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# Prevalence, Risk Factors, and Prognosis of Systemic Fungal Infections in the Hospitalized Children in the Northwest of Iran

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**ABSTRACT**

**Introduction:** The present study aimed to investigate the prevalence, inductive agents, potential risk factors, and prognosis pertaining to the specific risk factors of fungal infections in the hospitalized children in the northwest of Iran.

**Materials and Methods:** This descriptive-analytical, retrospective study was conducted on all the children who were hospitalized in the Pediatric Hospital of Tabriz, Iran due to positive fungal culture during 23 August 2010-23 September 2013. The culture samples were collected from various positive fungal body fluids, secretions, and/or catheters.

**Results:** In total, 40,638 patients were hospitalized during the study period, 191 of whom had fungal cultures and were enrolled in the study. Among the studied patients, 58% were male, and 42% were female. The prevalence of fungal infections in the pediatric healthcare center was 0.47% (approximately four infections per 1,000 cases). The most common comorbidities in the hospitalized children with positive fungal culture were aspiration pneumonia (15%), urinary tract infections (9%), and septicemia (7%). In addition, the most frequently infected area was the urinary system (37%). Candida albicans and mycelial fungi accounted for the most common varieties of the fungal isolates obtained from the patients. The mortality rate among the studied children with fungal infections was estimated at 27%.

**Conclusion:** According to the results, the main risk factors for fungal infections included the use of intravenous catheters, urinary catheters, intubation, and history of surgery. Therefore, it is recommended that the potential risk factors of these infections be screened and investigated in the patients admitted to the Pediatric Teaching Hospital of Tabriz.

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## Introduction

The advancement in healthcare systems within the past two decades has influenced the treatment methods of common diseases in the general population and hospitalized patients (1). However, the development of technological therapeutic approaches, such as bone marrow transplantation, solid organ transplantation, and chemotherapy, has led to the spread of immunodeficiency disorders and the associated complications in the patients admitted in healthcare centers across the world (2, 3). Despite the significant contribution of novel technological methods to treatment processes, adverse outcomes have been reported as a result of invasive monitoring methods, parenteral nutrition, broad-spectrum antimicrobial use, and mechanical ventilation in specialty and subspecialty units (4). The subsequent immunodeficiency disorders and acute diseases have increased the rate of hospitalization. The AIDS epidemic is considered to be another contributing factor in the prevalence of immunodeficiency disorders, which imposes a significant burden on patients (5, 6).

Patients with immunodeficiency disorders are highly susceptible to the opportunistic infections caused by fungal and non-fungal pathogenic agents, which were not considered to have pathogenicity in the past. These patients are severely affected by progressive fungal infections, which are associated with challenging diagnosis and treatment procedures since fungi are


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eukaryotic cells with more complex structures compared to bacteria and viruses (7, 8). Therefore, proper recognition of the diseases induced by fungal infections is a scientific, practical concern among physicians and microbiologists, enabling them to use effective diagnostic modalities and therapeutic methods to address these infections.

Several studies have focused on the risk factors for fungal infections in healthcare centers. Accordingly, some of the main risk factors include antimicrobial treatments, dose and duration of antimicrobial therapy, corticosteroid prescription, chemotherapy, blood and solid organ malignancies, previous colonization, placement of various catheters (e.g., central venous catheter), complete parenteral nutrition, neutropenia, major surgeries, extensive burn injuries, mechanical ventilation, hospitalization in general or intensive care units, hemodialysis, and malnutrition (9). The most frequent pathogens of fungal infections have been reported to be Candida albicans, non-albicans Candida species, Aspergillus species, yeasts, Zygomycetes, hyalohyphomycetes, and phaeohyphomycetes (10).

Several studies conducted in different countries have assessed the epidemiology and prevalence of fungal infections and their risk factors in healthcare centers, proposing variable results (11). Nevertheless, data are scarce on the status of fungal infection among the children in the northwest of Iran. Although recent findings denote the increased prevalence of the nosocomial infections caused by various organisms, the incidence of fungal infections has been reported to be relatively higher, especially those caused by Candida albicans and the species compared to the other opportunistic organisms (12, 13).

The present study aimed to assess the prevalence, causes, potential risk factors, and prognosis of the specific risk factors of fungal infections in the patients admitted in the Pediatric Teaching Hospital in Tabriz, located in the northwest of Iran.

## Materials and Methods

This descriptive-analytical, retrospective study was conducted on all the children admitted in the Pediatric Hospital of Tabriz, which is the largest teaching hospital in the northwest of Iran, during 23 August 2010-23 September 2013. Patients with positive fungal cultures were enrolled in the study (age range: neonates-15 years).

Samples of body fluids, secretions, and/or catheters were examined using smear and microbial culture tests to confirm positive fungal cultures. To isolate the fungal pathogens, the clinical samples obtained from the patients were inoculated on general and specific cultures and investigated using standard microbiological methods.

After the approval of the study protocol by the Ethics Committee of the Vice Chancellor's Office for Research, demographic data of the subjects were collected using a checklist. To this end, demographic and clinical data of the patients with fungal infections were extracted from their medical records, including age, gender, weight, admission unit, results of culture tests, risk factors, length of hospital stay, duration of antibiotic use, type of fungal isolates, and infected area. The collected data remained confidential.

Data analysis was performed in SPSS Version 20 using Chi-square, and P-value of less than 0.05 was considered significant in all the statistical analyses.

## Results

In total, 40,638 patients were hospitalized during the study period, 191 of whom had fungal cultures and were enrolled in the study. The prevalence of fungal infections in the selected pediatric healthcare center was estimated at 0.47% (approximately four infections per 1,000 cases). In terms of gender, 112 patients (58%) were male, and 79 patients (42%) were female. The age range covered the neonatal period to the children aged 15 years.

The most common comorbidities in hospitalized patients with positive cultures were aspiration pneumonia (n=29; 15%), urinary tract infections (n=19; 9%), septicemia (n=15; 7%), and esophageal atresia (n=8; 4%). The prevalence of fungal infections was 21% (n=41) in the neonatal intensive care unit (NICU), 21% (n=41) in the internal medicine unit, 18% (n=35) in the pediatric unit, 15% (n=30) in the pediatric intensive care unit (PICU), 11% (n=22) in the infection unit, 8% (n=17) in the hematology and oncology unit, 2.1% (n=4) in the ear, nose, and throat (ENT) unit, and 0.5% (n=1) in the surgery unit. According to the results, the most frequently infected areas were the urinary system (37%), endotracheal tube (5%), intravenous catheter (5%), and throat (4%). Moreover, the most frequent fungal isolates in these patients were Candida species (98.5%) and mycelial fungi (1.5%) (Figure1).

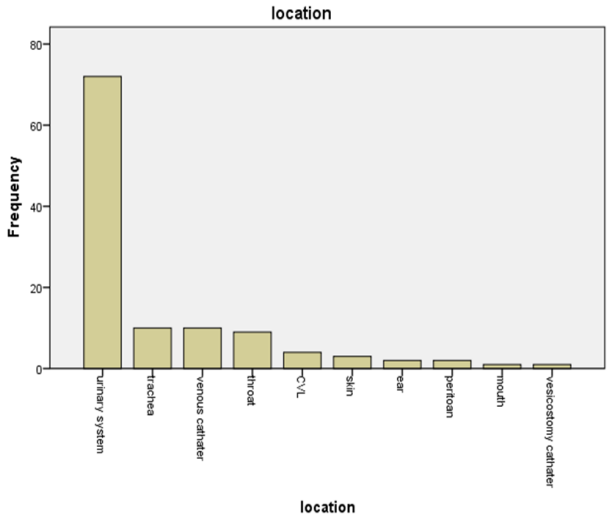
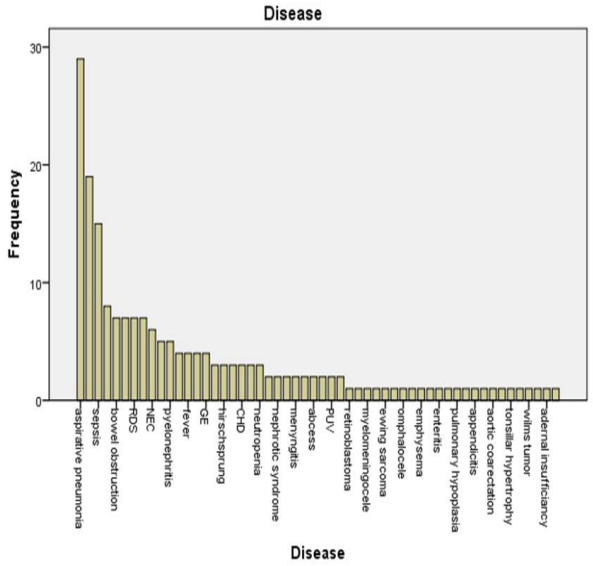



**Figure1: Frequency of organs involved in fungal infection in patients under study**

Among 191 investigated patients, 109 cases (57.1%) were discharged after complete recovery, 52 patients

(27%) died, and five patients (2%) were referred to other healthcare centers for further treatments. Among all the subjects, 100 patients (57.6%) had an intravenous catheter, 80 subjects (41.8%) had an artery catheter, and one patient (0.52%) had a subclavian catheter. In addition, 108 patients (56.5%) received bladder catheterization.

In the present study, five patients (2.6%) underwent cerebrospinal fluid sampling, and 61 patients (31.9%) received intubation. Nasogastric intubation, chest intubation, and cerebral shunting were performed in 36 (18.8%), three (1.5%), and one (0.52%) cases, respectively. Additionally, two patients (1%) had diabetes mellitus. Chemotherapy, surgery, vesicostomy, bone marrow transplant, and dialysis were carried out in seven (3.6%), 20 (10.4%), four (2.1%), one (0.52%), and one (0.52%) subjects, respectively (Figure 2).




RDS: respiratory distress syndrome
NEC: necrotizing enterocolitis
GE: gastroenteritis
CHD: congenital heart disease
PUV: posterior urethral valve

**Figure 2: Frequency of underlying deasise in children with fungal infection**

A significant correlation was observed between the prognosis and type of the infectious fungus ($\chi 2$= 0.01; df=1; P<0.01), so that 27% of the patients with Candida infection died, while all the cases with mycelial fungal infections were discharged.

## Discussion

According to the results of the present study, the prevalence of fungal infections in the Pediatric Teaching Hospital of Tabriz was 0.47% (approximately four infections per 1,000 cases), and Candida species were the major causes of fungal infections (98.5%). According to a report by the Centers for Disease Control and Prevention (CDC), the prevalence of fungal infections increased from two cases to 8.3 cases per 1,000 discharges from 1980 to 1990 (14). Furthermore, during 1980-1990, the reported hospital data to the CDC denoted Candida species as the major cause of nosocomial fungal infections (78%), followed by Torulopsis glabrata (7%), and Aspergillus species (1%) [ibid]. This is consistent with the results of the present study in terms of the prevalence and etiology of fungal infections.

According to the literature, the highest prevalence rate of fungal infections has been noted in immunocompromised patients (15), while fungal infections were observed to be most frequent among the patients with aspiration pneumonia in the current research. In this regard, the most prevalent comorbidities in the hospitalized patients with positive fungal cultures were aspiration, urinary tract infections, septicemia, and esophageal atresia.

In the current research, the highest prevalence of fungal infections was observed in the NICU, internal medicine unit, pediatric unit, PICU, infection unit, hematology and oncology unit, and ENT unit. On the other hand, the results of previous studies have indicated that fungal infections are more prevalent in surgery and burn injury units. Our findings demonstrated that the patients in intensive care units were most commonly affected by fungal infections, and the frequently involved areas were the urinary system, endotracheal tube, intravenous catheter, and throat. The discrepancy in the mentioned findings could be due to the lack of the admission of patients with burn injuries in our healthcare center.

According to a study in this regard, the urinary system, surgical sites, circulatory system, and respiratory system are the most common areas affected by infections (16, 17), which is in line with our findings. With respect to the risk factors for fungal infections, the results of the present study indicated that the transmission of the infection from outside the main infected area could cause fungemia; the colonized fungi in the gastrointestinal system are considered to be the important pathogens in this regard (18, 19).

In two studies conducted by Anaissie and Richet, it was stated that the most prevalent candidemia was endogenous, resulting from the fungal colonization in the mouth, gastrointestinal tract, vaginal canal, and skin (20-22). Depending on the source of infection, a variety of organs might be involved in candidemia.

For instance, the initial involvement of the gastrointestinal system may lead to abscessed liver and spleen, followed by the involvement of the related mucosal and epithelial systems. In contrast, when the central venous catheter, as the source of fungal infection, causes candidemia, the major prognosis will involve endocarditis and the kidneys (15, 21).

In a research by Banerjee, candidemia was reported to be the most common primary nosocomial infection of the circulatory system (23-27).

Consistent with the findings of the previous studies, the results of the present study were indicative of the high prevalence of Candida infections and low

prevalence of mycelial fungal infections (1.5%) in the hospitalized patients. Similarly, Harvey isolated mycelial species, including Aspergillus, from the blood cultures of patients, denoting the low prevalence of these fungi in the normal blood culture media to hinder fungal growth (23), which could be the reason for the low prevalence of mycelial fungi in the present study.

Since infections mostly occur in the patients with acute conditions, the estimation of the mortality rate associated with aggressive Candida species is difficult.

In the current research, 27% of the patients died due to fungal infections, which a relatively lower mortality rate compared to the majority of the studies in this regard (38%). Moreover, other findings have estimated the mortality rate to be 50-60% in the patients with candidemia, which is the cause of death in one-third of the patients with fungal infections (28-30). The low mortality rate in the present study could be due to the inaccurate diagnoses of fungal infections as the cause of death and/or discharge of some patients. According to the results of the present study, using intravenous, urinary, artery catheters, receiving nasogastric intubation, surgeries, and undergoing chemotherapy were the main risk factors for fungal infections. In this regard, Reingold conducted a study in the United States, demonstrating that severe diseases, immunodeficiency, and malnutrition were among the inductive agents of fungal infections (31). On the other hand, Bodey concluded that the risk of fungal infections due to transplantation for immunodeficiency is 2-42%.

Therefore, healthcare organizations such as oncology centers, university hospitals, and general hospitals are considered high-risk environments for the nosocomial infections primarily caused by fungal microorganisms (15, 21, 23). Previous studies in this regard have denoted some other risk factors for fungal infections, including the use of antimicrobial agents before infection, chemotherapy, use of central venous and pulmonary artery catheters, and hemodialysis (18, 19, 28, 32). Furthermore, Candida species have been confirmed as the major cause of nosocomial fungal infections (23).

In the present study, a significant association was observed between the risk of fungal infections and gender, with the prevalence rate observed to be higher in the male patients. Moreover, a significant correlation was noted between the prognosis assessment and type of the involved fungi, so that the mortality rate was estimated at 27% in the patients with fungal yeast infections, whereas all the patients with mycelial fungal infections were discharged. Some of the limitations of the present study were the lack of investigation into fungal resistance against antifungal medications and undetected fungal infections in the negative cultures obtained from the patients. Considering the high mortality rate in the patients with fungal infections, particularly those admitted to intensive care units (ICUs), timely prevention, control, and treatment of fungal diseases could remarkably lower the mortality rate and prevent the associated complications. The present study aimed to assess the prevalence, causes, potential risk factors, and prognosis of the specific risk factors of fungal infections in hospitalized patients. Identification of the prevalent types of infective fungi and determining the risk factors of these infections in various geographical regions could contribute to the effective detection and isolation of high-risk patients and preventing the spread of fungal infections in healthcare centers.

## Conclusion

According to the results, the main risk factors for nosocomial fungal infections in the Pediatric Teaching Hospital of Tabriz (Iran) were aspiration pneumonia, urinary tract infections, and sepsis, which were significantly more prevalent in the patients admitted to the ICU and NICU. In addition, Candida species were regarded as the most frequent and fatal fungal isolates, with an estimated mortality rate of 27% in the children with fungal infections. Among the other risk factors for fungal infections were the use of intravenous and urinary catheters, intubation, and history of surgery.

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