Cluster Analysis of Candida infections evolution in urban and rural areas in Romania

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Abstract: -Candida infections are some of the most common fungal infections, which are generally found in persons with weakened or compromised immune systems. In the first part of this paper is analyzed statistically and epidemiologically the spread in the urban and rural environment, in Romania, of Candida infections, these producing great problems especially to the people included in the risk groups. The data collected from Romania from 2008-2014 were investigated. The estimates were made by years, by categories of urban / rural areas, but also by expressing the results as persons (cases) per 100,000 inhabitants, to estimate the real incidence of such infections in Romania. The statistical analysis was performed with the well-defined purpose of observing in which of the environments of origin of the patients (urban or rural) predominate the infections like Candida. The period chosen for the study, although not recent, does not influence the conclusions of the analysis, as the living conditions of the population in urban and rural areas have not evolved significantly in recent years in Romania. In the second part of the paper, through the cluster analysis, the differences between the spread of *Candida* infections from the above mentioned period were analyzed, in the urban and rural areas, using common criteria. Cluster analysis is a multivariate analysis method, which includes algorithms capable of effectively identifying and grouping, in a given set of objects, similar groups in terms of common properties. The analysis was performed using Excel and Matlab software.

*Key-Words: -*Candida, Epidemiology, Urban and rural, Estimations, Cluster.

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1 Introduction

The human body is a complex collection of numerous biological cycles and systems, which in most cases is difficult to fully understand. The body's set of defence mechanisms is such a system, which sometimes cannot protect us, such as *Candida* infection situations. *Candida* yeast infections are some of the most common fungal infections, which are generally found in persons with weakened or compromised immune systems (for example, as a result of cytotoxic or antibiotic treatment). *Candida* genus comprises yeasts that are multiplied by budding and by blastospores formation. *Candida* forms biofilms on the mucosal elements of different body areas: the oral cavity, the vagina, the pharynx, the skin and others. Inside the biofilm, billions of pathogenic microorganisms communicate with each other through an intercellular signalling system called "quorumsensing", which provides them with food, development and resistance to antifungal and antibiotic treatments.

Yang [1] lists the genes responsible for pathogenicity factors in *Candida albicans* and other Candida species by categories: adhesion, hypha formation, proteinase and phospholipase enzymes development, phenotypic transformation from yeast to filamentous fungus. Mayer et al. [2] consider pathogenicity factors: adhesion, tigmotropism, biofilm formation, dimorphism-polymorphism, change in the shape and colour of the colonies, different structural and functional characteristics and particularities. Montazeri and co-authors [3] demonstrate that environmental factors are essential for morphological and physiological changes in this species, including the concentration of substances in the environment, the types of substances and their abundance, as well as the temperature and the contribution of oxygen and microelements that influence the formation to the *Candida* spores. Some studies show that yeast is a diploid eukaryotic organism with a high degree of heterozygosity [4]. *Candida dubliniensis* is not as common as *Candida albicans*, who is otherwise related. This species appeared only in one of the cases [5]. According to

the WHO (W*orld* H*ealth* O*rganization*), fungal diseases are classified in mycosis (included in codes 110–118) and infections with *Candida* are included in code 112. Numerous studies of epidemiology and statistics on infections with *Candida* spread throughout the world. several years and including both healthy persons for the study of the portage of these species, as well as infected persons for the detection of the causes and mechanisms of infection and their spread, as well as establishing ways to reduce the infections and their severity.

The problems generated by this type of infection are not only those related to human health, but also those that affect his standard of living and way of life. The paper analyzed the differences between urban and rural areas of *Candida* infections in Romania, between 2008 and 2014. The epidemiological data were provided by the Medical Statistics Directorate of the Ministry of Health, based on the observations and clinical records and data provided by family physicians. Data were analyzed using Excel software. The epidemiological aspects of Candida infections in Romania are part of the worldwide trend of increasing their frequency and increasing the number of infections with Candida non-albicans strains (species). At the same time, there is an increase in the resistance to antifungal used in therapy currently and here we speak of toothpastes. What's worse is that there are strains that are resistant to several antifungal compounds. Then, for the comparison of several groups, a multivariate analysis was used using the Matlab program. Multivariate analysis (cluster analysis) refers to the methods used to identify groups of similar objects in a set of objects. The data is or can be organized as a table (lines are observations, objects, columns are variables, attributes). The data investigated, collected from all over the country, were from 2008-2014. The period under study, although not recent, will not influence the final conclusions of the statistical analysis.

2 Epidemiological differences in *Candida* genus infections between urban and rural areas

Candida infections are very different in manifestation and appearance, which are divided according to the place of infection and the intensity of the infection. Thus, there is superficial candidiasis, which manifests itself on the mucous membranes (here entering most other types of infection with the *Candida*), and systemic, invasive candidiasis.

Candidiasis is current for everyone, regardless of age and gender. A classification of these by location and type looks like this [6]:

- candidiasis of the oral mucosa: mucus, glossite, stomatitis, and other type oral candidiasis [7];
- skin candidiasis: the Candidal intertrigo [8], perionixis and onixis [9];
- candidiasis of the genital mucosa: candidial balanopostitis [10], candidial vulvo-vaginitis [11];
- chronic muco-cutaneous candidiasis: chronic muco-cutaneous candidiasis of the adult, candidal granuloma [12];
- systemic candidiasis: pulmonary, intestinal, uro-genital and candidiasis septicaemia [13].

A percentage of 43.6% of the population of Romania lives in the rural area. The processing and data analysis shows the situation of these infections (Tab.1).

Table 1.Candidiasisin Romania, patients leaving hospitals

Year 2008	TOTAL	RURAL
TOTAL COUNTRY	2354	974
Stomatitis through Candida	920	328
Pulmonary candidiasis	24	8
Candidiasis skin and nail	37	13
Candidiasis vulva and vagina	306	168
Candidiasis other uro-genital locations	38	9
Meningitis through Candida	1	1
Endocarditis through Candida	4	1
Sepsis through Candida	12	6
Esophagitis through Candida	67	33
Candidiasis with other locations	407	163
Candidiasis, without specifying	538	244

Year 2009	TOTAL	RURAL
TOTAL TARA	2002	928
Stomatitis through Candida	752	322
Pulmonary candidiasis	45	21
Candidiasis skin and nail	45	21
Candidiasis vulva and vagina	439	266
Candidiasis other uro-genital locations	48	16
Endocarditis through Candida	1	0
Sepsis through Candida	18	2
Esophagitis through Candida	52	19
Candidiasis with other locations	424	184
Candidiasis, without specifying	178	77

Year 2010	TOTAL	RURAL
TOTAL COUNTRY	1673	774
Stomatitis through Candida	581	274
Pulmonary candidiasis	10	5
Candidiasis skin and nail	27	10
Candidiasis vulva and vagina	371	201
Candidiasis other uro-genital locations	45	15
Meningitis through Candida	1	1
Sepsis through Candida	20	7
Esophagitis through Candida	34	12
Candidiasis with other locations	450	194
Candidiasis, without specifying	134	55

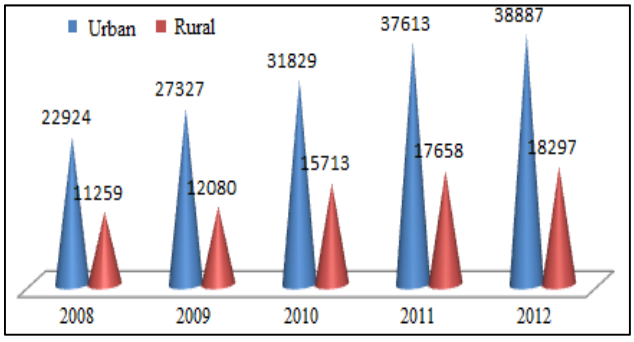
Year 2011	TOTAL	RURAL
TOTAL COUNTRY	1695	736
Stomatitis through Candida	949	392
Pulmonary candidiasis	19	4
Candidiasis skin and nail	26	6
Candidiasis vulva and vagina	160	99
Candidiasis other uro-genital locations	22	5
Meningitis through Candida	2	0
Endocarditis through Candida	2	0
Sepsis through Candida	11	4
Esophagitis through Candida	63	27
Candidiasis with other locations	336	147
Candidiasis, without specifying	105	52

Year 2012	TOTAL	RURAL
TOTAL COUNTRY	1205	537
Stomatitis through Candida	761	336
Pulmonary candidiasis	14	8
Candidiasis skin and nail	13	6
Candidiasis vulva and vagina	118	68
Candidiasis other uro-genital locations	13	5
Meningitis through Candida	1	0
Endocarditis through Candida	3	0
Sepsis through Candida	11	3
Esophagitis through Candida	29	11
Candidiasis with other locations	189	68
Candidiasis, without specifying	53	32

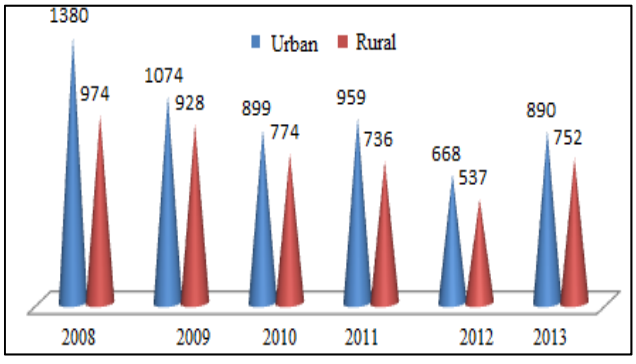
Year 2013	TOTAL	RURAL
TOTAL COUNTRY	1642	752
Stomatitis through Candida	845	335
Pulmonary candidiasis	16	5
Candidiasis skin and nail	14	7
Candidiasis vulva and vagina	305	189
Candidiasis other uro-genital locations	14	5
Meningitis through Candida	0	0
Endocarditis through Candida	0	0
Sepsis through Candida	9	3
Esophagitis through Candida	16	6
Candidiasis with other locations	351	163
Candidiasis, without specifying	72	39

Year 2014	TOTAL	RURAL
TOTAL COUNTRY	1642	752
Stomatitis through Candida	798	321
Pulmonary candidiasis	15	6
Candidiasis skin and nail	12	5
Candidiasis vulva and vagina	265	107
Candidiasis other uro-genital locations	12	7
Meningitis through Candida	0	0
Endocarditis through Candida	1	0
Sepsis through Candida	10	4
Esophagitis through Candida	21	12
Candidiasis with other locations	211	101
Candidiasis, without specifying	63	35

Considering all cases during the investigated period (from the clinical records and from the data provided by the family doctors), the infections with Candida, in Romania, were as follows [14]:
- 63302 cases (12660 / year average), from the data provided by family doctors (Fig.1a), of which 42342 from the urban area (66.8%; average 8468.4 / year) and 20960 in the rural area (33.2%, 4192 / on average);
- 10571 cases (1762 / year average), for patients discharged from the hospital, of which 4701 from the rural area (44.4%; average 783.5 / year) and 5870 in the urban area (55.5%, 978.4 / year average), in 2008
- 2354 cases; in 2009, 2002 cases, in 2010 a number of 1673 cases, in 2011 1695, in 2012, 1205 cases, and in 2013, 1642 (Fig.1b).



a)



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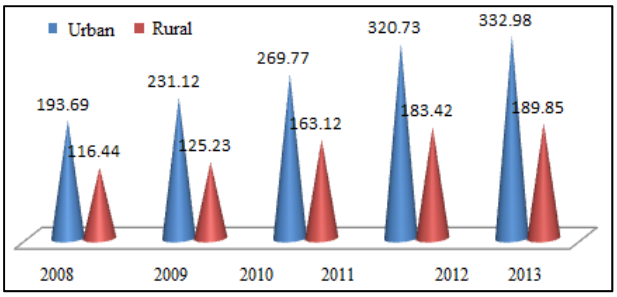


c)

Figure 1.The evolution of the cases of infections with the candidate in Romania during the analyzed period: a) in the situation of patients leaving the hospital; b) patients declared by the family doctor; c) cases per 100,000 inhabitants.

Stomatitis was also in the case of Romania, a very common infection with a large number of cases during the total investigated period, of which there were 4808 cases (801 / year average), for patients leaving the hospital, of which 2821 from the urban area (58.7%; average 471 / year) and 1987 in the rural area (41.3%, 332 / year average) occupying an average percentage of 22.2% of the total *Candida* infections (Fig. 2).

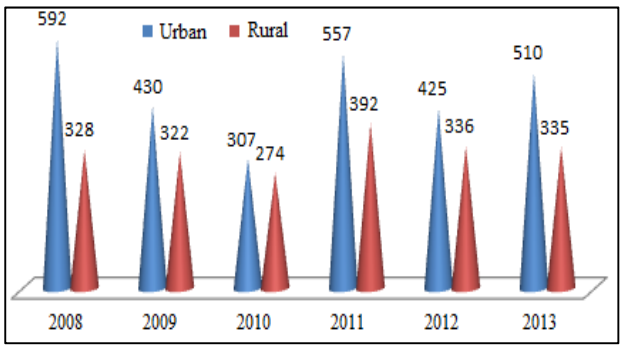


Figure 2.Evolution of cases of *stomatitis* during the investigated period based on observations and clinical records.

Another type of infection spread exclusively to women is vulvo-vaginitis, a number of 1699 cases per total period (average 283 / year), with an average of 16% of total *Candida* infections (Fig. 3).

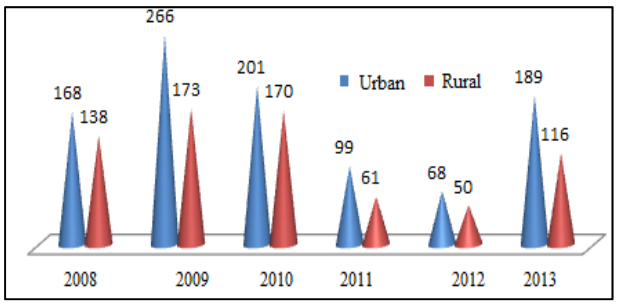


Figure 3.Evolution of *vulvo-vaginitis* cases during the study period based on clinical records.

Skin and nails candidiasis was a total of 162 cases per total study period (27 cases on average per year), of which 63 persons from rural areas and 99 from urban areas (Fig.4).Candidiasis with other locations (2157 cases, Fig.5a) and candidiasis without any specifying (1726 cases, Fig.5b) are two categories that made together an important percentage of the total infections (36.7%).

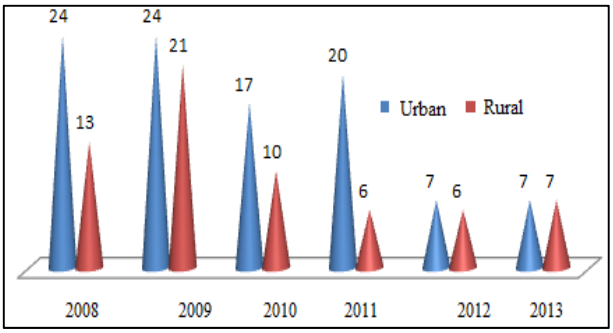
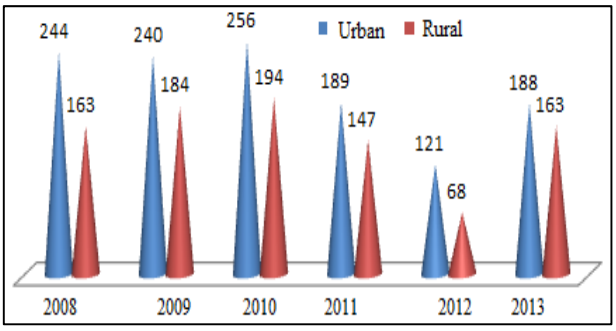


Figure 4.Evolution of cases of skin and nail candidiasis in Romania based on clinical records.

Both groups are noted for a balance in terms of the area of residence, as well as the large number of days of hospitalization. The days of hospitalization seem to come from other serious, chronic illnesses, the infection with *Candida* being secondary or intervening during the hospitalization probably in persons with low immunity.



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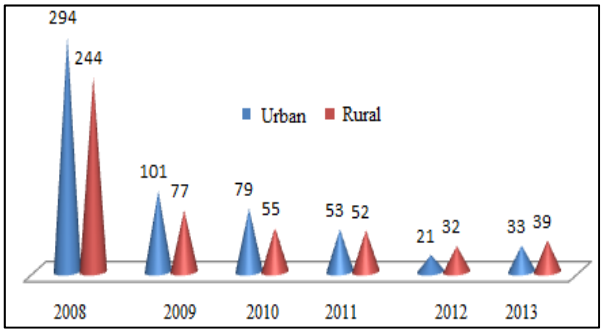


b)

Figure 5.Evolution of cases of infections with the candidate: a) candidiasis with other locations; b) candidiasis without any specifying.

For candidiasis with other uro-genital locations (Fig. 6), which represents on average of only 1.7% of the total infections with *Candida*, a number of 180 cases were registered for the study period from which 55 cases were from the rural area (30.5%).

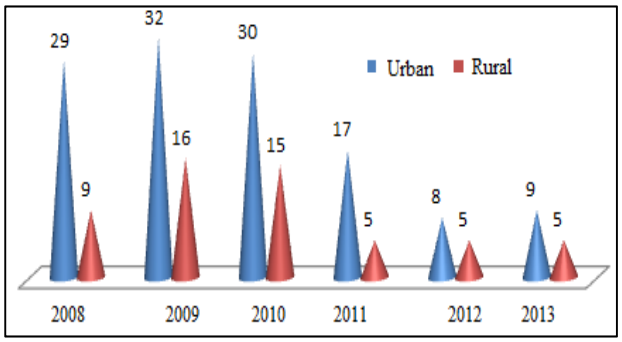


Figure 6.Evolution of cases of candidiasis with other urogenital infections based on clinical registry.

Candida esophagitis is an infection of the lining of the oesophagus. There were 261 cases analyzed in the analyzed period, of which from the rural area, Fig. 7, there were 108 patients (41.3%), from the urban area being more sensitive (153 (58.7%): The infection is more pronounced in the urban environment, male patients from the small age groups or the third age.

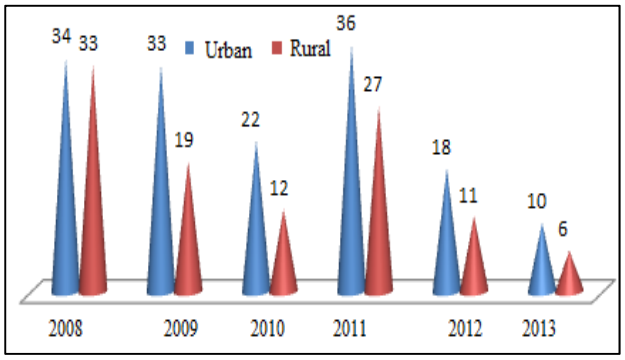


Figure 7.The evolution of esophagitis cases in Romania based on the clinical records.

The following categories of infections, although they have had a small number of cases, are serious, are disseminated infections of some immune compromised or immune depressed patients. Only 128 cases were registered. Of all the patients, 60.1% came from the urban area (77 cases). It was noted that patients had a large number of days of hospitalization and were persons over 50 years.

Sepsis with *Candida* implies immune compromised patients and candidaemia. During the entire investigated period there were 81 cases (13.5 / year on average) from which in rural areas, (Fig. 9), there were 29 patients (35.8%).

Endocarditic with Candida were only 11 cases, of which 10 men and a woman, people with a large number of days of hospitalization, most of them over 35 years old.

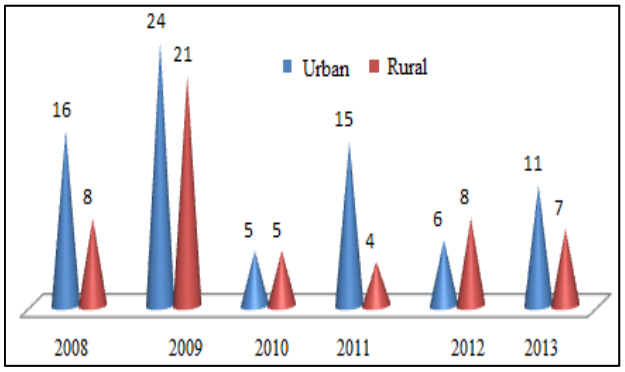


Figure 8.Evolution of cases of candidial pulmonary infections based on clinical records.

All those infections were associated with long hospitals stay

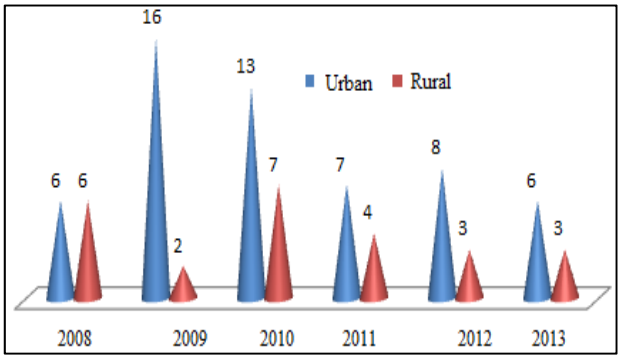


Figure 9.Evolution of cases of Sepsis according of clinical records.

Although the analysis illustrates the incidence of infection and of *Candida* species, what is missing is its presence in the different categories. of patients. These statistics are useful in order to decide on the measures to be taken to prevent and treat these infections according to their prevalence in the population.

The differences consist in the smaller number of cases in rural areas, the influence of the frequency of interpersonal relationships and lifestyle, the type of patients, sex, age, and other parameters on their infections and epidemiology. We do not have data on the correlation with comorbidities and other parameters and local socio-economic factors and this is what we will study in the future.

We will better study the correlation between comorbidities and Candida infections, and the link between their evolution and the social environment.

3 Evolution of *Candida* infections based on Cluster Analysis

By classification is meant the grouping of entities (observations, objects, etc.) into classes (groups) of similar entities. There are essentially two types of automatic classification: predictive (for example, discriminate analysis) and descriptive (for example, cluster analysis).

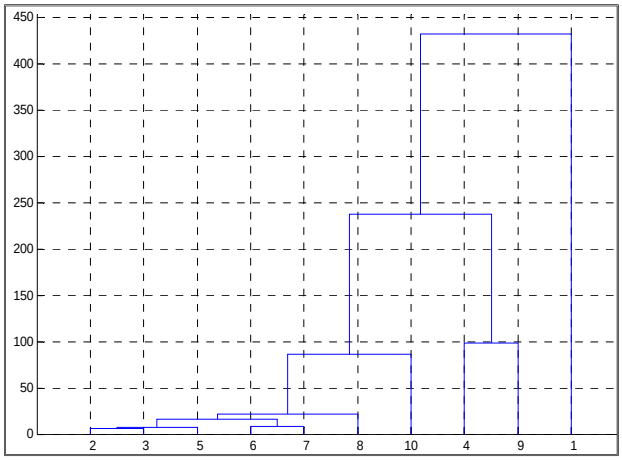
The cluster is a lot of objects (elements) similar to each other and not similar to objects in other classes. The essential problem in determining (identifying) clusters is that of specifying proximity (proximity, similarity) and how it is determined. There are several types of classification algorithms: ascending, (aggregation, synthesis), descending (division) and partitioning algorithms. The first two categories can be combined in the hierarchical classification,

The fundamental algorithm of hierarchical ascending classification assumes that there are the n elements that are classified and, in the first stage, the pair of elements closest to each other is determined and a new element is produced by their aggregation. In the second stage there will be n-1 elements that are classified. Repeat steps 1 and 2 until the set of items to be classified has only one item. There are the usual methods of calculating distances between objects, elements or groups already constituted (the nearest or furthest neighbour method, the average link, the distance from the centres, or the Ward distance).

Choosing a certain distance changes the groups that are formed. As a result of the algorithm the classification tree (dendrogram) is obtained. The usual evaluation procedures are: partition visualization (dendrograms, profiles, projections), quality indicators (*divisive coefficient* - DC and *agglomerative coefficient* - AC), or silhouette indices (*Silhouette*).Procedures that solve classification problems are grouped into analyze – classify, of which K-means clusters and hierarchical cluster are mentioned (for hierarchical classification). a single cluster.

The analyzed data set (Tab. 1) contains the incidence of each species of candidate in the urban area during the period 2009-2014. The following 10 variables are measured: Stomatitis through *Candida* (1), Pulmonary candidiasis (2), Candidiasis of vulva and vagina (3), Candidiasis with other uro-genital locations (4), Meningitis through *Candida* (5), Endocarditis through Candida (6), Sepsis through *Candida* (7), Esophagitis through *Candida* (9), Candidiasis with other locations (9), Candidiasis, without specifying (10). For data processing, a multivariate analysis method was used, namely Cluster analysis. For this, the `pdist` function from Matlab is used [15,16].

In Fig. 10 the data are presented in a graph. From this dendrogramm (Fig. 10a) it can be observed that in urban areas infections 2 (Pulmonary candidiasis) and 3 (Candidiasis of vulva and vagina), 3 and 5 (Candidiasis of other uro-genital locations), 6 (Endocarditis through *Candida*) and 7 (Sepsis through *Candida*) are grouped taking into account the fact they are grouped after the most little differences, of about 1, they importance being about equal in the four years of analysis from importance of the treatment. Of the same importance for physicians are the infections 4 (Candidiasis other uro-genital locations) and 9 (Candidiasis without specifying).



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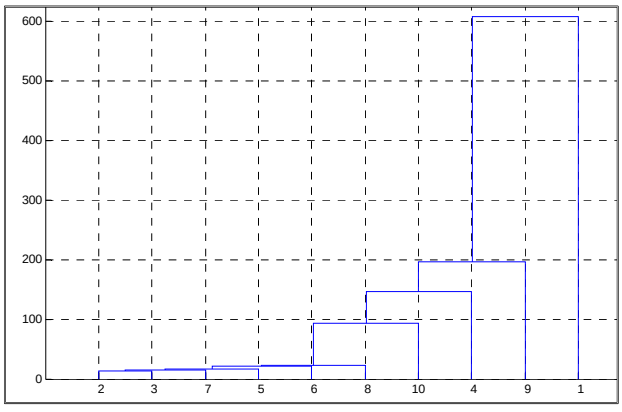
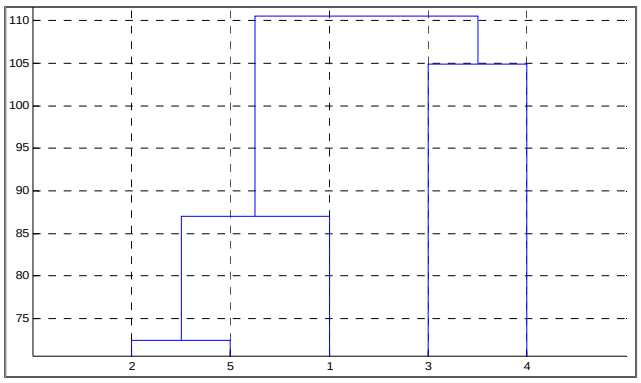


b)

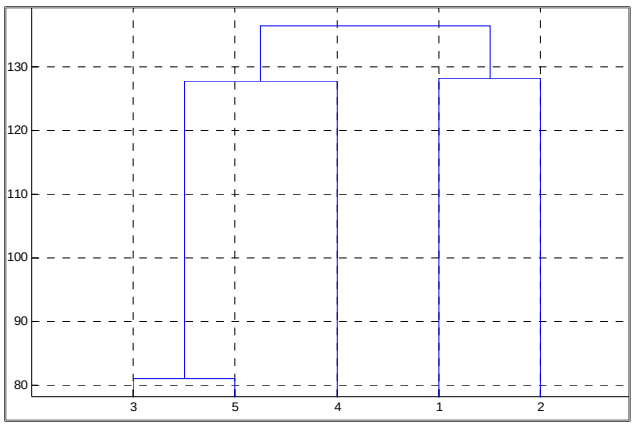
Figure 10.Dendogramm: a) infections with *Candida* in urban area; b) infections with *Candida* in rural areas.

Conversely, considering the period variable, the distance between the data in the tables corresponding to the years 2009 (1) and 2010 (2), respectively, 2009 (1) and 2011 (3) is calculated, and so on, until all the distances between all pairs of data. Information about the Euclidean distance between set 2 and set 3 is returned in a vector, Y

where each element contains the distance between a pair of sets. After the proximity between the groups in the dataset has been calculated, it determines how the objects in the dataset should be grouped into clusters, using the `linkage` function. This function takes over the distance information generated from the distances (`pdist`) and links the pairs of nearby objects in binary clusters (ie, clusters formed by two objects).Then, these newly formed groups are linked to other objects, to create larger groups, until all the objects in the initial data set are linked together in a hierarchical tree. The hierarchical binary tree created by the `linkage` function is easy to understand when is graphically viewed. Figure 11 shows these data sets in a graph.



a)



b)

Figure 11.Dendogram, if it is considered as a variable for a period of time: a) in case of *Candida* infections in the urban area; b) in the case of *Candida* infections in the rural area.

In the figure, the numbers along the horizontal axis represent the indices of the years in the data set, and the links between the years are represented as lines up and down in the form of a U. The height U indicates the distance between the years (for example, the link representing the cluster that contains the years 3 and 4 has a height of 2700).

The connection height represents the distance between the two groups that contain those two objects. This height is known as the *copenetic distance* between the two objects.

One way to measure how well it reflects the function-generated cluster tree is to compare the *copenetic* distances with the original distance data generated by the `pdist`.If the grouping is valid, the connection of the objects in the cluster tree should have a strong correlation with the distances between the objects in the `cophenet` distance vector. The function compares these two sets of values and calculates their correlation, returning a value called the *copenetic correlation coefficient* (*C*). In a narrow sense, the correlation is a measure of the degree of statistical connection between the quantitative variables, the sub-names of *correlation coefficient*. The correlation coefficient measures the degree of connection between the variables. Regarding the fast interpretation of the coefficient we have for $C\epsilon[0; 0.2]$ a very weak correlation, non-existent, for $C\epsilon[0.2; 0.4]$ a weak correlation, for $C\epsilon$ [0.4; 0.6] a reasonable correlation, for $C\epsilon$ [0.6; 0.8] the high correlation, for $C\epsilon[0.8;1]$ a very high correlation, so a very close relationship between the variables.

The closer the value of the correlation coefficient *C* is to 1, the more accurately the clustering solution reflects the data [17]. As a rule, the *copenetic correlation coefficient* is used to compare the agglomeration results of the same data set using different distance calculation methods or clustering algorithms. If the value (close to 0) does not have to be concluded, there is not necessarily a statistical link between the two variables - the link can exist.

One way to determine the natural cluster divisions in a data set is to compare the height of each link in a cluster tree with the height of the neighbouring links. A connection that is about the same height as the links below that there are no distinct divisions between objects united at that level of the hierarchy. These links have a high level of consistency, because the distance between the objects that are joined is about the same as the distances between the objects they contain. On the other hand, a connection whose height differs significantly from the height of the links below, indicates that the objects joined at this level in the cluster tree are much farther from each other than their components when they were joined. It is said that this connection is in contradiction with the links below.

In cluster analysis, inconsistent links may indicate the boundary of a natural division in a data set. The relative coherence of each link in a

hierarchy tree can be quantified and expressed by an inconsistency coefficient (I), which compares the height of a link in a cluster hierarchy to the average height of the links below it. Connections that combine distinct clusters have a high coefficient of inconsistency; the links joining indistinct groups have a low coefficient of inconsistency.

To generate a list of the inconsistency coefficient for each link in the cluster tree, the Matlab `inconsistent` function [18] is used, which compares each link in the cluster hierarchy with adjacent links that are below two levels below it in the cluster hierarchy. This is called the depth of comparison. The objects at the bottom of the cluster tree, called leaf nodes, which have no other objects underneath them, do not have a coefficient of zero inconsistency.

Clusters that unite two leaves also have a coefficient of zero incoherence. For example, the `inconsistent` function is used to calculate the inconsistency values for the links created in the situation analyzed in Fig. 11:

```
I= 72.4155     0    1.0000          0
   79.6991 10.3006 2.0000     0.7071
  104.9333     0    1.0000          0
  100.8170 12.3039 3.0000     0.7898
```

where: column 1 of the matrix represents the average of all link heights included in the calculation, column 2 represents the standard deviation of all the links included in the calculation, column 3 indicates the number of links included in the calculation, and column 4 is the value of the inconsistency coefficient.

According to the analysis, an upward trend of these infections results. The incidence of infections is higher in women than in men. The annual fluctuations do not have a statistically significant significance. Regarding the age of the patients, the incidence of Candida infections was highest in children under one year old or in those aged 0-4 years, according to other estimates, of the female versus the male gender.

The most at risk of complications are children, pregnant women, the elderly, those with chronic medical conditions and those with low immunity. Older age and adjacent conditions increase the risk of complications.

The analysis in the paper confirms that the epidemiological aspects of *Candida* infections in Romania are part of the worldwide trend of increasing their frequency and the increase in the number of infections of the spotted infections (species) of *Candida* non-albicans. *Candida* infections, spread in both rural and urban areas in Romania, pose particular problems to people in risk groups. Treatment for the elimination of *Candida* infections is important, as for some types of *Candida* (*Candida albicans* fungal infection) it has been confirmed to be one of the causes of cancer [19].

The fight against *Candida* yeast infections in Romania should be carried out on several levels, such as: public hygiene measures (to reduce the chances of contamination), educating the population through doctors, internet and media (radio, television, brochures, newspapers), attracting the attention of people in the risk groups (including mothers with young children), research to identify new effective antifungals, new solutions for the care of the immune compromised ones, but also solutions to avoid the intra-hospital infections.

4 Conclusions

Data collected from all over the country from 2008-2014 were investigated. A total of 12,336 cases (average 1,762 cases per year) of Candida infections. There were 5,072 male patients (41.3%) and 7,264 female patients (57.4%). There were 5,455 cases from rural areas (44.2%) and 6,881 from urban areas (55.8%).

Regarding the environment of origin of patients, in urban areas there were more cases (eg 2014 - 319.12 / 100,000 inhabitants) compared to rural areas (eg 2014 - 232.77 per 100,000 inhabitants). We have not identified the reason that led to the registration of these differences. It would be possible that the higher density of urban inhabitants which favors interpersonal contacts, is an explanation.

A significant number of cases of *Candida* infections were investigated and, according to the analysis of the resulting graphs, an upward trend was observed overall, the origin of patients having a role in epidemiology. Thus, in the urban environment there were more cases, and in the rural area fewer. So, as a general conclusion, resulting from the analysis of the data provided, the urban area favours some infections, probably due to the higher density of inhabitants favouring human contacts. This conclusion is perfectly valid in the case of infections with *Candida*, based on the data provided by family doctors, where the percentage is (33.2%) in the rural area. As the rural population in Romania is getting older, it is possible to have some serious *Candida* infections with high severity index. In the cases of infections with the candidate, based on the observations and clinical records, the

percentage (44.4%) of the cases of infections with the candidate in the rural area is approximately with the percentage (43.6%) of the population of Romania living in the rural area.

The analysis of the evolution of *Candida* type infections, carried out in this paper, is useful so that in the future Romania can take proactive measures in the fight against infections, identify the infections as soon as possible and be more effective in implementing the restrictions / treatment. The comparative analysis of the population disease with Candida genus infections in the rural and urban regions of the country becomes all the more important as it can be regarded as a manifestation at national level if we consider reducing the differences between living standards.

Cluster analysis aimed to identify a set of homogeneous groups by grouping elements so as to minimize variation within groups and maximize variation between groups. Variables or cases have been sorted into groups (clusters) so that members of the same cluster have similarities as large as possible, and members of different clusters have weaker similarities.

The authors appreciate that the result of the statistical analysis on the upward trend of cases of Candida infections for the environment of origin of patients can be generalized for countries with a standard of living conditions similar to that in Romania..

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