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CHALLENGES ON INVASIVE FUNGAL INFECTIONS POSSIBLY ASSOCIATED WITH HEALTHCARE

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Abstract: *Background and Aims.* Healthcare associated infections are one of the most frequent events threatening patients' safety worldwide. Invasive fungal infections usually occur in immunosuppressed people. These events raise significant medicolegal issues regarding the responsibility to protect the population from harm. The aim of this study was to reduce the medicolegal implications of the invasive fungal pathology possible associated with healthcare in the context of the complexities of the current medical practice.

Methods. A cross-sectional study was developed in order to evaluate the invasive fungal infections among patients hospitalized in an Infectious Diseases Department between January 2010 and December 2016.

Results. 211,609 patients were hospitalized in an Infectious Diseases Department, between January 2010 and December 2016. Among these subjects we identified 79 cases with IFI (which correspond to a frequency of 37.3 cases per 100,000 population). The most frequent fungal pathogens were Candida spp. (78.16%). The current analysis showed that the factors with a significant influence on IFI mortality included: age ($p = 0.0002$), HIV positive status ($p = 0.0012$), organ failure ($p = 0.0142$), and a low value of hemoglobin ($p < 0.0001$).

Conclusion. Often it is possible and probable that an invasive fungal infection to be associated with healthcare, which is the result of synergic actions of a complex of factors that involved the healthcare providers (healthcare workers), the environment (hospitals or other healthcare associated settings), and the host (immunosuppressed or not). In these conditions medicolegal issues may arise.

Keywords: invasive fungal infections, healthcare associated infections, medicolegal issues

INTRODUCTION

Healthcare associated infections – public health issue

Healthcare associated infections (HAI), known as hospital-acquired infections until the mid-1990s, are those infections acquired during hospitalization, healthcare service unit or health care provided to the patient and are neither present nor incubating as at the time of admission. They are not related to the original disease that brings patients to the hospital [1]. This type of illness also includes occupational infections acquired by the staff [2]. So, these are infections that are acquired and associated with healthcare activities in any given environment. The major implications for public health arise from the great impact upon hospital mortality, length of hospitalization, and costs. The factors that can contribute to this situation include: the lack of qualified human resources, an inadequate physical structure for healthcare services and limited knowledge of HAI control measures [3].

HAI are one of the most frequent events threatening patients' safety worldwide, after adverse drug events and followed by surgical complications [2, 4, 5]. However, because of the lack of data the reliable estimates of the global burden are missing [4].

Hundreds of millions of cases with HAI were identified worldwide each year. The consequences of these infections include a significant mortality and important financial losses for health systems, but also

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come at a high cost for patients and their families: increased length of hospital stays, long-term disability, resistance to antimicrobials, financial costs, and unnecessary deaths. HAI produced 37000 deaths in Europe, and 99000 deaths in the USA. Annual financial losses due to HAI are also high: they were estimated at about €7 billion in Europe (only the direct costs) for 16 million extra days of hospitalization, and at around US$ 6.5 billion in the USA [2].

Healthcare associated infections frequently generate medico-legal issues

Now we are in an era of an increasing disquiet with patient safety in the healthcare system. All these events raise significant medico-legal issues regarding responsibility, disclosure of information to patients and reporting to decision making factors, regulatory authorities, professional colleges, government agencies and others parts that have the authority and the duty to protect the population from harm [5].

There are a lot of contributing factors that influence the occurrence of a HAI and this way has an impact on patient safety: crowded Emergency Units, more acutely ill patients, shorter hospitalization periods, lots of visitors (everyone carrying some pathogens on them), staff as a source of pathogenic agents, inadequate conditions for hand washing, and appropriate isolation [6]. These factors are grouped in three categories: the risk factors related to patient includes: the severity of illness or injury for which the patient was admitted, the function and capacity of the immune status during the visit, and duration of hospitalization in a clinical setting. Organizational risk factors were: cleanliness of hospital and treatment setting in general, cleanliness of water systems, cleanliness of building surfaces, sterility of medical devices, the filtration of the heating, ventilation, and air conditioning (HVAC) system, and concentration of patients. The last category includes the iatrogenic risk factors, which means the care with which the healthcare workers and other care providers perform: the individual activities of physicians and staff (the frequency with which hands are washed, use of antibiotics, and level of care during invasive procedures) [7].

Invasive fungal infections – increasing frequency due to a continue increasing in the number of immunosuppressed people

Fungi are a complex group of microorganisms living independently in the environment or being part of the normal flora of human or animals. These agents can contribute to the occurrence of mild superficial infections to severe invasive infections, which can threat the patient life. IFIs are defined as the infections in which the pathogenic agent penetrates and establishes at the level of the deep tissues while maintaining a long-lasting pathological process [8].

According to Invasive Fungal Infections Cooperative Group (IFICG) of European Organization for Research and Treatment for Cancer (EORTC) and Mycology Study Group (MSG) of National Institute of Allergy and Infectious Diseases (NIAID) an IFI can be also defined as the presence of fungal components as mold or yeast in deep issues, identified using the biopsy or using the needle aspirates and confirmed on culture and histo-pathological examination. By definition an IFI diagnostic is supported by the presence of the host factors and clinical elements and is confirmed on culture [8].

These kinds of infections occur frequently in immunosuppressed subjects.

The following pathogenic agents can cause IFI: yeasts (Candida spp, Cryptococcus spp) and moulds (Aspergillus spp, Fusarium spp, Scedosporium prolificans, Mucor, Rhizopus and Rhizomucor Absidia). Among these fungi Candida spp, Cryptococcus spp, Aspergillus spp, Mucor and Rhizopus are saprophytes in soil and environment, commensally in human and animals or could be attributed to the immunosuppression caused by infections (especially AIDS), cancer or metabolic disorders (diabetes mellitus) [8].

The link between the invasive fungal infections and healthcare associated infections – possible and probable

The frequency of IFIs registered an important increase as a result of the advances in healthcare available for the immunosuppressed individuals [9]. The overall burden of healthcare associated fungal infections is significant. The limitations of the available diagnostic tests used to establish an early diagnosis of fungal infection and the emergence of new fungal pathogens that are resistant to antifungal agents place the prevention of fungal HAIs among the very sensitive healthcare issues [10].

The most significant risk factors are: neutropenia (less than 500 cells/mL for a period longer than 10 days), hematological malignancies, bone marrow transplant, prolonged corticotherapy (more than 4 weeks), long duration of stay in invasive care units (more than 7

days), chemotherapy, HIV infection, invasive medical procedures and devices, solid organ transplantation, the use of immunomodulatory agents, severe burns, major surgery, and malnutrition [9, 11]. There are also IFI which occurs in immunocompetent patients without the symptoms of an immunocompromised condition [9]. As the result of these risk factor IFI are very common within the hospital settings and will continue to raise [10-12].

The most important nosocomial fungal pathogens include: Candida spp., Aspergillus spp., Mucorales, Fusarium spp., and other molds (Scedosporium spp.). The diagnosis of these infections is very difficult and the mortality due to IFI associated to healthcare is high in spite of the antifungal treatment [11].

The aim of this study was to reduce the medico-legal implications of the invasive fungal pathology possible associated with healthcare in the context of the complexities of the current medical practice.

OBJECTIVES

The objectives of our study were: the assessment of the frequency of invasive fungal infections; discrimination between an invasive fungal infection associated with healthcare or/ and an infection which occurred independent of the nosocomial risk; the identification of arguments that support or exclude medico-legal issues in hospitalized patients with invasive fungal infections; the assessment of prognostic factors in patients with fungal infections possibly associated with healthcare.

MATERIALS AND METHODS

A cross-sectional study was developed in order to evaluate the invasive fungal infections among patients hospitalized in an Infectious Diseases Department between January 2010 and December 2015. For the identification of invasive fungal infections we have used the EORTC guidelines. The data regarding the demographic characteristics of the cases identified with IFI and the factors with an impact on mortality among these cases were retrospectively collected. Then the information were included in an Excel database that have been further processed using Excel and Epi Info 7 programs. The variables under the study were analyzed and the values within the statistical confidence interval (CI) 95% ($p < 0.05$) were considered with statistical significance.

RESULTS

211,609 patients were hospitalized in an Infectious Diseases Department, between January 2010 and December 2016. Among these subjects, in the present study, we identified 79 cases with IFI (which correspond to a frequency of 37.3 cases per 100,000 population). More than a half of these people were men (62%) and 38% were women. The calculated mean age was 45 years, with a range between 2 and 85 years. Also, the majority of the identified IFI cases were from urban area (83.5%).

Among the total number of IFI cases, 7% were the result of immunosuppression and 93% were healthcare associated infections.

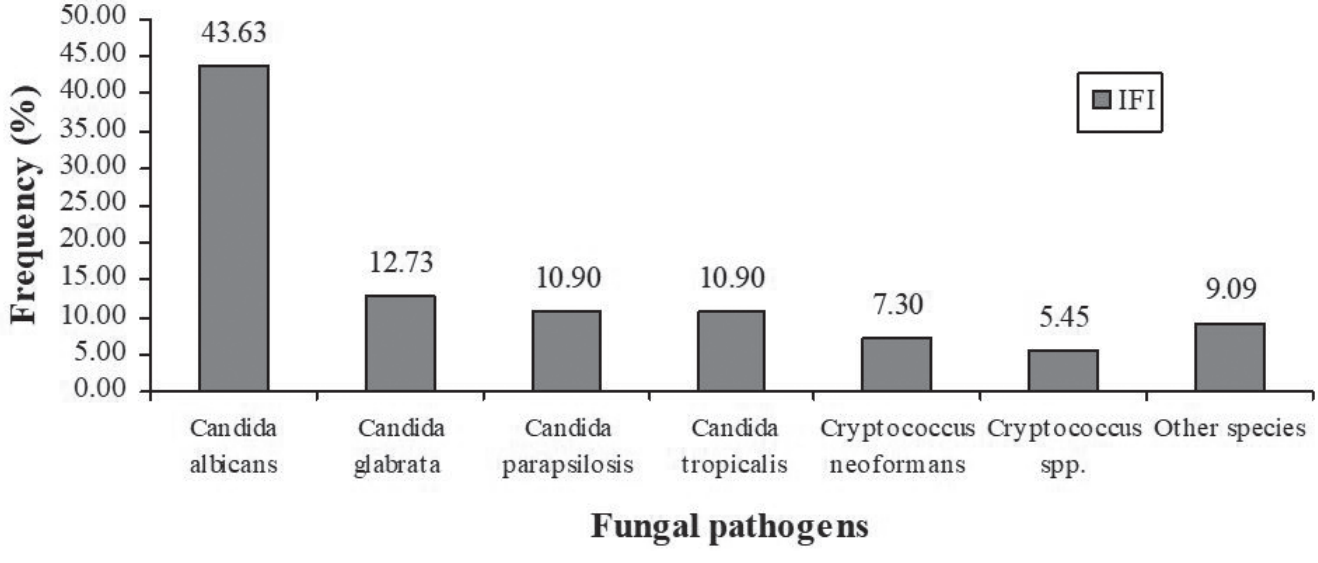

Figure 1. The distribution of fungal pathogens identified among IFI cases.

Regarding the fungal pathogens identified, Candida albicans was on the first place with 43.63%. With an important significance for this pathology, Cryptococcus neoformans was found in 7.30% (Fig. 1).

In the current research the fungal pathogens were isolated from bloodstream (blood culture) (61.90%), catheter (23.80%), and cerebrospinal fluid (14.30%).

Among the risk factors for healthcare associated infections were the long hospitalization duration, the long period of stay in an Intensive Care Unit (ICU), the type of fungal pathogens involved in the etiology of IFI, and the immune status of the host. 36.53% from the studied individuals have visited the ICU and the mean stay in ICU was around 3 days, with a variation between 1 and 46 days. The mean duration of hospitalization was 25.33 days (Table 1).

From the total 79 cases identified with IFI in our study, 21.15% died. In order to evaluate the impact of different factors on the mortality among the patients with IFI included in our study we have used a logistic regression model.

The current analysis showed that the factors with a significant influence on IFI mortality included: age ($p = 0.0002$) (this variable needs a careful interpretation because it could be influenced also by HIV status), HIV positive status ($p = 0.0012$) (HIV positive subjects had a risk of death eight times higher compared with HIV negative patients), organ failure ($p = 0.0142$) (for each organ failure the risk of death increase two times), and a low value of hemoglobin ($p < 0.0001$) (Table 2).

DISCUSSION

In our study the frequency of IFI was higher (37.3 cases per 100,000 population) than the value found in the literature (20 cases per 100,000 population) [11].

The relative frequency with which fungal pathogens produce healthcare associated infections is inversely related to the intensity of immunosuppression required to predispose to them. This way, to be predisposed to invasive Candida infections a patient needs a relatively minimal degree of immunosuppression, and Candida is the most frequent cause of healthcare associated fungal infections [11]. Our research found the same pathogenic agents as being the most common involved in IFI etiology - Candida spp (C. albicans, C. glabrata, C. parapsilosis, and C. tropicalis) (78.16%).

Recent studies have shown that Candida spp. are the third most frequent healthcare associated bloodstream isolates, after Staphylococcus epidermidis and Staphylococcus aureus. It is well known that half of the cases of disseminated candidiasis are missed by blood cultures [11].

Table 1. Duration of hospitalization and ICU stay for the studied population

	Mean	CI 95%	Min - Max	Standard deviation
Hospitalization period (days)	25.33	19.31 - 31.36	1 - 94	22.50
Intensive Care Unit stay (days)	3.09	0.91 – 5.27	0 - 46	7.91

Table 2. Factors that have a contribution to the mortality produced by IFI

Variable	β	Standard error	Degree of freedom	p	Odss Ratio Exp(β)	CI95% for Exp(β) Min	Max
Age	-0.0315	0.00840	1	**0.0002**	0.96	0.953	0.985
Sex - female	Reference	-	-	-	1.00		
Sex - male	0.5207	0.4259	1	0.2214	2.83	0.534	15.042
Rural area	REFER.	-	-	-	1.00	-	-
Urban area	0.5709	-	-	0.3001	1.76	0.748	Infinite
HIV (-)	Reference	-	-	-	1.00	-	-
HIV (+)	1.0460	0.3224	1	**0.0012**	8.10	2.289	28.668
Lymphocytes	-0.0892	0.0291	1	**0.0022**	0.91	0.864	0.968
Monocytes	-0.1461	0.0582	1	**0.0120**	0.86	0.771	0.968
Hemoglobin	-0.1412	0.0354	1	< **0.0001**	0.86	0.810	0.931
Platelets	-0.00563	0.00165	1	**0.0006**	0.99	0.991	0.998
Organ failure	0.9483	0.3865	1	**0.0142**	2.581	1.210	5.506
Candida albicans	Reference	-	-	-	1.000	-	-
Others	0.5995	0.6789	1	0.3772	2.036	0.361	11.479
Candida glabrata	-0.1627	0.9461	1	0.8635	0.950	0.086	10.499
Candida parapsilosis	-0.1627	0.9461	1	0.8635	0.950	0.086	10.499
Candida tropicalis	-0.1627	0.9461	1	0.8635	0.950	0.086	10.499

The most frequent risk factors considered to predispose patients to the occurrence of invasive Candida infections/disseminated candidiasis are iatrogenic and/or healthcare associated condition: colonization, the use of the antibacterial agents with broad spectrum, invasive devices (central venous catheter, parenteral nutrition), gastrointestinal or cardiac surgery, transplants, hemodialysis, a long duration of hospitalization, ICU stay, burns, premature neonate, and hand hygiene (33% of the healthcare workers in a surgical Intensive Care Unit and 29% of the healthcare staff from a neonatal Intensive Care Unit were identified with Candida spp. on their hands) [10, 11]. Although Candida is an opportunistic pathogen, 80% of patients who develop disseminated candidiasis are not immunosuppressed in the classical sense (e.g., neutropenia, corticosteroid-treatment, HIV infection, diabetes mellitus, etc.) [10, 11]. The incidence of disseminated candidiasis in hospitalized patients with many of these risk factors is 50-fold higher compared to individuals with fewer risk factors [11].

Aspergillus is the most important source of invasive fungal infections for decades in a variety of immunocompromising conditions. The level of the immunosuppression required to predispose to invasive Aspergillus infections is higher than for Candida infections. Also, to be predisposed to develop aspergillosis an individual needs an intermediate to severe level of immunosuppression, and Aspergillus is the second most common cause of healthcare associated invasive fungal infections. Others fungal microorganisms such as the Mucorales, Fusarium, and Scedosporium are less common, and are identified merely in subjects with a very severe immunocompromised status, and in hosts that are compromised for a long period of time [11]. In our research Aspergillus was not identified as a fungal pathogen involved in the etiology of IFI cases, but we found some cases produced by Candida lipolytica, Candida ciferrii, Candida guilliermondii, and Fusarium oxysporum.

Generally, the hospital is the most likely to be blamed because the way of transmission for an infection is difficult to be proven. From a medico-legal perspective, identifying liability for injuries or death produced by HAI can be an important challenge. The investigation has to answer the following points: the circumstances for the infection to be acquired; why the treatment was not promptly used and if the event could or should have been prevented [7].

The medico-legal aspects generated by HAI are related to four major points. First, the duty, an obligation to conform to a recognized standard of care provided to the patient, fact which means to assume that between physician and patient there is a contract which must be fulfilled. Secondly, the breach of duty, a deviation from the recognized standard of care, which means that if the duty is not fulfilled, then the contract is breached. Thirdly, the causation, an act or conduct departing from the recognized standard of care that caused the injury, which means that the damage that occurs is the result of the unfulfilled contract. The last element is the injury, the result of the deviation from the recognized standard of care. The plaintiff (the patient) has to prove factual as well as legal causation (chain of events) between the inappropriate act and the resulting injury in order to claim compensation [13]. In fact, the plaintiff has to prove that there are national and local standard of care that the healthcare worker has to respect, and the healthcare institution has to provide infection-free environment and has to apply the national and local standard of care. Then, if the contract is breached the plaintiff has to prove that the national or local standard of care was not followed and also the own policy was not followed. The last step, the causation is very difficult to be proved in a HAI case and it is the major issue related to HAI liability cases (points to be analyzed – the damages are not caused by patient or family actions and the existence of informed consent which means the assumption of risk by the patient) [14].

Usually, the most involved inappropriate acts include: the failure in diagnoses or effective treatment of the disease and the lapses in infection prevention. So, a failure to follow evidence-based practices can raise the amount of medical negligence [7].

It is estimated that around 10% of the hospitalized patients are subjects of an adverse event and that half of them are avoidable [14]. In our society, the epidemiologists have to be used by the hospitals as safeguards for compliance and being recognized as doing the right thing for patient.

Establishing the causality of a healthcare associated fungal infection is difficult (medical negligence, environment, host). For example, if it is about hand washing, there are guidelines and standards, but nobody is "perfect", there are always some "missing steps". But how many steps (wash hands) are allowed to be missed until to consider the medical negligence? Or, if it is about the host, why does one patient develop healthcare associated IFI and not the next.

Unfortunately, IFI are often diagnosed too late because the symptoms can be mild and non-specific,

and there is no guidelines to recommend which patients should receive antifungal prevention, when prevention should be given, which antifungal agents should be used, and which is the appropriate duration for the treatment to be effective.

In conclusion, often it is possible and probable that an invasive fungal infection to be associated with healthcare, which is the result of synergic actions of a complex of factors that involved the healthcare providers (healthcare workers), the environment (hospitals or other healthcare associated settings), and the host (immunosuppressed or not). In these conditions medico-legal issues may arise.

Clinical negligence may arise from different actions or inactions, including failure to apply the guidelines or standards of care, delay to diagnose or treat a disease, failure to obtain the informed consent, incorrect or inappropriate treatment or the failure to prevent the occurrence of an avoidable healthcare associated infection. Controlling the spread of HAI depends on a complex of measure, including epidemiological surveillance and other preventive measures and it is unfair to pointing out one particular factor.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

RAA conducted the data collection. DA and MCM participated in data analysis. RAA, DA and MCM contributed to drafting of all sections of the manuscript. AA, DA and MCM were involved in the writing of the final form of this manuscript. All authors read and approved the final manuscript.

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