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Major Article

# Epidemiologic and microbiologic evaluation of nosocomial infections associated with *Candida* spp in children: A multicenter study from Istanbul, Turkey





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Key Words: Systemic candidiasis candidemia candiduria Candida albicans non-albicans Candida children **Background:** The purpose of this study was to establish species distribution of *Candida* isolates from pediatric patients in Istanbul, Turkey, and to determine risk factors associated with nosocomial *Candida* infections.

**Methods:** This study was conducted between June 2013 and June 2014 by participation of 7 medical centers in Istanbul. *Candida* spp strains isolated from the clinical specimens of pediatric patients were included. Clinical features were recorded on a standardized data collection sheet.

**Results:** A total of 134 systemic *Candida* infections were identified in 134 patients. The patients were admitted in pediatric and neonatal intensive care units (41.8% and 9.7%, respectively) and in pediatric wards (48.5%). *Candida albicans* was the most prevalent species (47%), followed by *Candida parapsilosis* (13.4%), *Candida tropicalis* (8.2%), *Candida glabrata* (4.5%), *Candida lusitaniae* (3.7%), *Candida kefyr* (2.2%), *Candida guilliermondii* (1.5%), *Candida dubliniensis* (0.7%), and *Candida krusei* (0.7%). Types of *Candida* infections were candidemia (50.7%), urinary tract infection (33.6%), surgical site infection (4.5%), central nervous system infection (3.7%), catheter infection (3.7%), and intra-abdominal infection (3.7%). In multivariate analysis, younger age (1-24 months) and detection of non-albicans *Candida* spp was found to be risk factors associated with candidemia (P = 0.040; odds ratio [OR], 4.1; 95% confidence interval [CI], 1.06-15.86; and P = 0.02; OR, 2.4; 95% CI, 1.10-5.53, respectively).

**Conclusions:** This study provides an update for the epidemiology of nosocomial *Candida* infections in Istanbul, which is important for the management of patients and implementation of appropriate infection control measures.

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Nosocomial fungal infections are important health careassociated problems with considerable morbidity and mortality. Incidence of nosocomial fungal infections are increasing because of extensive use of chemotherapeutics, new immunosuppressant

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agents, broad-spectrum antibiotics, and the rising number of transplanted patients who need intensive care.

*Candida* spp remain the most important pathogens in opportunistic fungal infections worldwide.<sup>1</sup> They are reported to be between the fourth and sixth most common nosocomial bloodstream isolate.<sup>2,3</sup> *Candida albicans* (CA) has long been the most common species isolated during candidemia. However, recently, a greater role of nonalbicans *Candida* (NAC) spp has been demonstrated.<sup>4</sup> This shift brings along the problem of choice of empirical antifungal treatment in patients with candidemia because of the potential resistance of

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some non-albicans species to commonly used empirical antifungal agents.

Nosocomial urinary tract infection (UTI) occurs with varying frequency in children, reported to be between 10% and 20%.<sup>5</sup> They are usually bacterial in origin and fungal etiology; particularly, *Candida* spp are responsible for approximately 10%-15%.<sup>6</sup> However, in pediatric intensive care units (ICUs), incidence of *Candida*-related UTI may increase up to 52%.<sup>7</sup> Instrumentation, broad-spectrum antibiotic use, and long hospital and especially ICU stay has been associated with risk factors for nosocomial candiduria.<sup>6</sup>

Invasive *Candida* infections other than candidemia and candiduria, such as intra-abdominal infection, empyema, meningitis, and surgical site infections, are rarely seen<sup>8-11</sup> and difficult to diagnose. Risk factors for *Candida* infections should be taken into consideration attentively when caring for these patients.

Epidemiologic and clinical data regarding nosocomial systemic *Candida* infections are important in recognition and management of *Candida*-susceptible patient profiles. There are a limited number of studies evaluating nosocomial *Candida* infections in the pediatric population. Taking into account that the epidemiology of systemic *Candida* infections varies in different regions, in different ages, and also across time, there is a need for updated local pediatric studies on this issue. To our knowledge, there is no multicenter pediatric study assessing nosocomial *Candida* infections in our region. Therefore, this study was conducted to identify the epidemiology, risk factors, and outcome of pediatric nosocomial *Candida* infections in Istanbul.

#### **METHODS**

#### Patients

The study was conducted in 7 pediatric departments of tertiary care teaching hospitals in Istanbul: (1) Istanbul University Istanbul Medical Faculty (93 beds), (2) Sisli Etfal Training and Research Hospital (128 beds), (3) Bezmialem Vakif University (65 beds), (4) Kanuni Sultan Suleyman Education and Research Hospital (96 beds), (5) Marmara University Medical Faculty (100 beds), (6) Istanbul University Cerrahpasa Medical Faculty (102 beds), and (7) Okmeydani Training and Research Hospital (90 beds).

Clinical information about pediatric patients (0-18 years) admitted to these hospitals between June 2013-June 2014 and in whom *Candida* spp were isolated in clinical specimens was collected. Age groups were classified as  $\leq 1$  month, 1-24 months, and  $\geq 24$  months. Patients with *Candida* spp isolated from respiratory secretions were excluded regarding difficulty in differentiation between colonization and infection in the respiratory tract.

Demographic, clinical, and laboratory features of the patients were retrospectively obtained from their medical records using standardized questionnaires. Presence of any of the following potential risk factors occurring within 3 weeks prior to the onset of nosocomial Candida infection were searched: placement of central venous catheter or urinary catheter, requirement and duration of mechanical ventilation, length of hospital stay (<30 days and >30 days), total parenteral nutrition, presence of candida colonization, broadspectrum antibiotic use (eg, carbapenems, β-lactam-β-lactamase inhibitor combinations, glycopeptides), glucocorticoid use, empirical antifungal use before detection of candidiasis, history of trauma or abdominal surgery, presence of renal failure and need for renal replacement therapy, presence of hyperglycemia (glucose level >180 mg/dL), and presence of underlying diseases (eg, malignity, neurologic diseases, chronic liver diseases, metabolic diseases, hematologic diseases, chronic lung disease).

Crude mortality was determined within 30 days from the occurrence of the episode of candidiasis.

#### Definitions

Nosocomial *Candida* infections were divided into a candidemia group and noncandidemia group. Nosocomial candidemia was defined as any patient having at least 1 positive blood culture yield-ing *Candida* spp plus signs and symptoms of infection (fever, hypothermia, leukocytosis, increased acute phase reactants, tachy-cardia, and hypotension) after at least 72 hours of hospitalization.<sup>12</sup>

The noncandidemia group consisted of those patients who had a UTI, intra-abdominal infection, pleural site infection, surgical site infection, and meningitis. They were defined according to the surveillance and diagnostic criteria stated by the Centers for Disease Control and Prevention.<sup>13</sup>

UTI (candiduria) was defined as isolation of *Candida* spp in urine together with sign and symptoms of UTI: fever >38°C (with no other recognized cause), suprapubic tenderness, costovertebral angle pain or tenderness, urinary frequency, urinary urgency, and dysuria.

Colonization of urinary catheter was defined as isolation of *Candida* spp in urine of patients with a urinary catheter in the absence of sign and symptoms of UTI.

Intra-abdominal infection was defined as isolation of *Candida* spp from culture of drainage or tissue obtained during invasive procedure or from an aseptically placed intra-abdominal drain and presence of at least 2 following sign and symptoms: fever >38°C (with no other recognized cause), nausea, vomiting, abdominal pain, and jaundice.

Pleural site infection (empyema) was defined as isolation of *Candida* spp from culture of pleural fluid and presence of fever >38°C (with no other recognized cause) and sign and symptoms of pneumonia.

Surgical site infection was defined as isolation of *Candida* spp from an aseptically obtained culture from the superficial incision or subcutaneous tissue and presence of at least one of the following sign and symptoms: pain or tenderness, localized swelling, erythema or heat, and purulent drainage from the superficial incision. Infection occurs within 30 days after any operative procedure and involves only skin and subcutaneous tissue of the incision.

Meningitis is defined as isolation of *Candida* from cerebrospinal fluid presence of at least 2 of the following signs and symptoms: fever >38.0°C (with no other recognized cause) or headache, meningeal signs, and cranial nerve signs.

The study was approved by the Ethics Committee of the Istanbul Medical Faculty.

#### Microbiologic procedure

Every institution identified *Candida* spp isolates from the clinical specimens in their own mycology laboratory using similar methods and equipment. The microbiologic procedure used in the microbiology department of Istanbul Medical Faculty was detailed hereinafter. Blood cultures were processed by an automated blood culture system (BACTEC; BD, Franklin Lakes, NJ). The fungal isolates were subcultured onto Sabouraud dextrose agar. Confirmation of species identification was performed according to morphologic appearance on corn meal-Tween 80 agar and biochemical tests using API ID 32 C strips (bioMérieux, Marcy l'Etoile, France).

#### Statistical analysis

Statistical analysis was performed with SPSS version 21.0 (IBM, Armonk, NY). Categorical data were compared by the  $\chi^2$  test and Fisher exact test. For variables not distributed normally, Mann-Whitney *U* test was used. Significance was considered when *P* < .005. The most significant predictors of candidemia by univariate

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