

The Epidemiology of Candida Infections in Romania

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Abstract

Background: *Candida* infections are the most frequent fungal infections, especially in immunocompromised patients. To this date in Romania there was not performed a national study, although some small previous studies were conducted.

Objectives: To have a general overview on the epidemiology of *Candida* infections in Romania.

Methods: The data were gathered from the registrations of clinics, hospitals and family practitioners. The data were analysed by statistical methods taking into account a significance level of 0.05. The analysis with ANOVA, and test of equality of the average values by Levene test and Fisher's and Games Howell test were performed, dividing the data in subsets with sig. = 0.05.

Results: A number of over 12,000 cases of *Candida* infections were registered in seven years (2008 - 2014), from superficial to invasive, systemic infections. There were 5,072 male patients (41.3%) and 7,264 female patients (57.4%). A number of 5,455 cases were from rural areas (44.2%) and 6,881 from urban areas (55.8%). The infections were divided in 10 categories. Superficial infections such as *Candida* stomatitis were the most frequent in men and babies 0 - 1 and 1 - 4 years old. Vulvo-vaginitis was frequent in the age group of 14 - 25 years, and young adults. Disseminated infections such as urinary, pulmonary and esophageal infections were also registered. The most dangerous were *Candida* meningitis, endocarditis and sepsis, which account for few cases, but are characterized by long hospitalisation periods. Other infections with *Candida* (with other localizations officially registered under this denomination); and the other types of *Candida* infections (they were registered officially under such denomination, because in the official documents were no mention about location, type and so on) represent together about 36% of all infections types. The main strains isolated from patients hospitalized in two hospitals from Bucharest were *Candida albicans* (76.9-90.2%), *C. glabrata* (1.5-13.5%), *C. krusei* (6.7-8, 4%), *C. parapsilopsis* (1.3-1.5%), and the minor strains *C. lusitaniae* (0.7%). There were important differences in strain prevalence from a hospital to another.

Conclusions: The results showed the same aspects of *Candida* infections registered in other countries with some exceptions, some strains could not be identified.

Keywords: *Candida* Yeasts Infections; Epidemiology; Romania

Introduction

From a total of over 600,000 species of fungi, only 600 are human pathogens [1]. The genus *Candida* contains yeasts which multiply by budding forming blastospores. These yeasts were isolated for the first time by Langenbeck in 1839 [2]. Candidiasis is an infection produced by the species [3] *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, which in some conditions become opportunistic

pathogens. It is one of the most common fungal infections. It looks like that Hippocrates [4] observed this infection for the first time. In the 19th century, first scientific observations were performed, thus in 1849 Wilkinson described the vulvovaginal candidiasis, and in 1875 Hausmann described the oral candidiasis and highlighted that the same organisms as in the case of vulvovaginal candidiasis [5] are involved. The genus *Candida* and the strain *Candida albicans* were described by the Hollander Berkhout in 1923 [2]. In 20th century, in the 50s, nystatin, an antifungal drug was developed [6].

There are many *Candida* species, pathogenic or potentially pathogenic for humans, about 90% of the species causing infections are represented by *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei* [2]. Less frequent species are *Candida guilliermondi* [7], *Candida stellatoidea* [8], *Candida dubliniensis* [9], *Candida famata* [0], *Candida lusitaniae* [11], *Candida Africana* [12], *Candida pseudotropicalis* [13], *Candida kefyr* [14], *Candida rugosa* [15] and *Candida lambica* [16]. They are usually part of the human micro flora becoming pathogenic in special conditions such as antibiotic treatment [17] (Shiefer 1997), immunosuppressive therapy [18], cancer [19], hepatic diseases [20], obesity [21], HIV infection [22], trauma [23], long term hospitalisation [24], diabetes [25], alcoholism [16], malignant blood diseases [26], and tuberculosis [27]. Other risk factors are burns [28], acute kidney failure [29], mechanical ventilation [30], venous [31] or urinary catheters [32], haemodialysis [33]. The disseminated candidiasis is a serious problem leading to high mortality mainly in patients with HIV infection or neoplasms [34].

The culture medium is Sabouraud with chloramphenicol, the yeast developing roundish smooth, wet, cream colonies in 24 - 48 hours at 30°C [35].

It represents about 6% of the genital isolates [12]. An important percentage of bacterial vaginosis was obtained by studying a group of 10,000 women (about 190,000 cervix swabs) of about 36.1%, followed by importance by the fungal vaginosis (*Candida*) of 12.6%. The frequency of *Candida* infection is less influenced by the residence of the patients (rural or urban). At the same time in urban area there is an increase infrequency of bacterial infection in vulvovaginitis, of papilloma viruses' infections and the presence of *Trichomonas* [36]. Studies on a large number of patients showed the structure and frequency of *Candida* species. Such a study has shown an unusual strain structure, *Candida albicans* being about 32.4%, and the non *albicans* strains being more frequent than usual, for example, 45% *Candida parapsilopsis* and 22.53% *C. Glabrata* [37]. This is the tendency, an emergence of infections with non-*albicans* strains. Other studies showed that of 350 women (16 - 45 years old) about 23.4% were infected with *Candida*, of which 74.4% - *C. albicans*, 9.11% - *C. glabrata*, 5.6% - *C. tropicalis*, 3.36% - *C. krusei*, *C. parapsilopsis* and *C. guilliermondii* 2.2% each [38].

The classical pattern is, with some possible exceptions, *C. albicans* as the most frequent, followed by the *Candida non-albicans* strains. Studies have shown that there is an increase in frequency of *Candida non-albicans* in those types of infections. In most cases *C. albicans* strains are isolated, but there is an increase in the presence of other species, such as *C. tropicalis*, *C. glabrata* and *C. Kefyr* [39]. In many studied cases about 70% are *Candida* species other than *albicans*, among them being some azoles resistant strains. Two scientists [40], performed a study regarding the structure of *Candida* in vaginal colonisation, identifying in vaginal swabs *C. albicans* (61.5%), *C. glabrata* (17.9%), *C. tropicalis* (7.7%), *C. stellatoidea* (5.1%), *C. parapsilopsis* (2.6%); the frequency in pregnant women was different from the control (non-pregnant women): *C. albicans* (73.7%), *C. glabrata* (7.7%), *C. tropicalis* (1.4%), *C. stellatoidea* (11.3%). Studies on vaginal microbiota revealed the fact that in the case of candidiasis the associated microbiota is more diverse and complex than scientists initially thought [41].

Some dermatologists [42] showed that fungi attack mainly the immunocompromised persons and the risk factors are as we shown previously, infection with HIV, medullar or other organs transplant, autoimmune diseases, cancer and haematological diseases. Studying the tendencies of *Candida* infections in the world, the authors placed, according to their frequency, on second place, in America, *C. glabrata*, but in Europe this species is not so frequent, instead this place being occupied by *C. parapsilopsis* in systemic infections.

In Japan, in 30 years only 3,287 cases of candidiasis (dermato-mycoses) were registered [43], and in 2011, about 378 *Candida* superficial and 46 cases of vaginal infections [44]. In Russia there were about 3 millions of patients suffering of mycoses in 2011 [45]. Other data were obtained in Europe – in Hungary there were 2,193 cases at 100,000 inhabitants, in Ukraine, a number of 893,579 women with recurrent vaginal candidosis [46] was estimated. In the Czech Republic were estimated 152,840 women suffering of this infection and 526 cases of candidemia and 79 cases of peritonitis [47] were registered. In Belgium the incidence of candidemia is estimated at 5 cases at 100,000 inhabitants. At the same time, in this country 174,760 women with recurrent vaginal candidosis were registered. About 6% of the women with recurrent *Candida* vaginitis are aged between 15 and 50 years [48].

In a Venezuelan region, the fungal infections were monitored during a 10-year period [49]. Candidosis was about 28.4%, with *C. albicans* and *C. parapsilosis* presence in about 80% of cases, and the other species, *C. guilliermondii*, *C. krusei* in small percentages.

In Africa, Nigeria, over one million women with recurrent vaginal candidosis [50] 253,000 cases of oral candidosis and 144,000 cases of *Candida* esophagitis were registered.

Materials and Methods

Candida infections in Romania were monitored, the data being provided by Romanian Health Ministry, by the Direction of Medical Statistics. The data were statistically analysed in order to establish the incidence of all types of infections with *Candida* strains and their incidence in different groups of population, depending on provenience area, age and gender.

The descriptive statistics with averages dispersion, average of standard deviation, square of standard deviation, means, minimum and maximum values. The analysis of variance (ANOVA) is the method of analysis of the differences between means of the groups and between groups and subgroups. The Levene test evaluates the equality of the variants for a variable calculated for 2 or many groups. The incidence of every infection type was statistical analysed. The sigma was 0.05.

F test (Fisher test) is an inferential statistical test for comparison of the statistical method used for the data sets and estimation of the method for the investigated population. Test Welch is used for verifying the hypothesis if two populations have equal means and unequal variants. Brown-Forsythe test is an inferential statistic test for equality of variants in a group. Games-Howell test for unequal variants is taking into account the unequal dimensions of the groups in study. Subsets were constituted in order to find easier statistical correlations.

In the database offered by the Romanian Ministry of Health, *Candida* infections are divided in several categories: 1. Stomatitis produced by *Candida*; 2. Pulmonary candidiasis; 3. Candidiasis of the skin and nails; 4. Vulvovaginal candidiasis; 5. Other urogenital infections with *Candida*; 6. Endocarditis with *Candida*; 7. Sepsis produced by *Candida*; 8. *Candida* esophagitis; 9. Other infections with *Candida* (officially registered under this denomination); 10. Other types of *Candida* infections (they were registered officially under such denomination, because in the official documents were no mention about location, type and so on).

Results and Discussions

1. The situation was presented by group of age, gender, categories of infections, and place of residence of the patients. Generally, there is a prominent incidence of the fungal infections in the group from 0 - 1 years of age and the group over 20 years of age.
2. The data obtained by the public health services from all the country from 2008 - 2012 (and some available data from 2013 - 2014) revealed a total number of 12,336 cases (approximately 1,762 cases/year) of *Candida* infections (2008 - 2,354 cases; in 2009 - 2,002 cases; in 2010 - 1,673 cases; in 2011 - 1,695 cases; in 2012 - 1,205 cases, in 2013 - 1,642 cases and in 2014 - 1,765). There were 5,072 male patients (41.3%) and 7,264 female patients (57.4%). A number of 5,455 cases from rural areas (44.2%) and 6,881 from urban areas (55.8%) were reported. The different infection types vary in frequency and number of cases (Figure 1).
3. The first data regarding age, gender and residence were expressed as cases on 100,000 inhabitants. The calculations showed an ascendant trend from 158.96 (2008) to 329.07 (average values) in 2014.
4. The frequency of this infection is higher in women than in men (ex: 2014 428.76/100,000/women inhabitants and 202.40 cases – average/100,000/men inhabitants). There are some infections that are related to the gender of the patients (Figure 2), significant results being available (as vulvovaginitis with *Candida*).

5. In urban areas a higher number of infections were registered (ex: 2014 319.12/100,000 inhabitants) than in rural areas (ex: 2014 232.77 at 100 000 inhabitants). It seems that the high density of people in urban areas favours the human contacts and the occurrence of infections. The general situation of fungal infections with *Candida* is shown in figure 3 highlighting the difference between the patient residence in urban or rural areas.
6. Regarding the age of the patients, the incidence of *Candida* infections was more important in children under the age of 1 year and according to other data, in children 0 - 4 years old, and higher in women (ex: 2014, 687.19/100,000 inhabitants) than men (ex: 2014, 550.08/100,000 inhabitants). There are important variation and case number upon the age of the patient (Figure 4).

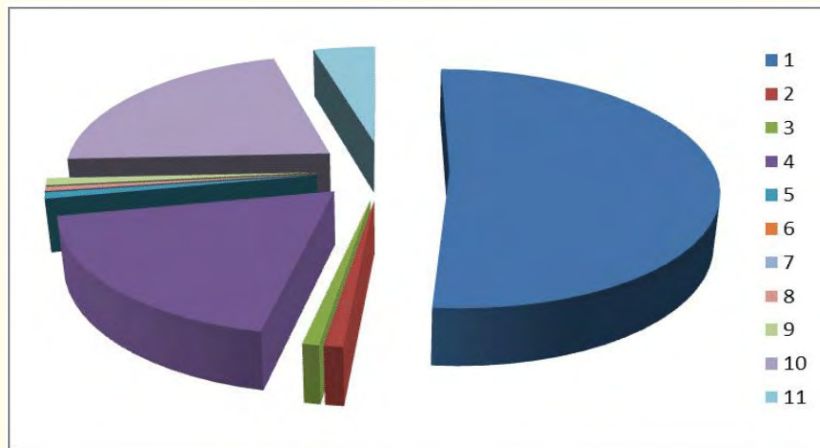


Figure 1: The view of number of cases of different categories of infection.
 Legend: 1. Candidal stomatitis; 2. Pulmonary candidiasis; 3. Skin and nails candidiasis; 4. Vulvo-vaginal candidiasis; 5. Other Candida infection in urogenital area; 6. Candidal endocarditis; 7. Sepsis; 8. Esofagitis with Candida; 9. Other infections with Candida; 10. Other types of Candida infections (without any explanation attached).

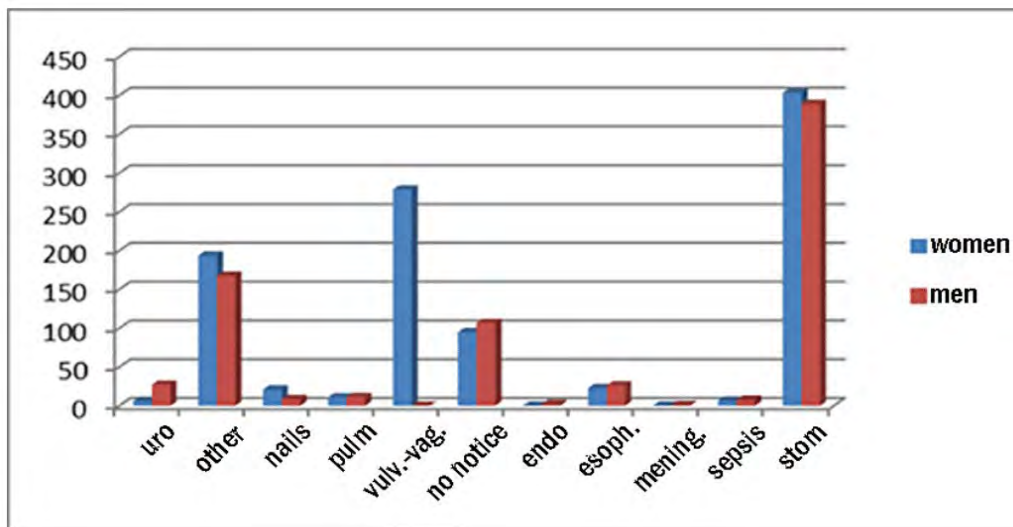


Figure 2: The incidence of Candida infections and sex of patients.
 Legend: 1. Candidal stomatitis; 2. Pulmonary candidiasis; 3. Skin and nails candidiasis; 4. Vulvo-vaginal candidiasis; 5. Other Candida infection in uro-genital area; 6. Candidal endocarditis; 7. Sepsis; 8. Esofagitis with Candida; 9. Other infections with Candida; 10. Other types of Candida infections (without any explanation attached).

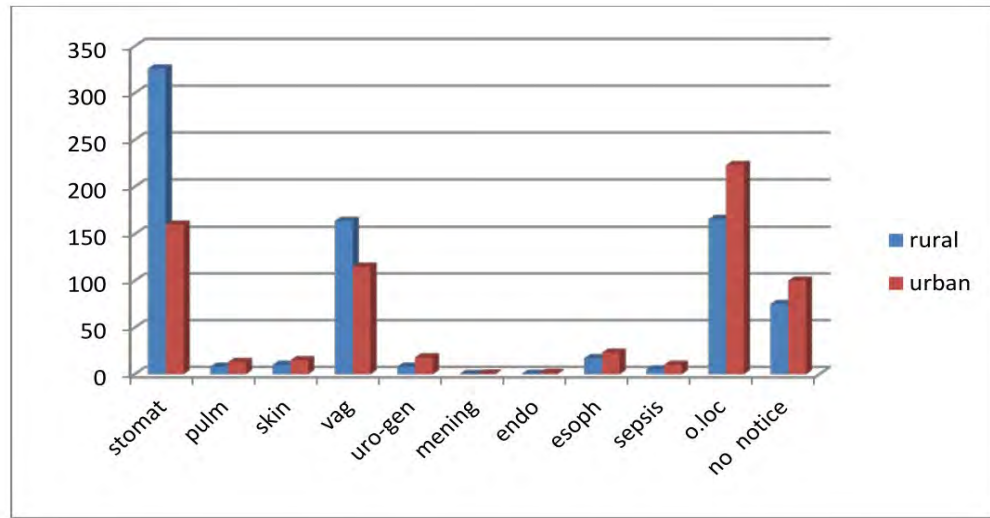


Figure 3: The different Candida infections and residence of patients.
 Legend: 1. Stomat: Stomatitis with Candida; 2. pulm: Pulmonary candidiasis; 3. Skin and nails candidiasis; 4. vag: Vulvo-vaginal candidiasis; 5. Uro-gen: Other Candida infection in uro-genital area; 6. endo: Candidal endocarditis; 7. Sepsis; 8. esoph: Esophagitis with Candida; 9. o. loc: Other infections with Candida; 10. Other type of Candida infections (without any explanation attached).

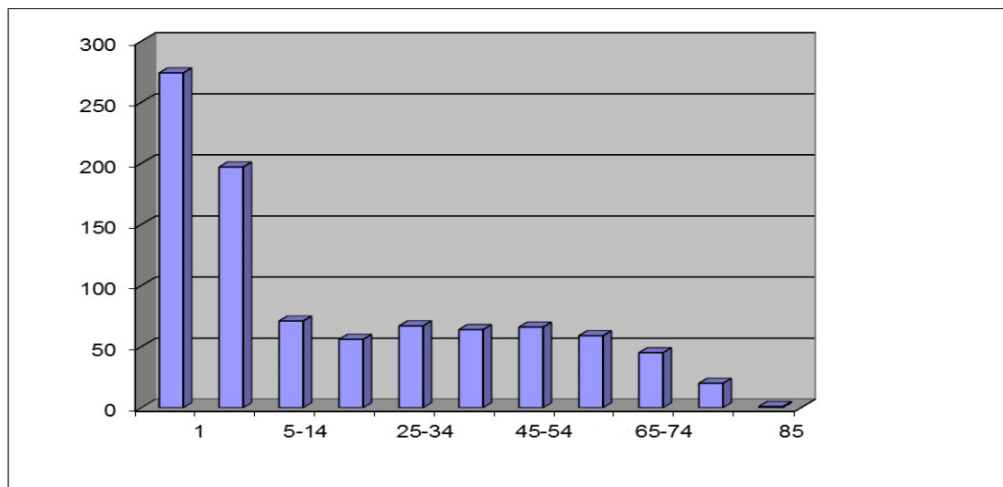


Figure 4: The overview of infections with Candida and age groups of patients (0 - 1; 5 - 14 years old: 14 - 24; 25 - 34; 35 - 44; 45 - 54; 55 - 64; 65 - 74; 75 - 84; Over 85 years old).

The situation of various types of infections is the following:

Candida stomatitis was a very common infection with many cases, being identified in a number of 5,632 patients (805/year in average), 2,280 from the country side (40.4%; average 124.8/year) and 3,352 from the urban area (59.8%, 478.8 average per year) which represents 41.55% from the total number of infections. The infection is very frequent in babies with a great number of cases registered under the age of 1 year. The cases of stomatitis were more frequent in men than women.

A type of infection, very frequent in women, is the vulvovaginitis. We registered 1,956 cases on all the investigated period (average 279/year), a percentage of 15.6% from the total number of *Candida* infections. It was more frequent in young women 14 - 24 years old and 25 - 34 years old.

Candidiasis of other urogenital infections represents an average of 1.46% from *Candida* infections, a total number of 188 cases, majority in men - 155 patients (83.3%) and 33 women (16.7%), 57 cases from rural areas (30, 6%). An important number of cases are in persons over 55 years old.

Regarding the candidiasis of skin and nails, there were registered 174 cases (24.8 cases average/year) of which 52 men, 122 women, 68 patients from rural area and 106 from urban area. Infection manifests especially in women over 45 years old.

Esophagitis with *Candida* - we registered 277 cases of which 149 men (53.8%) and 128 women (46.2%); 117 patients from rural areas (42.2%), and 160 from urban area (57.8%): Infection is most frequent in urban areas, in men.

Other infections with *Candida* (2,726 cases) and other types of *Candida* infections (1,125 cases) represent together about 36% of all the infections. Both groups showed equilibrium between the sexes and residence areas and a high number of hospitalisation days. It seems that a long hospitalisation may be caused by other serious and chronic diseases, *Candida* infections being secondary or occurring during the hospital stay, in persons with reduced immunity.

With respect to pulmonary candidiasis, in all the seven years of the study only 144 cases were registered, being an equilibrated ratio in men (74 cases) and women (70 cases). Of all the patients, 38.9% were from rural areas (56 cases). The patients recorded a high number of hospitalisation days, being especially persons over 50 years old.

The following categories of infections had only few cases but were very serious disseminated infections in immunosuppressed patients.

Candida meningitis is one of the most dangerous, only 6 cases being reported, 4 men and 2 women in 2008-2014.

Endocarditis with *Candida* - we registered only 11 cases, 10 men and 1 woman, patients with long hospital stay.

Sepsis with *Candida* - we registered a number of 99 cases (14.1/year average), 52 men (52.5%) and 47 women. There were 32 patients from rural areas (32%). Of all patients, 16 deceased (16.2%). All the infections were associated with long hospital stay.

Statistics

The Levine test showed that dispersions are not equal (Sig = 0.05). The Fisher test resulting from ANOVA showed significant differences between mean numbers of cases registered in case of almost two types of infections. The tests Welch and Brown-Forsythe were performed for more information, but even here the means number of cases significantly differ almost for two groups. In this case, a non-parametric test was preferred - Games-Howell, based on multiple comparisons between groups and were divided in homogenous subsets.

Statistically, the yearly average number of cases are differing significantly for other infections with *Candida* and other types of *Candida* infections from rest of the types of infections, the last have similarities with a subset which contains sepsis, pulmonary candidiasis, esophagitis, candidiasis of skin and nails and urogenital candidiasis. These results are not a surprise, taking into account the types of analysed infections and the ways these categories were recorded.

The number of cases of stomatitis differs significantly, most of infections occur in men and in early years of life. For other types of infections, the division in homogeneous subsets is not clearly defined.

Some results underline the gender's importance for the interpretation, for example in endocarditis the men are more affected than women, and also in other urogenital infections with *Candida*. For candidiasis of skin and nails the women are more sensitive to these infections.

Conclusions

The epidemiology of *Candida* infections in Romania follows the general tendencies from other countries. The different infections are practically in the same general trend. The present analysis is the first study covering all Romania regarding *Candida* infections. This will support public health authorities and medical personnel to take measures in order to prevent and control the infections, even a more descriptive epidemiological analysis should be performed in the nearest future, in special for the infections not explained in the official documents.

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