

# Trend of consumption of the antifungal agents fluconazole, voriconazole and itraconazole in an adult ICU from 2009 to 2020 in a university hospital in Salvador-Bahia

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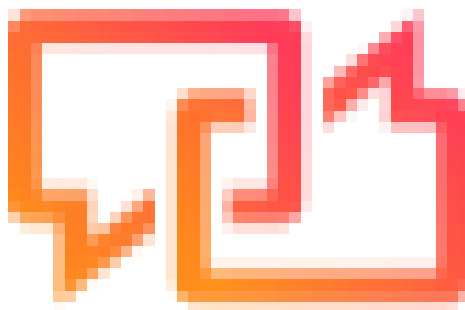
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## Abstract

Invasive fungal infections have a high morbidity and mortality rate in Brazil. In this aspect, antifungal agents used in hospital units represent the only treatment alternative. This work aims to analyze the trend of antifungal consumption in an Intensive Care Unit (ICU) for adults, in a university hospital, in Salvador-Bahia. Retrospective descriptive study, which evaluated the trend of consumption of antifungal agents in the adult ICU based on the consumption records of standardized systemic antifungals that were dispensed to patients over the period and expressed in Defined Daily Dose (DDD)/100 patients -day. The most consumed antifungals, in descending order were: Fluconazole (91.58%;  $p=0.1726$ ) voriconazole (7.2%;  $p=0.9356$ ) and itraconazole (0.45%). Antifungals were widely used in the adult ICU of the university hospital and the growing consumption trend demonstrates that it is necessary to monitor and promote the rational use of these drugs, since the inadequate and/or excessive use, in addition to burdening the health system, can increase fungal resistance to the only agents available to fight fungal infections.



**Trend of consumption of the antifungal agents fluconazole, voriconazole and itraconazole in an adult Intensive Care Unit (ICU) from 2009 to 2020 in a university hospital in Salvador-Bahia**

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## Trend of consumption of the antifungal agents in an adult ICU from 2009 to 2020 in a university hospital.

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## ABSTRACT

**Background.** Invasive fungal infections have a high morbidity and mortality rate in Brazil. In this aspect, the antifungal agents used in hospital units represent a single treatment alternative. **Objectives.** This study aims to analyze the trend in antifungal consumption in an Intensive Care Unit (ICU) for adults, in a university hospital, in Salvador-Bahia. **Methods.** Retrospective descriptive study, which evaluated the trend of consumption of antifungal agents in the adult ICU based on the consumption records of standardized systemic antifungals that were dispensed for patients over the period and expressed in Defined Daily Dose (DDD) / 100 patients-day. The most consumed antifungals, in descending order, were: fluconazole (91.58%;  $p=0.1726$ ) voriconazole (7.2%;  $p=0.9356$ ) and itraconazole (0.45%). **Conclusions** Antifungals were widely used in the adult ICU of the university hospital and the growing consumption trend demonstrates that it is necessary to monitor and promote the rational use of these drugs, since the inadequate and/or excessive use, in addition to burdening the health system, can increase fungal resistance to the only agents available to fight fungal infections

**Keywords:** antifungals; intensive care unit; trend of consumption

What is already known about this subject:

Antifungal drugs are costly to the health system, belong to a small therapeutic class, are used empirically, prophylactically and therapeutically in invasive fungal infections.

What this study adds:

This study brought unprecedented data on the use of the main antifungal drugs used in the adult ICU of a Brazilian university hospital, scarce information in the literature and little discussed in pharmacoepidemiology

## Introduction

Systemic fungal infections represent an emerging problem in current clinical practice. In Brazil, it is rare and difficult to obtain statistical data on the incidence rates of such infections. What is known are the causes that contribute to the increase in this rate. The intensive use of broad-spectrum antibiotics, conditions associated with immunosuppression (transplantation, cancer, chemotherapy treatment, and Acquired Immunodeficiency Syndrome) and currently, in a pandemic context, severe cases of COVID19. All of this has contributed to the increase in invasive fungal infections and to the emergence of outbreaks of infections across the country. It is estimated that nearly 4 million people must have fungal infections in Brazil each year<sup>7</sup>.

One of the main concerns regarding the rational use of medications is related to the use of antibacterials, which often leave antifungal agents in the background of control. However, the increase in resistance to various agents is a global reality and causes difficulties in the therapeutic management of these infections, in addition to contributing to the increase in treatment costs in the public and private health system. In developing countries, few resources are used in actions related to the rational use of antifungals. Furthermore, there are limited data on the use of these agents in hospitals, and the Brazilian scenario is no different<sup>21</sup>.

In this context, antimicrobials are among the groups of drugs most used in the hospital environment, with the aim of reducing nosocomial infection rates, but their excessive use can lead to the emergence of resistant strains. Antifungals in this aspect are highlighted, as they are drugs used in the treatment of fungal infections in many public hospitals<sup>3</sup>.

The study of antifungal consumption in public hospitals is a pharmaco-epidemiological practice, developed and based on studies of drug use. This practice gained uniformity and internationalization with the creation and implementation of the Anatomical-Therapeutic-Chemical classification system and defined daily dose - ATC/DDD (Anatomical Therapeutic Chemical/Defined Daily Dose), a tool that categorizes drugs according to the acting sites. This made it possible to standardize the studies in such a way that without this information previously defined and outlined, it would not be possible to conceive or study the consumption and consumption trend of this type of medicine in health institutions<sup>23, 1</sup>.

Therefore, studies on the use of these drugs become important to draw a profile of their use in different contexts, with a view to promoting rational use and measuring hospital costs. For, a significant increase in use implies higher costs<sup>17, 1</sup>.

Thus, the trend study can be used to understand how drug consumption varies over a given period, in order to manage care practices and protocols, whether in national or international institutions, as well as to make comparisons between hospital units and establish parameter and usage reference<sup>18</sup>.

Therefore, studying, knowing and measuring data on the temporal evolution of antifungal consumption, over 12 years in an adult Intensive Care Unit (ICU), in a University Hospital, in Salvador-Bahia, gains even more importance within the patient safety context and rational use of medications. In this intensive care environment, hospital costs are higher, adverse reactions and drug interactions are potentially more frequent. Therefore, factors such as these, which directly influence patient care, must be monitored with accurate information, to infer measures and strategies, in the management of these drugs, in costs, in the management and monitoring of therapy with a focus on rational use<sup>18, 17, 1</sup>.

Within the pharmacological universe, there are many antifungal agents that are divided according to their origin and can be natural or synthetic. Natural drugs are polyenes and echinocandins; the synthetic ones are represented by the azoles (Fluconazole, Voriconazole and Itraconazole)<sup>10</sup>.

They are drugs for systemic use, which differ according to their chemical structure. Ketoconazole and miconazole belong to the group of imidazoles; fluconazole, itraconazole and voriconazole to the triazole group. The azoles act on the fungal cytochrome P450 enzymes, inhibiting the demethylation of C-14 $\alpha$  from lanosterol, resulting in the accumulation of C-14 $\alpha$  methylsterols and decreasing the concentration of ergosterol. Thus, the cell membrane of the fungus cannot be maintained, due to lower ergosterol production<sup>10, 11, 13</sup>.

Among the Azoles, the highlight is for the triazoles, which is a pharmacological group with an excellent safety profile, used in the treatment of invasive fungal infections. Since 1979, several newer azoles (the triazoles)

have been commercialized <sup>10</sup>.

Fluconazole, one of the most commonly used antifungal agents, was the first antifungal of a new subclass of synthetic triazole antifungals, developed by the Pfizer® laboratory in Sandwich, England, in 1970, being approved by the Food and Drugs Administration (FDA) and introduced in the United States of America (USA), in 1990 under the name of Diflucan<sup>24, 3</sup>.

All azoles are lipophilic and can be administered orally, with satisfactory bioavailability. Itraconazole is highly protein bound and therefore achieves high concentrations in adipose tissue and low concentrations in Cerebrospinal Fluid (CSF). Fluconazole and voriconazole are minimally protein bound (voriconazole > fluconazole) and therefore can reach high concentrations in the CSF. With the exception of fluconazole, which is metabolized and excreted almost unchanged in the urine, all azoles are metabolized by the liver<sup>14</sup>.

Fluconazole has excellent in vitro activity against *Candida albicans* and is also effective against some non-*albicans* species such as *C. parapsilosis*, *C. tropicalis* and *C. glabrata*, although high doses of the drug are required for these species. Itraconazole is a broad-spectrum triazole antifungal agent with antiangiogenic properties, indicated for the treatment of endemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, onychomycosis) and for rescue treatment for aspergillosis. It has variable bioavailability, with significant differences between capsule and solution formulations, as well as fasting versus feeding administration. The efficacy of itraconazole was associated with the drug's serum concentrations and due to its erratic absorption, therapeutic monitoring is recommended<sup>4, 5</sup>.

## MATERIALS AND METHODS

The research was a study of antifungal consumption trends using retrospective data at a University Hospital in Salvador, Bahia, Brazil. The study was carried out in the Intensive Care Unit for adult patients at HUPES, linked to the Federal University of Bahia (UFBA). It is certified as a Teaching Hospital. The HUPES ICU has 20 active beds and receives patients with some type of comorbidity (hypertension, diabetes, heart disease, kidney failure, cancer, autoimmune disease), who have suffered hemodynamic instability and need 24-hour monitoring. The consumption of antifungal agents for the period from January 1, 2009 to December 31, 2020 was measured, totaling 12 years. Information on antifungal consumption was obtained through annual consumption reports, provided by the hospital's Material Management System. These reports were processed based on daily records of drug dispensing, carried out by the Hospital Pharmacy Service and generated month by month, corresponding to the study period, the database was consolidated in Microsoft® Excel® version 2010.

Data regarding the number of patient-days were obtained through hospital reports, prepared by the Hospital Center for Epidemiology (NHE) of HUPES, the sector that prepares epidemiological indicators and disseminates these reports to the entire internal (HUPES intranet) and external community. This information was stored in file folders and cataloged by year. This study included antifungals from the HUPES standardized azole class, namely: fluconazole, itraconazole and voriconazole defined as anti-infectives for systemic use, according to the Anatomical Therapeutic and Chemical (ATC) classification system of drugs, from the WHO Collaborating Center for Drug Statistics Methodology. Topical antifungals, those dispensed outside the study period or to other units (other than the adult general ICU) were excluded, in addition to non-standardized hospital antifungals.

To calculate the presumed consumption of antifungal agents, the annual consumption of each drug was considered, based on the amount dispensed to the adult ICU by the Hospital Pharmacy Service of HUPES, expressed by consumption density in DDD/100 patient-days (pd).

The next step took place through the process of converting the quantity of dispensed units to the quantity in grams of the active ingredient. The absolute consumption of each drug obtained per year was multiplied by the amount of active ingredient, corresponding to each standardized pharmaceutical presentation, the result being expressed in grams.

The DDD value of the fluconazole, voriconazole and itraconazole was obtained from the ATC/DDD index<sup>http-</sup>

ps://www.whocc.no/atc-ddd-index and are respectively (J02AC01) 0.2g, (J02AC03)0.4g and (J02AC02)0.2g. Data were subjected to statistical treatment of descriptive pattern and to obtain relevant results. To calculate the trend, the Mann-Kendall statistical method was used. In this study, a significance level ( $p < 0.05$ ) and a 95% confidence interval (95%CI) were adopted.

## DECLARATION OF ETHICS

The authors confirm that the journal's ethical policies, as noted on the journal's author guidelines page, have been respected. No ethical approval was required, as the research used in its entirety statistical data and hospital indicators to carry out the work.

## RESULTS AND DISCUSSION

Fluconazole, Voriconazole and Itraconazole belong to the class of triazole azoles; however, the first two are the most frequent medications used for fungal infections, due to their safety and tolerability profile, in relation to the imidazole azoles that present greater toxicity.

According to Figure 1, it was possible to observe an initial growth of 75.75% (16.99DDD/100pd to 29.86DDD/100pd) in the consumption of this class, expressed in DDD/100pd. Over the subsequent years, consumption decreased by 48.19% (2011-2016). Based on this oscillation, the consumption of azoles proved to be non-linear and highly variable, with an average of 42.13 DDD/100pd. Vallabhaneni *et al* (2016) evaluated the trend of use of antifungals in intensive care hospitals in the United States of America (USA) (2006-2012) and azoles accounted for 80% of all antifungals used<sup>23</sup>. Unlike the results of Siope *et al* (2020), in the university hospital in France (2009-2018), which azoles accounted for 54% of total consumption<sup>21</sup>. In the survey, the results were different from both previous studies and represented 62.76% of the ATF used.

Data regarding the consumption of azoles in the ICU were also obtained from the studies by<sup>6</sup>. This research found an average of 12.54 DDD/100 pd in the ICU of hospitals in Catalonia, Spain, much lower than that found in this study(42.12DDD/100pd).

It can be seen by looking at Figure 2 that, of this group, itraconazole was the agent with the lowest consumption in DDD/100 pd in the study. It was also observed that in the first four years, there was practically no use of itraconazole in the ICU and, over the period, the growth was small, with the highest consumption being 0.58 DDD/100pd in 2015. Similar data were obtained by Fondevilla (2015) who presented a low density of itraconazole consumption (0.18 DDD/100pd) in relation to other azoles, however, studies by katja *et al* (2005) and other collaborators (2005) that evaluated the density of antifungal consumption in five hospitals in Germany from 2001 to 2003, obtained results (mean 2.5 DDD/100pd) very different from the one found in the Research<sup>25</sup>. According to Figure 2, this drug had a low consumption in the study, compared to the others, for the same period. The trend was up, however little expressive in relation to other antifungals. As the value of  $p=0.400$  (95% CI), it did not present statistically significant relevance.

Itraconazole is recommended for endemic fungal infections such as Histoplasmosis and paracoccidioidomycosis, in addition to being widely used for prophylaxis in transplant patients. This can justify the low consumption, since patients with this profile have a low incidence in the ICU, which shows the low use of the drug.

As for voriconazole, a second-generation triazole, in the first year (2009), there was an increase of 136.7% (0.79 DDD/100pd to 1.87), followed by a very significant reduction of 68.44% (2011). It is noteworthy that in three years (2016-2018), the growth was 46.4%, showing a growing consumption curve. Overall, it grew by 243% in the period studied, going from 0.79 DDD/100pd in 2009 to 2.71 DDD/100pd in 2020. Thus, the trend was upwards, but it was not statistically significant. significant ( $p=0.372$ ). Similar results were obtained in the studies by Lai *et al* (2012), that evaluated the consumption of antifungal agents at the medical center in Taiwan (2000-2010). Voriconazole showed an increasing trend in the 10 years of study with a mean of 5.69 DDD/100 pd and a significant consumption variation ( $p=0.001$ ).

Of all the triazoles, fluconazole was the most consumed drug in the adult ICU, in all years, compared

to voriconazole and itraconazole. The most prominent years were: 2010 (24.7 DDD/100pd); 2011 (29.17 DDD/100pd), 2012 (25.6 DDD/100pd); 2014 (23.78 DDD/100pd) and 2017 (24.31 DDD/100pd) (Table 1)

Such results, referring to the increase in consumption, were consistent with the studies by Hidalgo (2008) carried out in the ICU of a hospital in São Paulo, which assessed the profile of antimicrobial consumption. In this study by Hidalgo, fluconazole showed a statistically significant ( $p=0.001$ ) growth of 3100% (0.2 DDD/100pd to 6.4 DDD/100pd) in the period (1995-2006).

And they were consistent with studies by Oberoi *et al.* (2012) in a tertiary hospital in New Delhi, India, which analyzed the change in the epidemiology of candidemia and the use of antifungals, identified that fluconazole was the most frequently prescribed antifungal and represented an increase of 25 % between 2000-2008 ( $r^2= 0.971$ ,  $p<0.001$ ).

Contrary to the data regarding the consumption trend presented in the studies of Hidalgo (2008), which was high, the trend of triazoles in the research obtained a reduction of 16.7%, showing a statistically significant difference ( $p=0.0163$ ) year after years in consumption<sup>8</sup>. Vallabhaneni *et al.*, (2016) also identified a 20% reduction in fluconazole trend in US hospitals, 2006-2012 ( $p=0.001$ ).

Camargo *et al.* (2010), in a similar study, obtained values of 63.3 DDD/100 pd in the use of fluconazole in an ICU and Salci (2011) found 12.5 DDD/100 pd in 2017, 19.8 DDD/100 pd in 2008 and 22.6 DDD/100pd in 2009, at a large University Hospital in southern Brazil. Studies of susceptibility and consumption of antifungals in intensive care in hospitals in France carried out by [18] obtained a percentage of fluconazole consumption of 84.3% in relation to other antifungals. These evidences, confirmed through the studies and the results presented, support the assertions that fluconazole, despite being a first-generation drug with 21 years of existence on the market, is still routinely used in clinical practice in ICUs around the world.

Some factors justify this expressive number in the consumption of this medication and one of them is the form of use in the ICU. According to Salci (2011), 42.6% of the use of this medication was empirical, against 51.1% therapeutic. Studies have shown that the time taken to start treatment for fungal infections was important for therapeutic success and, especially, for reducing morbidity and mortality.

As for empiricism in treatment, there is a consensus among researchers on the need for this practice, but this form should be reserved for patients at high risk of developing invasive fungal infection. Long exposure to repeated fluconazole therapies is also another important factor that is associated with reduced susceptibility to antifungals as occurs with strains of *C. glabrata* and, which often triggers an excessive and/or inadequate use, thus increasing consumption<sup>14</sup>.

Furthermore, the studies by Salci (2011) also showed that patients treated based on microbiological evidence of fungal infection had longer survival (60%), when compared to individuals treated empirically (50%). Risk factors for developing IFI, such as the use of invasive devices such as central and indwelling venous catheters, in addition to previous therapies are interfering that can contribute to the increase of this medication in the ICU.

Another highlight that may be related to the consumption of fluconazole in the adult ICU is the affordable price of this drug compared to other antifungals. According to the federal government's price panel, the average purchase price of fluconazole is R\$14.26 for intravenous and R\$5.32 for oral therapy. Although the work did not assess the cost of ATF, it is worth emphasizing the importance of these values for health institutions at the time of evaluation and acquisition of the drug<sup>15</sup>.

## CONCLUSION

In general, in hospitals in Brazil there are specific circumstances that interfere in the variation in the consumption of antifungal agents in the ICU, such as the profile of strains' sensitivity to antifungal agents, the prescription practices and the epidemiology of the IFIs, which despite not being included in this study, influence the consumption of these agents. The vast majority of studies greatly reinforce the pattern of consumption of antimicrobials, emphasizing antibacterials, and this limits the number of studies that serve

to counteract the results for systemic antifungal agents. Therefore, observing the variation in the consumption of these drugs helps to better assess the dispensing process and, consequently, their rational use. This pharmacoepidemiology practice, widely used in Europe in drug use studies, it is important not only for the knowledge and monitoring of adverse reactions and consumption, but also for the rationing of hospital expenses. According to the data, fluconazole showed a smaller growth trend in relation to the other studies compared, but it was still considered the most consumed drug in the analyzed period, different from itraconazole, which, with a reduced consumption density, was not very expressive in terms of use in the ICU, and voriconazole presented a growing scale of consumption, which shows its use in fungal infections in this sector.

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