Comparison of Monomicrobial versus Polymicrobial Candiduria: Time to Awareness of Candiduria

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Purpose: Candiduria, which is the presence of Candida species in urine, is becoming increasingly common in hospital settings. These normal commensals in humans are often associated with the presence of other microorganisms. In this study, patients presenting with monomicrobial and polymicrobial candiduria were compared.

Materials and Methods: A retrospective study was performed on the demographic, clinical, and laboratory data of 185 patients presenting with candiduria between July 2014 and June 2015 at Chung-Ang University Hospital. The threshold for a positive Candida species urine culture was set to $10^3$ CFU/ml. Data on the following were evaluated: distribution of Candida species; patient age and sex; length of hospital stay; presence of diabetes mellitus (DM), chronic kidney disease (CKD), a urinary catheter, and fever; antibiotic administration; urinalysis; complete blood cells; and C-reactive protein.

Results: Monomicrobial candiduria was more common (128/185, 69.2%) than polymicrobial candiduria (57/185, 30.8%). The most prevalent species was Candida albicans (monomicrobial vs. polymicrobial candiduria, 61.7% vs. 54.4%), followed in order by Candida tropicalis (18.8% vs. 24.6%), and Candida glabrata (14.8% vs. 12.3%), with no significant difference between the two groups. Significant differences in the length of stay, underlying DM or CKD, accompanying symptoms, and urine white blood cells (WBC) and bacterial counts were observed between the two groups ($p<0.05$).

Conclusions: The length of stay, underlying DM or CKD, accompanying symptoms, and urine WBC and bacterial counts were more associated with polymicrobial candiduria. The early detection and treatment of candiduria will become increasingly important as the Korean population ages.

Keywords: Candida; Urinary tract infections; Candidiasis; Polymicrobial infection

INTRODUCTION

Candida species, which are distributed as normal commensals throughout the human gastrointestinal tract, can cause opportunistic infections in their host. The presence of Candida species in the urine is known as candiduria, the risk factors for which are well known, such as an advanced age, anatomic abnormalities of the urinary tract, concomitant diseases (including uncontrolled diabetes mellitus [DM]), prior use of broad-spectrum antibiotics, the
presence of a urinary catheter, and female sex [1,2]. The presence of Candida species in the urine can be due to an infection, contamination, or colonization, highlighting the need for a clear distinction. To date, the clinical significance of candiduria and its treatment guidelines have not yet been established [1]. Similarly, the effects of a candiduria treatment on the prognosis of patients are also unknown [3], but the incidence of candiduria is increasing [4,5]. Moreover, reports have shown that candiduria affects patient morbidity and mortality [6-9]. Furthermore, there are reports showing that candiduria can lead to candidemia [6,10]. Candiduria is highly undervalued, but the presence of Candida species in the urine can mean extensive candidemia [4]. The rate of progression to invasive candidemia is higher in patients with Candida colonization in the urine than in those without [8].

Candiduria is becoming increasingly common in hospital settings, with a 6.5% to 25% increase in prevalence according to the patient’s age [4]. The incidence of candiduria in hospitalized patients is increasing, particularly in intensive care units (ICU) [11]. The importance of candiduria is also expected to increase with the gradual increase in average life expectancy and the number of severely ill patients. Therefore, it is imperative to understand the characteristics of patients with candiduria to distinguish true infections that can cause candidemia.

Polymicrobial infections are those caused by a combination of viruses, bacteria, fungi, and other parasites. In these diseases, the microorganisms can exhibit microbial interference interactions (i.e., where one microorganism inhibits the growth of other organisms), or synergistic effects that promote mutual infection [12]. Candiduria is often associated with the presence of other microorganisms. Among patients with candiduria, the rate of candidemia progression is higher in individuals with a polymicrobial infection [8]. Therefore, the analysis of polymicrobial infections among patients with candiduria would help better understand the traits that can lead to candidemia. Therefore, the aim of this study was to compare patients presenting with monomicrobial and polymicrobial candiduria in a tertiary hospital in Korea.

**MATERIALS AND METHODS**

1. **Study Design**

This was a retrospective study conducted at Chung-Ang University Hospital. From July 2014 to June 2015, the medical records of patients with Candida species identified in urine cultures were reviewed. The urine culture was carried out as follows. A 1-μl of urine was inoculated on blood agar and MacConkey agar plates, which were then incubated for 24 to 48 hours at 37°C under an atmosphere containing 5% CO2. When the culture exceeded $10^3$ CFU/ml [13,14], the Candida species were isolated by a microscopic examination and Vitek II (bioMérieux Inc., Durham, NC, USA). The patients were divided into two groups according to the number of microorganisms identified in their urine culture, i.e., monomicrobial candiduria and polymicrobial candiduria. For each patient, only the first urine culture results were selected among several urine cultures obtained. Data on the patient’s age, length of hospital stay, underlying disease (i.e., DM or chronic kidney disease [CKD]), presence of a urinary catheter, administration of antibiotics in the previous three months, accompanying symptoms (fever, general weakness, voiding difficulty), urinalysis parameters (white blood cells [WBCs] ≥ 10/high-power field, bacteria, yeast, Candida, pH), complete blood cell analysis (WBC count, neutrophil-to-lymphocyte ratio), and C-reactive protein level were evaluated along with the urine culture results. The Institutional Review Board of Chung-Ang University Hospital approved this study (IRB no. 1903-008-16255).

2. **Statistical Analysis**

The data are expressed differently according to the characteristics of the variables, where the qualitative variables are expressed as a percentage, and the quantitative variables are expressed as a mean, standard deviation, and range. A Mann–Whitney U test was performed to confirm the significance of the differences between the two groups (i.e., monomicrobial candiduria vs. polymicrobial candiduria). p-values less than 0.05 were considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows (ver. 22.0; IBM Corp., Armonk, NY, USA).
RESULTS

Of the 185 patients included in this study, 128 (69.2%) had monomicrobial candiduria and 57 (30.8%) had polymicrobial candiduria. The ratio between male and female in both groups was comparable and the age distribution was similar (Table 1). The distribution of Candida species was similar in the two groups, with the most common species in both groups being Candida albicans, Candida tropicalis, and Candida glabrata (Table 2).

The presence of underlying DM and CKD was significantly higher in the polymicrobial candiduria group (p=0.025 and p=0.004, respectively). This group also had longer hospital stays (p=0.018), and more accompanying symptoms, such as general weakness and voiding difficulty. On the other hand, there was no significant difference between the groups with regard to the presence of a urinary catheter (p=0.425). The test results revealed differences in some urinalysis parameters between the two groups. The urinanalysis Candida counts were similar in the two groups (p=0.168), but there was a significant difference in the WBC and bacterial counts, with both being higher in those with polymicrobial candiduria (p=0.013 and p<0.001, respectively) (Table 1).

In the patients with polymicrobial candiduria (n=57), gram-positive bacteria (n=35, 61.4%) were the most common microorganisms associated with Candida species with Enterococcus faecium (n=23, 65.7%) being the most common. Six cases of polymicrobial candiduria were encountered, in which two Candida species were identified together. Of these, C. albicans (five cases) and C. glabrata (four cases) were the most common species identified with other Candida species (Table 3).

DISCUSSION

The pathophysiology of candiduria can be divided into ascending infections due to microorganisms ascending from the lower urinary tract to the upper urinary tract, and

### Table 1. Clinical characteristics and comparison of the patients with monomicrobial candiduria and polymicrobial candiduria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monomicrobial candiduria (n=128)</th>
<th>Polymicrobial candiduria (n=57)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>64.1</td>
<td>63.2</td>
<td>-</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71.1±19.2 (2-99)</td>
<td>73.0±14.2 (35-95)</td>
<td>0.718</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>62.1±57.8 (3-342)</td>
<td>95.1±82.1 (4-354)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>36.7</td>
<td>54.4</td>
<td>0.025</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>7.8</td>
<td>21.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Presence of urinary catheter (%)</td>
<td>80.5</td>
<td>75.4</td>
<td>0.425</td>
</tr>
<tr>
<td>Administration of antibiotics (&lt;3 mo) (%)</td>
<td>90.6</td>
<td>94.7</td>
<td>0.345</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>71.1</td>
<td>80.7</td>
<td>0.170</td>
</tr>
<tr>
<td>General weakness (%)</td>
<td>8.6</td>
<td>24.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Voiding difficulty (%)</td>
<td>0.0</td>
<td>8.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinanalysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBCs</td>
<td>1.3±1.2 (0.0-3.0)</td>
<td>1.7±1.2 (0.0-3.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Bacteria</td>
<td>1.8±0.9 (0.0-4.0)</td>
<td>2.5±1.0 (0.0-4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yeast</td>
<td>2.0±1.4 (0.0-4.0)</td>
<td>2.2±1.5 (0.0-4.0)</td>
<td>0.381</td>
</tr>
<tr>
<td>Candida</td>
<td>1.3±1.4 (0.0-4.0)</td>
<td>1.6±1.3 (0.0-4.0)</td>
<td>0.168</td>
</tr>
<tr>
<td>pH</td>
<td>5.7±1.1 (5.0-8.5)</td>
<td>5.8±1.1 (5.0-8.0)</td>
<td>0.441</td>
</tr>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBCs (×10³/µl)</td>
<td>11.2±6.1 (0.2-47.7)</td>
<td>10.7±5.8 (1.3-34.7)</td>
<td>0.398</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio (%)</td>
<td>10.4±13.8 (0.4-97.0)</td>
<td>8.0±9.0 (0.1-47.7)</td>
<td>0.153</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>80.4±75.6 (0.2-379.8)</td>
<td>62.1±60.1 (0.2-230.3)</td>
<td>0.171</td>
</tr>
</tbody>
</table>

Values are presented as % only or mean±standard deviation (range). WBCs: white blood cells, hs-CRP: high-sensitivity C-reactive protein.

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hematogenous infections caused by the penetration of bloodstream microorganisms into the tissue [15]. Candiduria can be one of the earliest findings of candidemia because it exhibits affinity for the kidneys [16]. A prospective observational study in France reported that 8% of patients with candiduria developed candidemia, which was caused by the same Candida species [9]. Many studies identified C. albicans as the most common species, followed by C. glabrata [15]. A comparison of the results of various countries revealed obvious regional differences. After C. albicans, C. glabrata was the second most common species in the United States, Spain, and Ethiopia [6,17,18], whereas C. tropicalis was the second most prevalent in Korea, Brazil, India, and Turkey [2,7,19,20]. In the present study, C. albicans, C. tropicalis, and C. glabrata were identified in this order, which can be explained by geographic differences.

The risk factors for candiduria are well known, and no difference in risk factors between the two groups in this study was found except for the presence of DM and CKD. To the best of the authors’ knowledge, there are no reports on the association between monomicrobial candiduria and polymicrobial candiduria. Consequently, previous studies could not be used to explain the difference regarding underlying diseases in these groups. Nevertheless, this analysis is meaningful in terms of disease characteristics.

In patients with DM, glycosuria can become a predisposing factor for infections, and the urinary stasis caused by a neurogenic bladder may promote infections and colonization. In addition, a weakened host defense due to impaired phagocytic activity in patients with DM is believed to be the cause of infection by a range of various microorganisms [15]. Candiduria is often associated with critically ill patients, where a Candida infection influences the renal function, suggesting that a more advanced polymicrobial infection is associated with CKD aggravation.

Polymicrobial candiduria can be accompanied by not only bacterial, but also yeast infections, occurring in approximately 5% to 10% of candidemia cases [4,9]. Simpson et al. [3] reported that 28% of patients hospitalized with asymptomatic candiduria had concomitant bacteriuria that did not affect the morbidity or mortality. On the other hand, Magill et al. [8], who examined the risk factors associated with the development of invasive candidemia according to the location of the Candida colonies in patients in the surgical ICU, reported different results. Invasive candidemia occurred in 5% of patients, whereas the colonization of urine by Candida species was confirmed before the diagnosis. Colonization was reported in the following order of prevalence: C. albicans (89%), C. glabrata (67%), C. tropicalis (33%), and Candida parapsilosis (11%); 89% of these patients had colonization of two or more Candida species. In another study, cell surface proteins of E. faecium were found to be attached to uroepithelial cells, where they have been reported to play a role in urinary tract infections [21]. Enterococcus faecalis, which is known to occur symbiotically with C. albicans, inhibited the hyphal morphogenesis of C. albicans, thereby affecting its virulence [22]. These results suggest that E. faecium is associated most frequently with polymicrobial candiduria because of its affinity to the genitourinary tract and its presence as resident flora. Because E. faecalis has a symbiotic relationship with Candida, it is believed to be the second most common cause of polymicrobial candiduria, and it is necessary to confirm the virulence factor to gauge the possible development of candidemia in these patients. In urine cultures with two or more Candida species identified, the combination of C. albicans and C. glabrata was most common, which was consistent with previous studies. On the other hand, the incidence of non-albicans Candida species has increased recently [19] and resistance to antifungal agents is being reported more frequently [23]. In a multicenter study conducted in South Korea, C. glabrata isolated from the bloodstream was highly resistant to antifungal agents [23]. Therefore, the Candida species identified in the culture
can help determine if treatment is necessary, and if so, what the treatment options should be. For this reason, care should be taken when identifying *C. glabrata* in the urine.

The limitation of this study was that the number of patients analyzed was small. A larger patient cohort will result in more relevant factors being obtained. Analyses of *C. albicans* and non-albicans *Candida* species were not conducted because of the small number of patients. Further analysis of non-albicans *Candida* species that are resistant to treatment and are becoming increasingly prevalent will be needed.

**CONCLUSIONS**

These results suggest that the length of hospital stay, presence of DM or CKD, accompanying symptoms, and urine WBC and bacterial counts are more associated with polymicrobial candiduria. Moreover, the early detection and treatment of candiduria will become increasingly important as the Korean population ages. On the other hand, the clinical significance of candiduria and guidelines for its treatment have yet to be established. Therefore, the establishment of evidence-based guidelines for this condition is urgently required.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**AUTHOR CONTRIBUTIONS**

H.K, participated in data collection, performed the statistical analysis and wrote the manuscript, M.K.L, participated in the study design and data collection, T.H.K, participated in the study design and coordination and helped to draft the manuscript, All authors read and approved the final manuscript.

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