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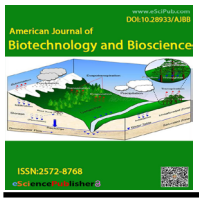

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ASPERGILLOSIS AND ADVANCES IN ITS TREATMENT IN THE LAST DECADE: A LITERATURE REVIEW

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ABSTRACT

Introduction: Invasive aspergillosis (AI) remains a fatal infection and difficult to treat in immunocompromised patients. Standard treatment is insufficient for these patients, often impairing their quality of life due to adverse effects, in addition to the short duration. Although mortality rates in patients with UA have decreased in the past two decades with the replacement of amphotericin B deoxycholate (AmB-D) with voriconazole as the first choice, treatment remains sub-ideal for patients due to adverse events and drug interactions with immunosuppressive drugs. **Objective**: This study aims to carry out a literary review about the scientific productions that address the treatment of AI published in the last 10 years, comparing the success and effectiveness rates of the treatments. **Methodology**: Through a literature review using the base dates PubMed, Lilacs and MedLine, accepting only articles published in the period 2010 to 2020, and only those in Portuguese or English, with 23 articles selected, of which 7 were included in this review. **Results and discussion**: There was a prevalence of treatments with voriconazole, used in six of the seven studies reviewed, in addition to being part of the standard Brazilian treatment. Studies related to the treatment of UA are heterogeneous, making it difficult to compare effectively between publications. Well-designed controlled, randomized and multicenter clinical trials are needed to adequately address the issue of the usefulness of the approaches used in Brazil. In addition, combined therapies come in many different forms, requiring cumulative evidence to support the use of combined antifungal therapy in AI, as they are still conflicting and of moderate strength.

Keywords: Aspergillosis; Treatment; Aspergillus spp; Voriconazole; Amphotericin B.

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INTRODUCTION

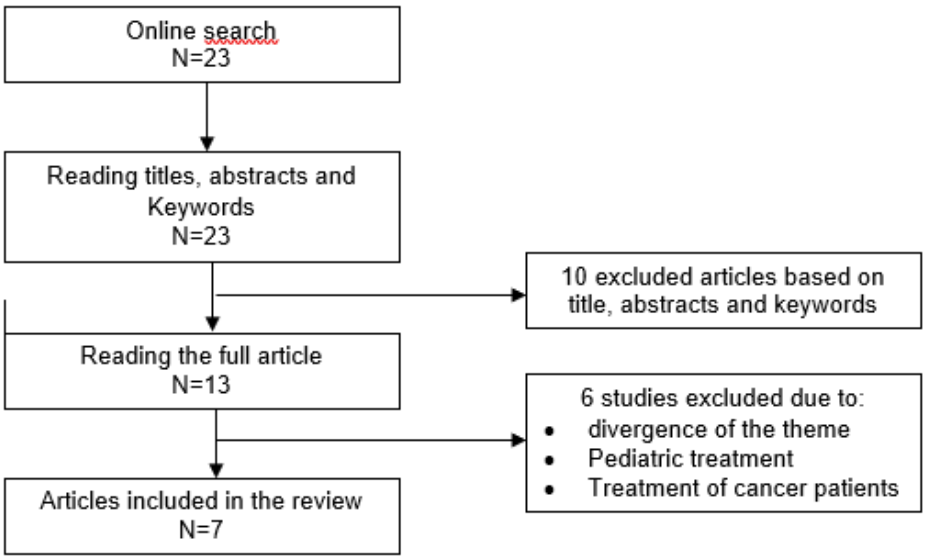
Aspergillosis is a fungal disease, with an opportunistic characteristic, caused by some species of the genus Aspergillus. They can infect both humans and several other animals, with the most common species being colonized in humans by *Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus* and giving prominence to *Aspergillus fumigatus*, as the main responsible[1].These are the most common fungi on the planet, being present in the soil, fertilizer, decomposing materials, and even in the hospital environment[2].

Asperillus infections come in several clinical forms, depending on two factors: the affected organ and the patient's immune status. The fungus penetrates the organism through the airways, and in normal hosts, it appears only as colonization. In immunologically compromised individuals, the phenomena most commonly described in the literature range from allergic rhinitis and asthma, to more severe conditions such as hypersensitivity pneumonitis and allergic bronchopulmonary aspergillosis[2].

Although mortality rates in patients with UA have decreased in the past two decades with the replacement of amphotericin B deoxycholate (AmB-D) with voriconazole as the first choice, treatment remains sub-ideal for patients due to adverse events and drug interactions with immunosuppressive drugs. Effective therapeutic options are limited when the infection is established, relying on the host's immune status to improve results[3].

There are few drugs available for the treatment of AI, and each has significant limitations. Amphotericin B formulations have been available for many decades, but the toxic effects of this restrict its clinical use, despite its broad spectrum antifungal activity. The first and second generation triazoles have increased the therapeutic options available, but in general they are characterized by variable pharmacokinetics, toxicity, resistance and drug interactions that complicate the therapy.

In view of this context, this study aims to carry out a literary review about the scientific productions that address the treatment of AI published in the last 10 years, comparing the success and effectiveness rates of the treatments.



METHODS

This article was conducted based on a systematic literature review, searching the PubMed, Lilacs and MedLine databases. Publication periods between 2010 and 2020 were stipulated, accepting only articles in

Portuguese and English. The keywords used were: therapeutics, therapy, drug therapy; aspergillosis, aspergillosis pathology. The terms were combined randomly using the terms and their synonyms through Boolean operators. The methods used are summarized in the flowchart.

RESULTS

AUTOR/YEAR	TYPE OF STUDY AND GROUP	TREATMENT	RESULTS
Peghin, et al (2015)[5].	Retrospective observational study. 412 lung transplant recipients, over 18 years old, followed for 10 years.	Prophylactic treatment against Aspergillus spp. receiving 25mg of nebulized liposomal amphotericin B 3 times a week for the first 60 days, followed by 25mg once a week between days 60 and 180, and 25mg once every two weeks for the rest of his life.	The total incidence of Aspergillus spp. was 14.3% and invasive aspergillosis was 5.3%. Regarding adverse effects and tolerability, only 12 patients had transient breathing difficulties (1.9%), nausea (0.7%) and dizziness (0.2%).
Wingard, et al (2010)[6].	Randomized, double-blind clinical trial. 600 patients undergoing myeloablative allogeneic hematopoietic cell transplantation preventive treatment for invasive fungal infection.	295 patients received treatment with fluconazole, 400mg, once daily. 305 received voriconazole, 200mg, twice a day, VO. When oral administration is not possible, it was used intravenously with the same doses. Treatment was followed for 100 days, or 180 days in high-risk patients. They were followed up for 1 year.	The average survival rate was 80.6% at 6 months, and 69% at 12 months. After 180 days after transplant, 55 patients developed fungal infection, and after 1 year, 79. Aspergillus was the most frequent pathogen, 47% and 28% on days 180 and 365, respectively. The cumulative incidence of infections was 11.2% and 7.3% for fluconazole and voriconazole, in 180 days; and 13.7% and 12.7% in 365 days.
Schwartz, Reisman & Troke (2011)[7]	Retrospective cohort. 192 patients, of whom 137 had confirmed infection and 55 with clinical suspicion of fungal infection in the central nervous system.	All patients were treated with initial doses of voriconazole 6mg / kg IV twice daily. On day 1 of follow-up, doses were 4 mg / kg IV, every 12 hours. Patients could then switch to 200mg VO twice a day.	120 patients were infected with Aspergillus species and 53 were associated with A. fumigatus. The positive response was presented in 48% of the cases, with an average duration of treatment of 93 days.
Beddley, et al (2013)[8]	Retrospective cohort. 361 transplant patients diagnosed with AI	48 therapies were used in this study, 64.5% of which were monotherapies, with voriconazole the most commonly used antifungal (39.9%), followed by amphotericin B with lipid formulation (33.5%).	The average treatment time after diagnosis was 115 days. Mortality within 6 weeks was similar among patients who initially received monotherapy (30.6%) or combination therapy (28.8%), and lower than in those who received rescue therapy (40.6%).
Egerer, et al. (2012)[9]	Multinational retrospective cohort. 42 patients, of which 3 had confirmed AI and 39 were suspected cases. In addition, 41 had pulmonary AI and 1 tracheal AI.	The standard caspofungin treatment initially adopted was 70 mg on day 1 and 50 mg on day 2. The average duration of treatment was 11 days. Caspofungin monotherapy was observed in 36 patients, 26 of whom received rescue therapy. Those who failed monotherapy, were associated with azoles, polyenes or other antimycotics, chosen according to the medical team.	Caspofungin was adopted as the first line of treatment in 26% of the cases, in the other 74% it was associated with the following drugs: 25 patients used azoles (9 posoconazole, 7 voriconazole and 6 fluconazole); 5 patients used polyenes (2 amphotericin B in colloidal dispersion and 3 liposomal amphotericin B). Among the 42 patients, 69% responded to treatment, and of these, 79% obtained a complete response.
Raad, et al. (2014)[10]	Retrospective cohort. 181 patients with haematological cancer and AI who received primary treatment or rescue therapy with	For analysis purposes, primary and rescue therapy consisted of: 4 mg / kg of voriconazole every 12 hours after 6 mg / kg twice daily on the first day; a loading dose of 70	Patients who used caspofungin were more likely to have used mechanical ventilation than those who used voriconazole (40% vs. 8%). The efficacy and safety of primary caspofungin therapies,

	caspofungin, voriconazole or a combination of both.	mg and then 50 mg for caspofungin; or both.	voriconazole and combination therapy were associated with response rates of 27%, 47% and 55%, respectively.
Maertens, et al (2015)[11]	Phase 3 clinical trial, double-blind, global multicentre, in a comparative group. 527 patients with proven or possible fungal infection caused by Aspergillus spp or another filamentous fungus. Random 1: 1 division between patients.	Those assigned to isavuconazole treatment received 372mg isavuconazone sulfate intravenously three times a day on days 1 and 2, followed by oral or intravenous administration of 200mg isavuconazole once a day, and followed by a corresponding placebo at 12 noon on day 3. Patients assigned to treatment with voriconazole received: 6 mg / kg intravenous twice daily on day 1, followed by 4 mg / kg intravenous twice daily on day 2.	The average mortality from days 1 to 42 was 19% for isavuconazole and 20% for voriconazole. The study achieved its primary objective by demonstrating the non-inferiority of isavuconazole versus voriconazole. The response to treatment is similar between isavuconazole and voriconazole (35% vs. 36%); clinical, mycological and radiological responses at the end of treatment were similar.

DISCUSSION

In our review, there was a prevalence of treatments with voriconazole, used in six of the seven studies reviewed, however it has a higher rate of toxicity and drug interactions than others in the same family, such as fluconazole. The use of voriconazole, however, remains the best choice for treatment, both prophylactic and primary, of Aspergillus spp[6] infection.

In this study, difficulties were observed in maintaining high rates of success in the pharmacological treatment of AI, both due to the long duration of therapy and the adverse effects. In studies with prescription of amphotericin B[6,9,10], regardless of the formulation, they were associated with a higher incidence of adverse effects, the most incident being headache, hypotension, thrombocytopenia and nausea, being described in the three studies that used this medication[5,9, 11]. As for the duration of therapy, studies vary from periods of inclusion, making comparison between them difficult. However, those with longer therapeutic time also showed better results in terms of the study's average survival rate[5,6,11].

None of the studies analyzed reported the correction of immunosuppression, an essential factor in the treatment of both AI and other fungal diseases, which are characteristic of the immunodepression state. This factor can be justified by the characteristics of the studied populations, the majority of whom are candidates for transplants or patients in the postoperative period, therefore, immunosuppression is essential for the effectiveness of the procedure. Because of this, the observed population becomes limited, also restricted to therapeutic evaluation.

In conclusion, studies regarding the treatment of AI are heterogeneous, making it difficult to compare effectively between publications. The limited number of eligible studies did not allow an assessment of the risk of bias between studies. In addition, national production is limited, causing data from other countries to be used and public measures that differ from the Brazilian reality are created from these data. Well-designed controlled, randomized and multicenter clinical trials are needed to adequately address the issue of the usefulness of the approaches used in Brazil. In addition, combined therapies come in many different forms, requiring cumulative evidence to support the use of combined antifungal therapy in AI, as they are still conflicting and of moderate strength.

References

1. FILHO, et al. Aspergilose cerebral em paciente imunocompetente. Arq Neuropsiquiatr. 2005; 63(4):1094-1098.
2. MEDENÇA, et al. Aspergilose pulmonar em paciente imunocompetente e previamente sadio.

Revista da Sociedade Brasileira de Medicina Tropical. 2011; 44(1):124-126

3. ANDES D, et al. Drug-drug interaction associated with mold-active triazoles among hospitalized patients. Antimicrob Agents Chemother. 2016; 60:3398-406. doi: 10.1128/AAC.00054-16
4. NETT J, ANDES D. Antifungal Agents: Spectrum of Activity, Pharmacology, and Clinical Indications. Infect Dis Clin North Am. 2016; 30:51-83.
5. PEGHIN, et al. 10 years of prophylaxis with nebulized liposomal amphotericin B and the changing epidemiology of Aspergillus spp. infection in lung transplantation. Transplant International. 2010 116 (24): 5111–5118. doi: 10.1111/tri.12679.
6. WINGARD, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010. 116(24), 5111–5118. doi:10.1182/blood-2010-02-268151
7. SCHWARTZ, S; REISMAN, A; TROKE, P.F. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection. 2011 Jun;39(3):201-10. doi: 10.1007/s15010-011-0108-6.
8. BADDLEY, et al. Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. Medical Mycology. 2013. 51(2), 128–135. doi:10.3109/13693786.2012.690108
9. EGERER et al.: Caspofungin for treatment of invasive aspergillosis in Germany: results of a pre-planned subanalysis of an international registry. European Journal of Medical Research. 2012, 17:7.
10. RAAD II, et al. Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies. Int J Antimicrob Agents. 2014, http://dx.doi.org/10.1016/j.ijantimicag.2014.08.012.
11. MAERTENS, 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. Feb 20;387(10020):760-9. doi: 10.1016/S0140-6736(15)01159-9.
12. AL-BADRIYEH D, LIEW D, STEWART K, KONG DCM. Cost-effectiveness evaluation of voriconazole versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia. J Antimicrob Chemother [periódico na internet]. 2008 [acesso em 10 jun 2020]; 63(1):197-208