de Cássia Orlandi Sardi et al., Trop Med Surg 2013, 1:5
DOI: 10.4172/2329-9088.1000141

Tropical Medicine & Surgery

Mini Review Open Access

# A Mini Review of *Candida* Species in Hospital Infection: Epidemiology, Virulence Factor and Drugs Resistance and Prophylaxis

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## Abstract

The introduction of more efficient diagnostic methods, new techniques in surgery and transplantation, antibiotics and chemotherapeutics more potent and novel materials for prostheses, catheters and probes significantly increased the life expectancy and quality of life of critically ill patients, on the other hand, hospital-acquired infections emerged as important iatrogenic complications. Invasive infections are a growing problem in public health hospitals in Brazil and worldwide. Among the various etiological agents found in the hospital environment, the genus *Candida* has been the third most frequently isolated pathogen. In general, invasive fungal infections are associated with high morbidity and mortality, difficulties in diagnosis, antimicrobial resistance, length of hospital stay and increased hospital costs. This mini review of the literature describes about epidemiology of hospital infection of *Candida* species, as well as its virulence factors and drugs resistance.

**Keywords:** *Candida* spp.; Epidemiology; Neutropenia; Nosocomial infection; Drug resistance; Virulence factors

## Introduction

Nosocomial infections, also called "hospital-acquired infections", are infections acquired during hospital care which is not present or incubating at admission. Infections occurring more than 48 hours after admission are usually considered nosocomial [1,2]. The transformation of the commensal yeast in important agent of infections in hospital due results of the very progress of medicine as: the emergence of a large number of invasive procedures, breaking barriers of natural protection, intensive use of broad-spectrum antibiotics and the ability to sustain life of people very weak and susceptible to opportunistic microorganisms [3]. Although increasing the number of commercially available antifungal agents in recent years, they are still at a disadvantage when compared to antibacterial drugs. Resistance to antifungal agents has represented a major challenge for the clinic and a major public health problem. Faced with the observed difficulties in the treatment of mycoses in some groups of patients it is recommended, where possible the isolation of the agent responsible for the infection and the determination of minimum inhibitory concentration (MIC) of drugs [4]. The literature on the presence of *Candida* species in hospital infection, their current epidemiology, virulence factors and drug resistance are reviewed in the present report.

## Epidemiology

Infections caused by *Candida* species are termed candidiasis or candidosis. Its spectrum is quite extensive, ranging from the colonization of tissues and mucosal, up to the systemic organ invasion, thus expressing the variety of relations that occur between the host and commensal microorganisms. Candidemia corresponds to the most important opportunistic mycosis in the world, besides being among the leading causes of nosocomial infections. The main risk factors are patients in ICUs, neutropenia related to cancer, major surgery and preterm infants [5]. Nosocomial infections constitute a serious public health problem, and are among the major causes of morbidity and mortality in humans, leading to increased hospitalization time and, consequently, generating high costs for patient treatment [6]. The epidemiological surveillance program in the United States has shown that 5-10% of patients who go into hospitals acquire nosocomial infection [7]. In the United States, the prevalence of fungal infections increased from 6% in 1980 to 10.4% in 1990, according to the National Nosocomial Infections Surveillance of that country. Of these, about 80% were caused by *Candida* species. Moreover, this same surveillance system reported that in the period 1989 to 1999 there were significant increases in the prevalence of infections caused by *C. albicans* and *C. glabrata* [8]. *C. albicans* is the sixth cause of most common nosocomial infection according to studies by CDC [9].

*C. tropicalis* has a high prevalence in cases of candidemia in Brazil and worldwide. Its transmission mechanism is essentially endogenous [10]. It is considered that 50 to 60% of patients colonized with this species develop systemic infections [11], frequently observed in neutropenic patients suffering from diseases such as cancer and hematological disorders or bone marrow recipients [12,13]. However, *C. glabrata* constitutes the fourth leading cause of nosocomial infection fungal yeast in Brazil, although it is reported less frequently in our country than in Europe or the United States and Canada [14-16]. This species is associated with both the cases of candidemia in elderly patients as in the case of candiduria. Moreover, this kind of infection is associated to intrinsic resistance to fluconazole [11].

The clinical manifestations of nosocomial fungal infections may present in various forms: bloodstream infections (fungaemia), Urinary Tract Infection (UTI), surgical wound infections, skin abscesses related to insertion of the catheter, infection of the heart muscle and other

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**Received** June 20, 2013; **Accepted** August 26, 2013; **Published** September 01, 2013

**Citation:** de Cássia Orlandi Sardi J, de Souza Pitangui N, Gullo FP, e Maria José Soares Mendes Giannini AMFA (2013) A Mini Review of *Candida* Species in Hospital Infection: Epidemiology, Virulence Factor and Drugs Resistance and Prophylaxis. Trop Med Surg 1: 141. doi: 10.4172/2329-9088.1000141

[17]. The state of immunosuppression occurs when the integrity of the defense system of the host is broken [18,19]. Polymorphonuclear cell phagocytic system, immunity mediated by T lymphocytes and physico-chemical barriers of the skin and mucous membranes are the primary defenses against fungal infections [20]. Several factors (Intensive Care Unit [ICU], vascular access, transplantation and neutropenia) can produce interference in these defense mechanisms and predispose individuals to mycotic processes [21]. However, the risk of infection is determined by the interaction between epidemiological factors, degree of immunosuppression, and exposure to potentially pathogenic fungi in the hospital environment [22]. The epidemiological pattern of infection observed in the ICU is the result of a combination of factors related to the condition of medical-surgical patients and the degree of iatrogenic intervention [23,24]. Intensive care units represent a point of interface between the more severe patients who receive multiple therapies and aggressive and more resistant pathogens, which are selected by prolonged antimicrobial therapy [25,26]. In the hospital environment, patients in intensive care units are the most vulnerable because they are exactly those whose management is done from intravascular catheters, probes bladder and mechanical ventilation, and other invasive methods, which increases the risk of opportunistic infection [23,27]. Invasive fungal infections are important complications or disseminated in immunocompromised and non-immunocompromised receiving special care in intensive care units [28,29]. The increased incidence of invasive mycosis in ICU patients is associated, in general, with antineoplastic chemotherapy, immunosuppressive therapy, broad-spectrum antibiotics, use of access devices and prostheses, orthopedic and abdominal surgeries complex, extensive burns, degenerative metabolic diseases, prematurity and environmental exposure and length of stay in the unit [30,31].

Catheterization is one of the most important aspects of modern medical practice, especially in the case of patients with neoplasms, surgical patients and transplant recipients and other ICU critical patients that require fluids, blood products, multiple drugs, nutritional support and monitoring [32]. However, such devices expose patients to local, systemic or metastatic infectious complications [33,34]. These infections can result in increased rates of mortality, longer hospital stays and higher medical costs [35-37]. The incidence of catheter-related infection varies considerably with the material composition and device type, length of stay, frequency of manipulation, ability to adhere to the catheter and virulence factors of pathogens and clinical condition of the patients [32,33]. The most serious infections are associated with central venous catheters [38]. These devices are a major source of infection in hospitals, accounting for over 90% of all bloodstream infections [39,40]. The central venous access may be needed for extended periods of time and the catheter can be manipulated several times a day for administration of substances, hemodynamic and to obtain samples for laboratory analysis, thus increasing the possibility of infectious events occur [32,41]. Although showing comparatively lower incidence of infection and more related to the occurrence of phlebitis, peripheral venous catheters have considerable morbidity due to their widespread use [33,42]. Urinary catheter to monitor urine output is also important causes of nosocomial infection, showing percentage of morbidity and significant mortality and hospital costs [25,43]. Colombo and Guimaraes [44] conducted a study involving cases of candiduria as epidemiology, diagnosis and therapy. This infection is an important cause of nosocomial infection, since 20% of hospitalized patients may present candiduria during hospitalization. Among isolates of *Candida* found in urinary infections, the species *C. albicans* is still the most prevalent (50 to 70% of cases), followed by *C. glabrata* (5 to 33%) and other non-*albicans* species such as *C. tropicalis*, *C. parapsilosis, C. krusei, C. lusitaniae and C. guillermondi*. The Table 1 adapted Colombo and Guimaraes [44] show an increased incidence of infections by non-*albicans* species in brazilian studies. In this table we can see the highlighted *C. tropicalis* (4.6 to 52.5%) and *C. glabrata* (7 to 8.8%). The Table 1 shows the significant incidence of non-albicans species in patients with candiduria in U.S. and Brazil hospitals, highlighting the species *C. glabrata* (16% of cases) and *C. tropicalis* (8%).

*Candida* spp. has been isolated in 8% of cases of nosocomial infection of the bloodstream and nearly half of the isolates are *Candida* non-albicans, including *C. glabrata* and *C. krusei* [32,45]. This finding, the emergence of strains resistant to antifungal drugs has been a trend [46-48]. Occasionally, the transplanted organ itself can be a source of infection [49,50]. Although bacterial and viral processes occur more frequently, those caused by fungi are associated with a high mortality rate [51]. The fungal species and the type of infection differ with the transplanted organ and geographic area. However, *Candida* spp. and *Aspergillus* spp. are responsible for over 80% of cases [41,52].

The cytotoxic chemotherapeutic affect the tissues with high replication, including hair, gonads, bone marrow and the epithelial cells of the gastro-intestinal and genito-urinary tract [53]. Mucositis and ulcerative lesions of the oropharynx, esophagus and intestines induced by cytostatic therapy have been related to the pathogenesis of opportunistic fungal infections in patients with oncohematologic colonizing processes [54-56]. It is well established that the use of broad spectrum antibiotics for prevention and treatment of bacterial complications, particularly those acting at high concentrations in the gastro-intestinal tract and which exhibit good activity against gram negative anaerobic bacteria results in a substantial increase in the population endogenous *Candida* spp. [57,58]. This increase, combined with the destruction of the epithelial barrier following antineoplastic chemotherapy has been considered an important factor for the development of endogenous acquisition of candidemia [37,59].

Chang et al. [60] evaluated 152 isolates of candidemia in Medicine Hospital of China in Taiwan, from October 2004 to December 2006. In this study 95% of the isolates belong to the four main species of *Candida*: *C. albicans* (52.6%), *C. glabrata* (8.6%), *C. parapsilosis* (14.5%) and *C. tropicalis* (19.7%). There is a considerable increase of candidemia by non-albicans species. The authors show a high prevalence of *C. parapsilosis* in candidemia in children, but non-albicans species with higher isolation rate in this study was *C. tropicalis,* as described in another study conducted in Brazil [61]. In Brazil, a study evaluating the

| | Etiological Agent | No de isolates | Percentage |
|---|---|---|---|
| **Hospital U.S.** | *Candida albicans* | 446 | 52,0% |
| | *Candida glabrata* | 134 | 16,0% |
| | *Candida tropicalis* | 68 | 8,0% |
| | *Candida parapsilosis* | 35 | 4,0% |
| | *Candida krusei* | 9 | 1,0% |
| | Others | 162 | 19,0% |
| **Hospital Brazil** | *Candida albicans* | 24 | 48,3% |
| | *Candida glabrata* | 5 | 7,9% |
| | *Candida tropicalis* | 19 | 30,7% |
| | *Candida parapsilosis* | 4 | 6,2% |
| | *Candida krusei* | 2 | 4,4% |
| | Others | 1,4 | 2,5% |

Adapted from Colombo and Guimarães [44]

**Table 1:** Etiology of 861 episodes of candiduria sample of hospitals in the U.S. and in hospitals in Brazil (2001-2006).

frequency and distribution of *Candida* species infections in hospitals, showed that *C. albicans* remains the species most important, accounting for 44% of clinical isolates obtained, but the non-*albicans* species have high significance between infections highlighting *C. tropicalis* 21.7% of the isolates, *C. parapsilosis* (14.4%), *C. glabrata* (11.2%) and *C. krusei* (3.5%). The authors show a significant increase in the incidence of *C. glabrata* reaching 23.5% and this increase may be related to risk factors and high prevalence of infection by this species in patients with malignant diseases [61]. Another study conducted in a rural tertiary hospital in India, showed a high incidence of *Candida* spp isolated in different hospital departments. The largest number of positive isolates of *Candida* was in ICU (32.69%), followed by surgical units (25%), department of medicine (19.23%), department of obstetrics (17.31%), department of pediatrics (3.85%) and orthopedic department (1.92%). The isolates were identified as 53.85% *Candida* non-*albicans*, 25% of which were identified as *C. glabrata, C. tropicalis* (21.43%), *C. kefyr* (21.43%) and *C. krusei* (17.58%). A greater awareness of the risk factors and transmission of fungal infections by health care workers helps to prevent nosocomial outbreaks caused by *Candida* spp infections [62].

A review of opportunistic fungal infections in Latin America, was conducted by Nucci et al. [5], reporting significantly the high incidence of *Candida* species infections in hospitals in Brazil, Argentina, Chile, Costa Rica and Mexico. In most studies of the epidemiology of candidemia, the primary agent is *C. albicans*, but two surveys in Argentina in neonates and a survey in Porto Alegre, Brazil, showed a higher incidence of infection with *C. parapsilosis*. The Brazilian Network Candidemia Study, has shown in recent studies that *C. albicans* accounts for 40.9% of all cases of candidemia, followed *C. tropicalis* (20.9%), *C. parapsilosis* (20.5%) and *C. glabrata* (3.5%). The candidemia caused by *C. tropicalis* is associated with cancer, especially in patients with leukemia and neutropenia [5].

Other species such as *C. rugosa* and *C. guilliermondii* are relatively uncommon in the development of candidemia, but Medeiros et al. [62,63] found an outbreak by *C. guillermondii* in a hospital in Brazil, which is very troubling, since these two species have low sensitivity to fluconazole and itraconazole and they are considered resistant.

## Virulence Factors Relevant for Nosocomial Candidemia

Virulence factors are genetically determined, but expressed by microorganisms when subjected to certain conditions [64]. Virulence attributes specialized and developed by *Candida* spp. are directly involved in adhesion and invasion of host tissues, biofilm formation and evasion of the immune system, factors that determine infection [65]. Hematogenous infections caused by *Candida* spp are preceded by colonization of yeast in the patient and in general these are responsible for yeast infection. The main risk factors that lead to candidemia include yeast colonization in catheters and hands of health professionals [66]. A study conducted at a hospital in Paraná, Brazil, evaluated the potential virulence of yeasts isolated from catheters and the hands of professionals in relation to adherence and hydrophobicity. The results indicate that yeasts isolated from catheters exhibited greater virulence potential, since they were more adherent and hydrophobic when compared to yeasts isolated from hands of workers [64]. Moreover, it is clear that numerous *Candida* species secrete proteins to survive in different environments of the host. Recent studies highlight the analysis of the secretome of *C. albicans* as an approach that has enabled a deeper understanding of virulence mechanisms adopted by the fungus to cause infection. It is predicted that the secretome of *C. albicans* includes more than 200 proteins involved in pathways that act in host tissue penetration, nutrient acquisition, tissue destruction, formation of the extracellular matrix of the cell wall remodeling, cell separation and thus biofilm formation [65]. Punctuating potential virulence factors, there is the production of proteases and phospholipases, which correlate directly to the ability of the microorganism to adhere to host cells, a fact that determines the success of colonization and infection. This adhesion is facilitated, since the production of proteases and phospholipases are capable of inducing a dysfunction or even rupture of membranes in host cells [67]. The secretion of these hydrolytic enzymes is a process that requires attention especially in ICU patients with candidemia associated with the use of catheters De Luca et al. [68,69] investigated the activity of proteases and phospholipases in 59 episodes of candidemia documented in the Clinical Institute Humanitas, Milan, Italy, and the results indicate that all strains of C. albicans exhibited phospholipase activity and 48% had proteinase activity. Moreover, the secretion of protease was identified in only one strain of *C. parapsilosis*. In *C. glabrata* no enzyme was detected. Therefore, in systemic infections, C. albicans has higher proteinase activity compared to the species Candida non-albicans. In addition, Candida species interact directly with host cells and this property is associated with the interactive surface adhesins. Regarding membership, physical integration between the yeast cells and the host is a process fully mediated structural integrity of the fungal cell wall and by virtue of its location, and this interaction can occur between proteins and proteins or between proteins and sugars. In general, the adhesins described have so far been identified by far-Western blotting, immunoprecipitation and affinity chromatography [70] and a group that has received considerable attention includes Als family proteins that have been identified as adhesins wall fungal cells that interact with multiple ligands of the host cell [71]. In this context, biofilm formation also involves surface interactions. Some studies have shown that als genes are up-regulated during biofilm formation of *C. albicans* [72-74]. Biofilms directly affect the quality of life and survival of patients with candidemia, since when installed in intravascular catheters, peritoneal dialysis catheters and other implanted devices serve as a reservoir of infectious particles, which then break off from an initial structure and spread occupying niches not previously colonized, creating a metastatic infection in other organs [75].

Two important aspects related to biofilms complicate therapy in systemic infections caused by *Candida* species. Initially, it is important to note that much of the clinical manifestations of candidiasis are uniquely associated with biofilm formation and, in a second aspect, the cells found in the structure of the biofilm exhibit high levels of resistance to most clinically used antifungals [76,77]. In this regard, several studies have focused on the investigation of biofilms of *Candida* species with the goal of finding new therapeutic targets. The latest innovation described in this context involves a study conducted by Srinivasan et al. [76] who developed a device named *C. albicans* biofilm chip (CaBChip), a high-density robotic microarray that consists of *C. albicans* nano-biofilms used to print yeast cells onto a solid substrate. The main advantages of CaBChip include automation, miniaturization, and cost savings in amount of reagents, qualities that make this device ideal for drug discovery using the real high-throughput screening.

## Drugs Resistance

The antifungal drugs may interfere with the synthesis of nucleic acids (pyrimidines), microtubules (griseofulvin), synthesis of ergosterol (azoles, allylamines, thiocarbamates, morpholines), cell membrane integrity (polyene), cell wall synthesis (echinocandins, nicomicinas) and protein synthesis (sodarinas) and other cellular sites [78-80].

The clinical use of systemic antifungal drugs are the most common amphotericin B and its lipid preparations, itraconazole, fluconazole, triazoles (voriconazole, posaconazole and ravuconazole) and derivatives of echinocandins (caspofungin, micafungin and anidulafungin) [81-83]. However, available in Brazilian public hospitals, are only derived polyene (amphotericin B) and azoles (itraconazole and fluconazole) [84]. The resistance can be defined in terms of clinical and microbiological [85,86]. The concept of microbiological resistance includes the resistance primary (or intrinsic) which is present in an organism that without prior exposure to secondary resistance and antifungal drugs (or acquired) which is one developed in response to exposure to these substances [87]. Typically, the secondary resistance is due to phenotypic changes and/or genotypic character stable or transitory [88,89]. In turn, the strength has been defined as clinical progression or persistence of an infection, despite the establishment of appropriate antimicrobial therapy [90]. The occurrence of clinical resistance is associated with host factors, pharmacological factors, iatrogenic factors and fungal factors [91]. Inside of invasive fungal infections, the clinical resistance typically manifests in patients with profound, prolonged neutropenia, patients undergoing multiple therapies and patients with prostheses and catheters [31,92]. The primary resistance to amphotericin B has a limited occurrence. Some emerging pathogens such as *Aspergillus* spp., *C. glabrata*, *C. guilliermondii, C. krusei, C. lusitaniae, Fusarium* spp., *Scedosporium* spp., *Scopulariopsis* spp. and *Trichosporon beigelii*, however, have shown some degree of primary resistance in vitro [93,94]. Likewise, the secondary resistance to polyene drug is hardly prevalent among fungal species. However, some cases of disseminated infection by strains of *C. glabrata, C. krusei* and *C. albicans* that have developed resistance to amphotericin B during the antifungal treatment have been described [90]. A polyene resistance is primarily related to qualitative and quantitative changes of the fungal cell membrane lipids [93]. The biochemical mechanisms of resistance include reduction of ergosterol content without concomitant change in its composition, replacement of sterols with greater affinity for polyene and reorientation of existing sterols, making the connection with the polyene and sterically less favorable thermodynamics [95,96]. Other sources of resistance are increased cell catalase activity that acts minimizing oxidative destruction produced by polyene drugs and decreased content of β-1,3-glucan that stabilizes the fungal cell wall, influencing access of macromolecules, such as amphotericin B the plasma membrane [87,97]. Different molecular mechanisms of resistance to azoles are possible [87,91]. The secondary resistance to these drugs is best described in yeasts [98]. In *Candida* spp. resistance may result from overexpression of pumps that enables elimination, regulating the transport and / or intracellular accumulation of azoles. ABC transporters and carriers MSF are the two major efflux pumps found in these fungi. Overexpression of ABC transporters in *C. albicans* genes coding for CDR1 and CDR2, and mdr1 gene encoding the MSF carriers determine decreased susceptibility to most clinical use and the fluconazole and azole respectively [85,99]. Different molecular mechanisms of resistance to azoles are possible [86,87]. A resistance mechanism is directly related to the structural change of the enzyme lanosterol 14-demethylase (ERG11p) which is the cell site and the azole derivatives key enzyme in the synthesis of ergosterol. Increased expression of the ERG11 gene also appears to contribute to resistance to azole derivatives [100]. The change in the ergosterol biosynthetic pathway is another mechanism associated with resistance. This toxic methylated sterol is formed by blocking ERG11p, being a consequence of the activity of azole drugs on the fungal cell. Erg3 gene mutation removes the toxic effect and is considered a mechanism of resistance [92,99].

Chang et al. [60] studied the susceptibility of 52 isolates of *C. guilliermondii* antifungal caspofungin, anidulafungin and micafungin and the results showed that these antifungals used exhibited good activity (98%) *in vitro* against this species of *Candida*. Studies performed in Korea for Jang et al. [99,101] to determine the fluconazole and voriconazole susceptibility of *Candida* bloodstream isolates (BSIs) using both the CLSI and EUCAST methods, demonstrated of the 341 BSIs of 3 common *Candida* species (i.e., *C. albicans, C. tropicalis*, and *C. parapsilosis*), presented 0.3% to 1.5% of isolates categorized as fluconazole and voriconazole resistant according to the CLSI and EUCAST.

Antifungal resistance of *Candida* species is a clinical problem in the management of diseases caused by these pathogens. Studies performed for Eddouzi et al. [100,102] identified from a collection of 423 clinical samples taken from Tunisian hospitals two clinical Candida species (*Candida albicans* JEY355 and *Candida tropicalis* JEY162) with decreased susceptibility to azoles and polyenes. For JEY355, the fluconazole (FLC) MIC was 8 μg/ml. Azole resistances in *C. albicans* JEY355 was mainly caused by overexpression of a multidrug efflux pump of the major facilitator superfamily, Mdr1. The regulator of Mdr1, MRR1, contained a yet-unknown gain-of-function mutation (V877F) causing MDR1 overexpression. *C. tropicalis* JEY162 isolate demonstrated cross-resistance between FLC (MIC>128 μg/ml), voriconazole (MIC>16 μg/ml), and amphotericin B (MIC>32 μg/ml). Sterol analysis using gas chromatography-mass spectrometry revealed that ergosterol was undetectable in JEY162 and that it accumulated 14α-methyl fecosterol, thus indicating a perturbation in the function of at least two main ergosterol biosynthesis proteins (Erg11 and Erg3). Sequence analyses of *C. tropicalis* ERG11 (CtERG11) and CtERG3 from JEY162 revealed a deletion of 132 nucleotides and a single amino acid substitution (S258F), respectively. The authors conclusion, in addition to identify to identifying a novel MRR1 mutation in *C. albicans,* constitutes the first report on a clinical *C. tropicalis* with defective activity of sterol 14α-demethylase and sterol α-(5,6)-desaturase leading to azole-polyene cross-resistance. Table 2 shows the mechanisms of resistance of clinical isolates of *Candida albicans* from HIV-positive patients to fluconazole and itraconazole. In this work, Cataldo and Petrosillo [103], which describe a review of antifungal susceptibility testing of *Candida* and their clinical break points.

## Prophylaxis in Nosocomial Infection

Health professionals can act as vectors of disease, disseminating new infections among patients if professionals do not use preventive strategies to reduce rates of disease transmission [103]. It is important to underscore that, beyond prophylaxis with antifungal agents, standard measures to prevent nosocomial infections should always be applied both for their efficacy and for their low cost. Because transmission of *Candida* could occur via the hands of health care workers, especially during the care of catheters, all hospitals need to improve their adherence to hand hygiene. Also, extremely important is adherence

| N° isolates (*Candida albicans*) | Molecular change |
|---|---|
| 1 | None (WT) |
| 3 | Increase in MDR1 mRNA |
| 4 | Mutation *ERG11* gene, loss of hetezygosity in *ERG11*, increase in *ERG11* mRNA |
| 2 | Increase in CDR mRNA |

Adapted from Pfaller and Diekema [103]

**Table 2:** Azoles resistance mechanisms in isolates of Candida albicans from an HIV-infected patient with recurrent oropharyngeal candidiasis.

to current recommendations for placement and care of central venous catheters. Finally, the correct use of antibiotics is another important component of candidemia prevention that would lead to a decrease in economic and ecological costs.

## Conclusion

Several studies have shown increased resistance of isolates of species *Candida*, as well as increased morbidity and mortality caused by this pathogen in hospitalized individuals, thus it is necessary to prevent infection with this pathogen.

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