolled adult patients with Philadelphia-chromosome-negative, primary refractory or relapsed (first relapse within 12 months of first remission, relapse within 12 months after allogeneic haemopoietic stem-cell transplantation [HSCT], or no response to or relapse after first salvage therapy or beyond, raising an international concern about this topic [8].

NEWS IN ANTIFUNGAL TREATMENT

In the coming years, new antifungals are going to be available, such as new echinocandins with better pharmacokinetic/pharmacodynamic profile. Nowadays, a new azole has been approved to fight fungal infections: Isavuconazole. Furthermore, in the future, new immunological approaches would be useful in improving patients' outcomes.

With regards to isavuconazole, we will first comment about the articles, by which this new antifungal was approved for the treatment of aspergillosis and mucormycosis [9,10]. First, the SECURE was a phase 3, randomized-controlled, non-inferiority trial comparing isavuconazole versus voriconazole for the treatment of invasive filamentous fungi. In this study, isavuconazole was non-inferior in mortality at 6 and 12 weeks, with significantly less side effects [9]. Secondly, the single-arm, open-label trial by Marty et al [10] assessed the efficacy and safety of isavuconazole for treatment of mucormycosis. All-cause mortality was reported to be around 40%. Additionally, a matched case control analysis was performed, using patients from the FungiScope Registry who had been treated with amphotericin B. No differences were found in terms of efficacy, with the arm of isavuconazole showing also less side effects. However, is important to point out that doses and surgical approach were not uniform in the patients from the FungiScope and a previous study with high doses liposomal amphotericin B and a high percentage of surgery showed higher response rates [11].

Meanwhile, an open-label, non-randomized phase 3 trial was conducted to evaluate the efficacy and safety of isavuconazole treatment in management of some dimorphic mycoses [12]. In this paper, rates of successful outcomes were like those previously described with other antifungals treatments, that is, isavuconazole has an acceptable safety profile and in turn, a possibly useful alternative in these patients.

The final paper of this section is an experimental mice model by Lionakis et al [13] based on the blockade of chemokine receptor CCR1. The authors were able to demonstrate that immunocompetent *Candida*-infected mice treated with this inhibitor improved its survival, decreased kidney fungal burden and provided protection from renal tissue injury.

MIX OF INTERESTING NEWS

The last group of articles revolve around three important aspects: empiric therapy, fluconazole toxicity, and difficult-to-treat fungal infections.

First, we will talk about the article of Timsit et al [14]. This is a multicenter double-blind and placebo-controlled study evaluating the empiric role of micafungin treatment in patients with ICU-acquired sepsis who had *Candida* colonization and multiple organ failure. A high number of patients were included (n=260) and randomized for receiving either placebo or micafungin, with high adherence to the intervention. No differences were found per prognosis between the control and intervention group. One possible limitation of this study is that they described a very low rate of patients being at high risk for invasive candidiasis (gastrointenstinal surgery, parenteral nutrition...).

Secondly, we will comment on a nationwide cohort study in Denmark with more than 1,400,000 pregnant women in order to assess a possible association between oral fluconazole use in pregnancy and the risk of spontaneous abortion and stillbirth [15]. Oral fluconazole-exposed pregnancies were compared with up to 4 unexposed pregnancies matched on propensity score, maternal age, calendar year, and gestational age. Importantly, the authors strongly related the use of oral fluconazole with spontaneous abortions. No association was found with stillbirths, but the number of stillbirths was quite low in the whole cohort. These results firmly preclude the use of oral fluconazole in this population.

Finally, Cuervo et al conducted a multicenter study in 9

Spanish hospitals to evaluate the role of echinocandins in patients with candidemia caused by a urinary tract source [16]. Although the current guidelines preclude the use of echinocandins for this kind of candidemia, these authors demonstrated via the use of a propensity score approach that early initial echinocandin therapy was not associated with clinical failure. The only factor related with improved outcome was the drainage of the urine focus.

FUNDING

Dra. Carolina Garcia-Vidal has received INTENSIFICACIÓ Grant- a grant supported by the Catalan Health Agency [PERIS (Pla estratègic de recerca i innovació en salut – "Strategic Plan for Research and Innovation in HealthCare")]. Our group is recognized by the AGAUR (Project 2017SGR1432) of the Catalan Health Agency.

ACKNOWLEDGEMENTS

We would like to thank the contributions made by Anthony Armenta in his corrections of the English language/syntax of the publication at hand.

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