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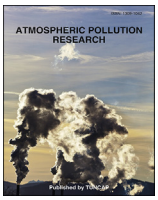

Original article

# Investigation of fungal volatile organic compounds in hospital air

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ABSTRACT

Fungal growth within the structure of buildings or in ventilation filters generates "hidden contamination", which cannot be detected only through visual inspection. At the beginning of development, the fungi release fungal volatile organic compounds (FVOCs) into the atmosphere, which can originate from metabolic pathways or from the enzymatic degradation of materials. This study analyzed the air quality of a public referral hospital in Fortaleza, Ceará, Brazil in terms of FVOCs, to establish ways to improve methods of monitoring and control of specific sectors in the hospital. For that, we created and validated a protocol for detection of FVOCs, using GC/MS, while fungal samples were identified by analysis of macro and micromorphology. In total, 48 samples (60.5% positive) were analyzed for FVOCs; 7 were detected in at least one of the sectors analyzed, with 2-heptanone (179.5 μg/m$^3$) and 2-methyl-1-propanol (121.5 μg/m$^3$) as the most abundant. With respect to fungal findings, 24 samples were analyzed, with a high number of colony-forming units per cubic meter (CFU/m$^3$) observed in all sectors. The airborne fungal spectrum revealed the existence of 19 genera, composed predominantly by hyaline filamentous deuteromycetes. Analysis with periodic monitoring is still needed to allow improvement in the data quality. Also, further discussion on the subject in the academic and legislative environment is needed to contribute to the systematic study of aerobiology.



## 1. Introduction

Monitoring the air quality and its biomarkers (fungi) in hospitals is increasingly important because of the growing number of patients with acquired or induced immunosuppression, due to cancer treatment, transplantation of bone marrow or solid organs, acquired immunodeficiency virus infection or prolonged administration of corticosteroids, which make patients vulnerable to opportunistic fungal infections (Moretti, 2007; Munoz et al., 2015).

According to the literature, in developed countries the overall prevalence of nosocomial infections in intensive care units (ICUs) in newborns varies from 8.4 to 26%, while developing countries, such as Brazil, have rates between 18.9 and 57.7%. The reasons for such high percentages are poor working conditions, insufficient numbers of health professionals and improper infrastructure (Pinheiro et al., 2009).

Simple habits, such as hand washing, use of personal protective items and compliance with aseptic procedures, as well as the strict control of the air quality, can avoid some opportunistic fungal infections, as these measures block the transmission of microorganisms.

The presence of hyaline filamentous and dematiaceous fungi in hospital environments must be considered, since they may be responsible for several infections in immunocompromised patients (Munoz et al., 2015). In the group of hyaline filamentous fungi, the genus *Aspergillus*, especially the species *Aspergillus fumigatus*, is one of the opportunistic agents most frequently cited in the literature, acting particularly in bone marrow transplant and neutropenic patients (Lang-Yona et al., 2016). Inhalation of fungal particles is the most common transmission route and aspergillosis outbreaks are commonly associated with remodeling and construction projects within and near hospitals (Diniz-Martins et al., 2005).

In this context, hospitals are environments that require close environmental monitoring, broken down by specific areas, to identify possible sources of contamination/dissemination and

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etiologic agents (Diniz-Martins et al., 2005). According to Li and Kuo (1992), indoor bioaerosols are considered a major cause of respiratory problems, causing the absence of students at school and employees at work, or low productivity in hospitals and other occupational environments (Sousa et al., 2011; Pantoja et al., 2012).

The literature indicates that current methods to monitor air quality have a number of drawbacks, such as slow count of colony-forming units and results that often do not relate to the actual environmental situation (Bastos, 2005). Therefore, more accurate methods to characterize the fungal composition in the air are necessary. Recent protocols aiming to analyze microbial volatile organic compounds (MVOCs) in samples with possible fungal contamination are fast and highly sensitive.

VOCs are defined as organic compounds, found in gaseous or vapor state, that can be measured by analytical methods (Tucker, 2004). A portion of VOCs found in the domestic environment comes from outdoor air. However VOCs levels can be higher indoors than outdoor, due to the fact that internal sources may be prevalent, especially in new buildings where materials exhibit higher initial rates of emission, decreasing with time. Factors such as season, temperature and relative humidity are also likely to alter concentrations of VOCs in the air (Wang et al., 2007).

Detection of MVOCs or, specifically, of fungal volatile organic compounds (FVOCs) in samples air, is an indication that microbial growth is occurring. These compounds can cause headaches, nasal irritation, dizziness, fatigue and nausea in humans (Wålinder et al., 2008; Nurmatov et al., 2013). For example, Kim et al. (2007) found an association between respiratory symptoms and MVOC concentration inside Swedish public schools.

Polizzi et al. (2012) described a broader influence of fungal volatiles in buildings, for instance in relation to the sick-building-syndrome, where analogous volatile organic compounds play a peculiar role in jeopardizing health. Similar studies have been carried out focusing on different genera of fungi (e.g. *Trichoderma* sp., *Aspergillus* sp., *Fusarium* sp.), as discussed by Lancker et al. (2008), Polizzi et al. (2009, 2011).

Therefore, examination and characterization of typical fungal distribution in a particular environment can be useful to identify associations between domestic fungal sensitization, clinical diagnosis and prevention of seasonal allergic diseases (Pei-Chin et al., 2000). Moreover, such studies contribute to the analysis of ecological relationships in the environment. Some researchers are particularly interested in determining the presence of FVOCs as markers of the contamination of environments (Rosch et al., 2014). In addition, fungal microbiota varies with location and season. The variation of environmental characteristics in regions makes it important to conduct national and international systematic studies to check the dynamics of fungal microbiota.

In this context and highlighting the lack of findings in the national literature, this study aimed to analyze the air quality based on FVOCs, to enhance the monitoring and control of sectors in a tertiary referral hospital in Fortaleza, and also to improve the systematic study of aerobiology.

## 2. Material and methods

### 2.1. Research typology

This study is explanatory, of the experimental (Gil, 2007), quantitative and qualitative type, as well as exploratory, applying the hypothetico-deductive method.

### 2.2. Ethical aspects

The project was approved by the hospital ethics committee.

### 2.3. Selection of the hospital sectors

Samples were collected from sectors of one of the largest public hospitals in the state of Ceará, located in the capital city, Fortaleza.

Four specific sectors were chosen elected in the hospital, since according to Hess-Kosa (2002), the collection sites should be indicated in advance, and such sites should be framed in one or more categories: (1) place where the worst case of indoor air quality (IAQ) is noticed; (2) areas with greater representation in size and occupation; and (3) special concern sites. In addition to these aspects, two types of air microbiota were considered: in closed and open environments, and also the type of ventilation, whether artificial (air conditioning) or natural (Table 1). Humans were present in all sectors during the collections.

### 2.4. Sample collection

Samples were collected during the two seasons that predominate in the state of Ceará, the dry season (September, October and November 2014) and rainy season (April, May and June 2015). Rainfall data were provided by the Ceará Foundation for Meteorology and Water Resources (FUNCEME).

Air samples for FVOC analysis were collected in duplicate in each of the selected sectors, by air suction with the aid of an active sampling pump, adapted for a flow range of 80–100 mL/min (USEPA, 1999b), for 1 h, using specific cartridges (Brand 226-01 SKC-ANASORB CSC), as recommended by Harper (2000). The system was mounted at a height equivalent to the area of human breath and away from the walls (Schleibinger et al., 2008; Wålinder et al., 2008; Araki et al., 2009; Sousa et al., 2011).

The samples were analyzed by gas chromatography/mass spectrometry (GC/MS), performed within 6 h after the collection in order to minimize the risk of interference. Ten external standards were used for monitoring: seven alcohols (2-methyl-1-propanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 3-octanol, l-octen-3-ol, 1-pentanol and 2-pentanol) and three ketones (2-hexanone, 2-heptanone and 3-octanone).

The analytic parameters in GC/MS were built from the analysis performance: a DB-5 ms column was used (non-polar, length 30 m, film thickness 0.5 mm, diameter 0.25 mm), with a temperature program from 35 °C (7 min), increase of 20 °C $min^{-1}$–75 °C, increase of 10 °C $min^{-1}$–125 °C (2 min). Helium (column flow 0.9 ml/min) was used as carrier gas. The FVOCs were identified by their mass spectra at an interface temperature of 250 °C, scanning range of 45 ± 300 m/z (USEPA, 1999a, 1999b) and according to the studies of Araki et al. (2009), Fiedler et al. (2001), Demyttenaere et al. (2004), Quadros (2008), Schleibinger et al. (2008) and Schuchardt and Kruse (2009).

For the analysis of fungi, the samples were collected using the passive sedimentation method in 150 mm diameter Petri dishes containing potato dextrose agar medium (Himedia®, India). The

**Table 1**
Selection criteria of the collection sites considering the categories suggested by Hess-Kosa (2002), the two types of air microbiota and the type of ventilation, at a public tertiary referral hospital in the city of Fortaleza, Ceará, Brazil.

| Specific sectors | Type of ventilation | Air microbiota |
|---|---|---|
| Adult Intensive Care Unit[c] | Artificial (air conditioning) | Closed |
| Transplant Ward[b,c] | | |
| Emergency Reception[b] | | |
| Elective Reception[a,b] | | |

[a] Place where the worst case of indoor air quality (IAQ) was noted.
[b] Areas with greater representation in size and occupation.
[c] Special concern sites.

dishes were exposed to each of the environments for 1 h, positioned 1.5 m above the floor, roughly the human respiration height (Pei-Chin et al., 2000). They were then sealed and sent to the microbiology laboratory at State University of Ceará.

### 2.5. Fungal isolation and identification

The samples were then incubated at 24–28 °C for 14 days. After colony counting, a triage based on macroscopic characteristics was performed to isolate all possible genera in each Petri dish. Chosen colonies were subcultured in tubes with potato dextrose agar (Himedia®, India), to purify the colonies and enhance the identification. Filamentous fungi were identified by macroscopic and microscopic examination of the fungal colonies' characteristics, with the aid of identification keys (Rainer et al., 2000). Yeasts were identified according to their morphological characteristics, biochemical profile and growth in differential culture media (Hoog et al., 2000).

### 2.6. Data analysis

The study was conducted by descriptive statistical analysis, using statistical programs such as Oracle® and Fitopac2®. For all tests, the significance level of 5% ($p < 0.05$) was chosen.

Data were organized into arrays of presence/absence of FVOCs and genera/species of fungi for each analyzed sector, as well as for the other variables (type of ventilation, collection period and climatic data).

The average fungal colony-forming units (CFUs) per cubic meter ($CFU/m^3$) was calculated according to the following definitions and formula, suggested by Bogomolova and Kirtsideli (2009):

$$N = 5a \times 10^4 (bt)^{-1} \quad (A.1)$$

Where:

N = $CFU/m^3$ of air per environment;
a = number of colonies per Petri dish;
b = surface area of the Petri dish (in $cm^2$);
t = exposure time (in minutes).

## 3. Results and discussion

### 3.1. FVOCs

A total of 48 samples (60.5% positive) were analyzed for FVOCs. Seven were detected in at least one of the sectors analyzed, with 2-heptanone (179.5 $\mu g/m^3$) and 2-methyl-1-propanol (121.5 $\mu g/m^3$) being the most abundant. 2-heptanone has already been described by Rudnicka et al. (2010) as commonly emitted from human tissues and fluids (e.g., blood, urine, breath, skin), while 2-methyl-1-propanol was also observed by Rosch et al. (2014), with maximum concentration of 57.49 $\mu g/m^3$. Such data are not in line with our findings, since the average was 121.5 $\mu g/m^3$, having a maximum observed concentration of 161 $\mu g/m^3$ coming from the Transplant Ward in May 2015.

The other FVOCs appeared in lower concentrations, with averages for 1-pentanol of 24.5 $\mu g/m^3$, 1-onten-3-ol of 20 $\mu g/m^3$, 3-methyl-1-butanol of 17 $\mu g/m^3$, 3-octanol of 15.5 $\mu g/m^3$ and 2-methyl-1-butanol of 9 $\mu g/m^3$. Despite the low concentrations of these compounds, proper attention should be given to their presence, since Wålinder et al. (2008) reported minor irritation of eye, nose and throat in human volunteers exposed to 10 $\mu g/m^3$ of volatilized 1-octen-3-ol for 2 h, whereas in this study the concentration of 1-octen-3-ol was double that reported by them.

The compounds not detected were 3-octanone, 2-hexanone and 2-propanol. The other FVOCs and their distribution by sector are described in Fig. 1.

To reinforce the analysis of these data, we plotted a dendrogram of similarity between the presence of FVOCs and the sectors analyzed, using the Bray–Curtis dissimilarity index (Fig. 2). The main finding was the same FVOC composition between the Intensive Care Unit and the Transplant Ward, so the managers of the nosocomial infection committees can implement similar control measures for both sectors.

### 3.2. Fungal findings

All the samples analyzed for fungi (24) were positive, with a high number of colony-forming units per cubic meter in all sectors, especially in Emergency Reception (monthly average of 1308 $CFU/m^3$), followed by Transplant Ward (average of 1086 $CFU/m^3$), Elective Reception (average of 877.5 $CFU/m^3$) and Intensive Care Unit (average of 833.5 $CFU/m^3$).

The average figures presented above are not in accordance with the regulations currently in force issued by Brazil's National Sanitary Surveillance Agency (Resolution 176 of 2003, containing technical guidance on reference standards of indoor air quality, in environments with artificial climate for public and collective use), along with Resolution 9 of 2003, which establishes the maximum value for microbiological contamination by fungi of 750 $CFU/m^3$.

To explain this unconformity, some situations can be mentioned, such as the fact that hospitals have sectors that are propitious to the rapid evolution and spread of fungi, especially in the reception areas, which have significant rates of pollutants and high turnover rates of people, besides facing difficulty in maintaining air filtration systems (Bastos, 2005).

Of particular concern is the finding that the Transplant Ward was the second most bio-contaminated environment, since this means immunosuppressed patients are subjected to poor air quality that can cause nosocomial infection. This finding should be analyzed by a nosocomial infection committee. In this environment, the spread of fungal propagules may be linked to human activities, environmental conditions, and special aspects such as ventilation, temperature, relative air humidity, as well as the presence of dust, dirt and other types of organic substrates, which

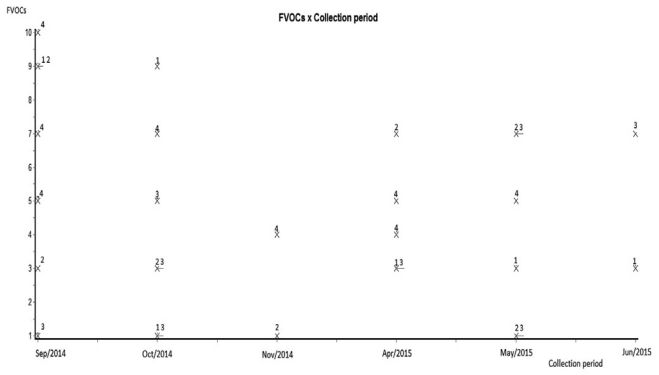


**Fig. 1.** Scatter plot of FVOCs by month of collection (x-axis) and monitored standards of FVOCs (y-axis). The sectors analyzed are represented numerically scattered throughout the chart. Legend: Collectoni month (1-September, 2-October, 3-November, 4-April, 5-May, 6-June). External standards monitored (1-(2-methyl-1-propanol), 2-(2-propanol), 3-(3-methyl-1-butanol), 4-(2-methyl-1-butanol), 5-(1-pentanol), 6-(2-hexanone), 7-(2-heptanone), 8-(3-octanone), 9-(l-octen-3-ol) and 10-(3-octanol)). Hospital sectors (1-Intensive Care Unit, 2-Transplant Ward, 3-Elective Reception, 4-Emergency Reception).

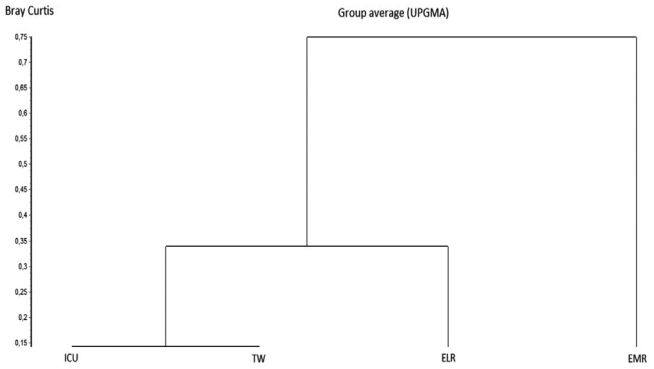


**Fig. 2.** Dendrogram of similarity between the presence of FVOCs and the sectors analyzed, using the Bray–Curtis dissimilarity index, where 0 means that the two sites have the same composition (that is, they share all the species). Legend: ICU (Intensive Care Unit), TW (Transplant Ward), ELR (Elective Reception), EMR (Emergency Reception).

can increase fungal growth (Diniz-Martins et al., 2005; Moretti, 2007).

The airborne fungal spectrum was composed of 19 genera, predominantly hyaline filamentous deuteromycetes, especially the genus *Aspergillus*, of which six species were identified (*A. flavus*, *A. niger*, *A. niveus*, *A. oryzae*, *A. terreus*, *Aspergillus* sp.). Other genera detected were *Acremonium* sp., *Chrysonilia* sp., *Fusarium* sp., *Paecilomyces* sp., *Penicillium* sp., *Scytalidium* sp., *Scopulariopsis* sp. and *Trichoderma* sp.

The zygomycetes present in the samples belonged to the genera *Rhizopus* sp. (present in all sectors except ICU) and *Mucor* sp. (present in the Transplant Ward and Elective Reception), which are important agents of opportunistic infections. They are characterized by having non-septate mycelium (coenocytic hyphae) and by being mainly associated with diabetic ketoacidosis, neutropenia and malignant hematology, posing high risk for newborns and patients with trauma (Diniz-Martins et al., 2005; Munoz et al., 2015).

In this study, yeasts of the genera *Candida* sp., *Trichosporon* sp. and *Rhodotorula* sp. were also detected (Fig. 3), with particular attention to the genus *Candida*, from which three species were identified (*C. albicans*, *C. parapsilosis* and *C. tropicalis*). Overall, yeasts of the genera *Candida*, *Rhodotorula*, *Cryptococcus* and *Trichosporon* (Pini et al., 2005; Wang et al., 2005) were also found, even though it is not clearly understood how they remain suspended in the air. All the mentioned genera have been described as

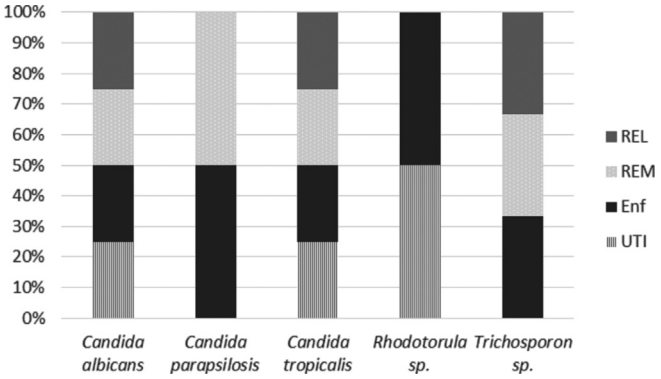


**Fig. 3.** Isolated yeasts in different sectors of a tertiary public hospital, during the dry and rainy seasons in the city of Fortaleza, Ceará, Brazil. Legend: UTI (Intensive Care Unit), ENF (Transplant Ward), REL (Elective Reception), REM (Emergency Reception).

potential human pathogens, especially the genus *Candida*, which is the main causative agent of hospital fungemia (Moretti, 2007; Munoz et al., 2015).

### 3.3. Climatic aspects

The average maximum temperature in the dry season was 31 °C and the average minimum was 25 °C, with rainfall of 0 mm. In turn, in the rainy season the average maximum temperature was 30 °C, the average minimum was 24 °C and rainfall was 184.5 mm.

The incidence of FVOCs was not statistically different between the two seasons ($p > 0.05$). Fungi were more prevalent during the rainy than the dry season (averages of 5426 CFU/m$^3$ and 2782 CFU/m$^3$, respectively), though the data were not statistically significant ($p > 0.05$). The fungal findings corroborate those of Pantoja et al. (2012) in a study of tertiary hospitals in Fortaleza, but they are not similar the findings of Solomon et al. (2006), who reported a direct relationship between the number of fungal colonies and seasonality in the city of New Orleans, USA.

## 4. Conclusions

Overall, both the FVOCs and the fungal findings are relevant and should be taken as a microbiological alert for the control of air quality in hospitals. The differences in fungal concentration in the analysed hospital air sectors are probably related to imbalances of human activities, such as environments with high turnover rate of people. Thus, considering the presence of microorganisms with pathogenic potential and the immune status of patients, monitoring the air is essential to evaluate risks to health.

Climatic data showed the incidence of FVOCs regardless the weather season and the fungal prevalence during the rainy season. Generally, field investigations suggest that fungal distribution, in terms of concentrations and generic compositions, varies among geographic areas, which is also influenced by seasonal environmental, climatic and other factors.

Finally, periodic monitoring is needed to improve the data quality, leading to further discussion on the subject among researchers and regulators, and finally contributing to the systematic study of aerobiology.

## Conflict of interest

No conflict of interest.

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