Review

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Management of Candida Urinary Tract Infection in the Elderly

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Candida urinary tract infections in elderly patients are becoming increasingly common. The risk factors for the development of candiduria include old age, use of broad-spectrum antibiotics, corticosteroids and indwelling urethral catheters, as well as diabetes mellitus, urological abnormalities, and hematological malignancies. The presence of signs and symptoms of infection are unusual, and the intensity of fungal growth in culture does not correlate with the outcome. Elderly patients often present with atypical signs and symptoms of infection. Careful assessment of the patient's clinical status should be undertaken before treatment is initiated. The indications for antifungal therapy are the same for older and younger individuals, and the initial antifungal therapy should be selected based on the infecting organism and local epidemiology. Fluconazole is the mainstay of treatment. On the other hand, *Candida glabrata* is more common in elderly patients and is often refractory to fluconazole therapy. The selection of drug therapy for elderly patients should consider the comorbidities, risk of drug-drug interactions, and dose adjustment for physiological function.

Keywords: Candida; Disease management; Frail elderly; Urinary tract infections

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INTRODUCTION

Fungal growth in the urine, although rare in healthy people, is often observed in immunocompromised or hospitalized patients. *Candida* species are the most common cause of fungal urinary tract infections (UTIs) [1,2].

Many reports have identified the risk factors for candiduria, such as increased age, female sex, prior antibiotic use, use of urinary drainage devices, prior surgical procedures, and diabetes mellitus (DM) [2-6]. In elderly patients, *Candida* UTI is becoming increasingly common [7]. Moreover, old age is correlated with the risk factors, because the elderly population has a higher incidence of previous antibiotic use, use of urinary devices, prior surgical procedures, and DM. Various changes related to aging make elderly people more vulnerable to infections and increase the mortality of fungal infections [8,9].

Although the cutoff age for the elderly population is not clearly defined, many prospective epidemiological studies and articles define the elderly population as the age group >65 years [8-11]. As the health status of the general population has improved and the life expectancy is increasing, the elderly population is currently large and still growing in proportion to the general hospitalized population.

This paper reviews the management and treatment options of *Candida* UTI with a focus on the elderly population.

EPIDEMIOLOGY AND MICROBIOLOGICAL ASPECTS

Candiduria is a rare phenomenon in the general population and occurs in <1% of clean-voided urine samples, but it affects 5-10% of positive urine cultures in hospitals and tertiary care facilities, particularly patients in the intensive care unit (ICU) with indwelling urethral catheters [1,3]. *Candida* species were reported to be the third most common organism isolated from urine, after *Escherichia coli* and *Enterococcus* species, in 1-day point prevalence surveys of urine cultures obtained from hospitalized patients in Europe [12].

Candida albicans is the most commonly isolated pathogen from urine, accounting for 50-70% of isolated pathogens [3,4,7]. *Candida glabrata* and *Candida tropicalis* are the next most common species, and each accounts for 10-35% of cases [13,14]. *C. glabrata* is increasingly reported as a cause of candidemia and develops in certain types of patients, such as those with hematological malignancies and transplant recipients. In the largest prospective study of renal transplant recipients, approximately 50% of all isolated organisms were *C. glabrata* and 30% were *C. albicans* [15]. In addition, *C. glabrata* is detected more commonly in elderly patients with candidemia and candiduria and is very uncommon in neonates and young children [16-22]. In elderly patients, the intrinsic resistance of *Candida* species to fluconazole and the need for treatment with amphotericin B is a concern that has an increased the risk of nephrotoxicity [23]. *Candida parapsilosis* (1-7%), *Candida krusei* (1-2%), and other unusual *Candida* species are detected less commonly in urine [23].

FEATURES OF ELDERLY PATIENTS

A range of physiologic and morphological changes occur during the aging process, resulting in older patients being potentially more vulnerable to infections, particularly from fungal species.

The aging process is characterized by a decreased immunological response to infection because of the functional insufficiency of monocytes and macrophages, which leads to inadequate phagocytosis [24]. Lymphocyte changes are also noted in the elderly population. Mature T-cells lose their memory capacity, resulting in poor and/or altered cytokine production [25]. Furthermore, there is a decrease in the number of circulating B-cells, and their response to antigenic challenges through immunoglobulin production is weaker [26].

The renal and hepatic function is also impaired during the aging process. The glomerular filtration rate (GFR) decreases by 1% per year. On the other hand, this is not confirmed by serum creatinine to a certain level, because a 25% rise in the serum creatinine level actually represents a substantial decrease in GFR, probably up to 50% [27]. The hepatic function is decreased during aging because of the decrease in the total liver volume, hepatic blood flow, and protein synthesis. These factors can affect various phase I drug metabolism reactions, such as hydroxylation, dealkylation, and reduction, which are performed by microsomal cytochrome p450 [28,29]. These renal and hepatic function impairments are associated with serious clinical problems with drugs dependent on renal and hepatic excretion.

Polypharmacy in the elderly is another important issue with regard to both the adverse effects and drug interactions. In a recent study, approximately 75% of the elderly population were treated with at least four drugs, which are more medications than in the younger population. Furthermore, elderly patients also receive drugs in a more inappropriate manner [30-32]. The drugs most commonly used in the elderly population include analgesics and medications for the treatment of other diseases, such as hypertension, DM, chronic obstructive pulmonary disease, heart failure, or cancer [32].

Opportunistic fungal infections are a problem in elderly patients because older patients are now receiving transplanted solid organs or bone marrow, undergoing aggressive treatment for malignancies, and taking immunosuppressive medications for dermatological and rheumatological diseases. Furthermore, prior surgical procedures, total parenteral nutrition, central intravenous catheters, and the use of broad-spectrum antibiotics all increase the risk of infection with *Candida* species [33]. *Candida* colonization occurs frequently in elderly people, particularly after treatment with broad-spectrum antibiotics, which is one of the main reasons why older people are vulnerable to bloodstream infections [24].

PATHOGENESIS

Candida species normally inhabit the genital tract, gastrointestinal tract, and skin. *Candida* species cause UTI by either by hematogenous routes from the bloodstream or ascending routes from a focus of *Candida* colonization near the urethra. Most *Candida* infections are the result of overgrowth and subsequent invasion by *Candida* species that are inherent to the host's gastrointestinal tract. In addition, a nosocomial infection of an exogenous source has also been documented.

The elderly populations are at particular risk for the development of candiduria. The weakness of cellular immunity with advanced age and changes in the vaginal pH in postmenopausal females can increase the risk of bacterial UTI. The altered bacterial substances may then allow for the colonization and infection by fungus, and antibiotics taken for other infections may enable the growth of fungi by eliminating bacteria.

1. Hematogenous Route

Hematogenous seeding is the most common route of renal infections, such as renal candidiasis during an episode of candidemia. Although this event is usually asymptomatic with regard to urinary symptoms, many experimental animal studies have reported the development of multiple microabscesses throughout the cortex after intravenous administration of *C. albicans* [34]. After the fungi penetrate through the glomeruli into the proximal tubules, the fungi are shed into the urine [35]. Autopsy studies have revealed the presence of renal cortical microabscesses in most patients who die with invasive candidiasis [36].

2. Ascending Route

Retrograde ascending infections are the most common routes for genitourinary tract infections. This infection is observed more often in females than males because females have a shorter urethra and frequently have a vulvovaginal colonization of organisms. Although the pathogenesis of ascending infection by *Candida* has not been studied extensively, spread from the perineum into the bladder leads to colonization and then retrograde spread leads to an infection of the upper urinary tract, particularly concomitant with vesicoureteral reflux or an obstruction of urinary flow [34,37]. Urethral catheterization can lead to infection by the introduction of organisms into the bladder during the procedure or by the migration of organisms along the surface of the catheter from the external periurethral surfaces. Chronic indwelling urethral catheters can aggravate the situation thorough biofilm formation and the persistence of the organism, which leads to obstruction and difficulty in eradicating the organism [37].

CLINICAL MANIFESTATIONS

Candiduria is asymptomatic in most patients, even in patients with hematogenous spread to the renal cortex [3]. If candidemia develops, however, the signs of a systemic infection, such as fever, chills, and hypotension, can be found.

Patients with *Candida* UTI from the ascending route show similar symptoms to patients with bacterial infections. Patients with *Candida* pyelonephritis usually exhibit fever, chills, and flank pain, similar to the symptoms of bacterial pyelonephritis [38].

If *Candida* UTI occurs in the bladder, the patients report urinary urgency, urinary frequency, dysuria, suprapubic discomfort, and pneumaturia, similar to the symptoms of bacterial cystitis. The systemic symptoms and signs of infection are usually absent if the infection is confined to the bladder. On the other hand, if patients have an indwelling bladder catheter, they do not have lower urinary tract symptoms and usually complain of few symptoms [39]. Patients in the ICU are often unable to communicate any symptoms that they might have. This ambiguity of symptoms makes it difficult to differentiate between infection and colonization.

If a fungus ball, which is a mass of hyphae and yeast cells, is formed in the collecting system, the patients may complain of increasing flank pain and may become oliguric. If the fungal ball leads to a ureteral obstruction, acute colicky flank pain and fever may develop [40]. A fungus ball that forms in the bladder can remain asymptomatic until it obstructs the ureters and/or urethra.

Elderly patients often present with atypical signs and symptoms of infection, and a delayed diagnosis is possible if combined with altered mentality [41].

DIAGNOSIS

When candidal organisms are present in the urine, the major concern is whether this finding represents a significant infection of the urinary tract, colonization of the bladder, or contamination of the urine sample [42]. Unfortunately, there is no optimal sensitive diagnostic method available to distinguish these different possibilities, and a clinical assessment must be relied on in many circumstances.

The contamination of a urine specimen is common, particularly if the specimen is from a catheterized patient or a female with heavy yeast colonization of the vulvovaginal area. Therefore, it is wise to first repeat the urine culture and ensure that a clean-catch midstream urine specimen has been obtained. Aseptic bladder catheterization should be conducted to obtain a urine sample if the patient is unable to perform clean-catch midstream urine collection. If the second sample does not yield organisms, it indicates the previous result was from contamination, so further workup is not needed.

If candiduria is found in a patient with an indwelling catheter, the catheter should be removed, if possible. A second sample should be obtained several days later to see if the candiduria has disappeared. If so, further workup is not needed. In patients who require a catheter, the catheter should be replaced and a urine sample should be collected through the new catheter. If the candiduria has disappeared, the first sample likely represents colonization and no more workup is needed.

In patients with persistent candiduria, the major concern is whether there is bladder colonization, cystitis, or upper tract infection. The clinical manifestations and laboratory studies can be useful for establishing whether a patient has a *Candida* UTI.

Diagnostic imaging can be an important evaluation. Excretory urography can detect hydronephrosis when obstructive uropathy, non-functioning kidney, or a fungus ball in the collecting system is present. In patients in the ICU or with impaired renal function, ultrasonography is the preferred initial examination because of its portability and absence of renal toxicity. Computed tomography, magnetic resonance imaging, and renal scintigraphy are sensitive methods for detecting renal abscesses, fungus balls, and nonfunctioning kidneys.

TREATMENT

The risk of developing candidemia from candiduria is low. In a large prospective surveillance study, only seven (1.3%) out of 530 patients with candiduria developed candidemia after a 10 week follow-up [3]. A similar study reported that only five out of 233 patients with candiduria in the ICU developed candidemia due to the same species 2 to 15 days later [43]. In a clinical and molecular analysis to examine the relationship between candidemia and concomitant candiduria, only four (2.8%) of cases with candidemia showed the genotypic same species of *Candida* strains between two specimens [44]. For these reasons, the significance and the necessity of treatment are often uncertain.

Prior to treatment, persistent indwelling urinary catheters should be removed, if possible, because catheters make the eradication of candiduria very difficult. After removing the catheter without administering antifungal agents, the following urine culture could show a negative result of candiduria [3].

When administering antifungal agents, an obstruction of urine flow in the genitourinary tract should be considered and bacteriuria should be treated first. Antifungal agents could be ineffective if urine flow is obstructed. In addition, by treating the concomitant bacteriuria with antibacterial therapy, the patient's symptoms may be improved and antifungal therapy might not be needed.

If the infection relapses or fails to clear despite treatment, an imaging study, voiding function test, such as urodynamic studies, and cystoscopy, should be performed. Prostatic abscess, bladder fungus ball, and chronic bladder changes can all affect the relapse or treatment failure. If obstructive uropathy is detected in patients with an upper urinary tract *Candida* infection, the obstruction should be resolved by a percutaneous nephrostomy or a ureteral stent.

1. Asymptomatic Candiduria

Generally, asymptomatic candiduria should not be treated except under specific circumstances, such as patients undergoing urological procedures, neutropenic patients, and very low birth weight neonates (<1,500 g). In a randomized double-blind study of treatment with fluconazole and placebo for asymptomatic candiduria patients, fluconazole therapy initially showed high eradication rates, but urine cultures at two weeks showed similar candiduria rates among the

treated and untreated patients [45].

In patients with candiduria, who undergo a urological procedure, the risk of candidemia following urinary tract instrumentation is high. Therefore, treatment with fluconazole should be given before and immediately after the procedure [46,47]. Neutropenic patients with candiduria should be treated because neutropenia can minimize any related symptoms, indicating a high likelihood that candiduria reflects the upper tract infection and candidemia [48]. In very low birth weight neonates, candiduria is often a marker of invasive candidiasis and infections of the upper urinary tract. Therefore, although related symptoms are not observed, candiduria should always be treated in this population [22].

In patients with an indwelling urethral catheter and asymptomatic candiduria, treatments with antifungal agents are ineffective in eradicating candiduria and the long-term clinical outcomes will not improve [49].

2. Symptomatic Candiduria

Symptomatic candiduria can present with cystitis, pyelonephritis, prostatitis, and epididymo-orchitis. Each specific *Candida* UTI must be treated with the appropriate antifungal agents.

In symptomatic *Candida* cystitis, fluconazole is the drug of choice for most species of *Candida*, particularly *C. albicans*. The recommended dose is 200 to 400 mg daily, administered orally, for two weeks. On the other hand, *C. glabrata*, *C. krusei*, and other less common resistant species sometimes do not show susceptibility to fluconazole. Flucytosine can be considered for refractory *Candida* cystitis. Flucytosine is also concentrated in urine and most isolated *C. glabrata* are susceptible [50]. Generally, flucytosine therapy is recommended at a dose of 25 mg/kg every 6 to 8 hours for 7 to 10 days only because resistance can rapidly develop when this agent is used for extended periods. In addition, the potential toxicity from a high rate of cellular turnover, such as in the bone marrow and gastrointestinal mucosa, is a major concern [23,51]. Intravenous amphotericin B injections can be considered in refractory infections or in patients with unusually severe symptoms. The dosage and duration have not been established, but a 0.3 to 1 mg/kg intravenous injection for one or more doses, generally 1 to 7 days, is recommended [23,51]. Bladder irrigation with amphotericin B is another approach for the treatment of *Candida* cystitis. The most common dose is 50 mg amphotericin B diluted in 1 L of sterile water to give a concentration of 50 μg/ml [52]. On the other hand, the relapse rate after bladder irrigation is high and this strategy is rarely needed except for persistent cystitis by fluconazole-resistant organisms [53].

Renal parenchymal infection is generally the result of an antegrade infection and is treated the same as candidemia. Retrograde infections of the kidneys can also develop due to the retrograde spread of the organism in patients with obstructive uropathy, DM, and concomitant bacteriuria. Fluconazole is the agent of choice for pyelonephritis [48]. Generally, a daily oral dose of 400 mg for two weeks is recommended. Flucytosine or intravenous amphotericin B injection may be necessary in patients who have organisms resistant to fluconazole. The recommended dose of flucytosine and intravenous amphotericin B for *Candida* pyelonephritis is the same as with *Candida* cystitis, but the duration is slightly longer: 14 days for both drugs [23,51]. Lipid formulations of amphotericin B should not be used for treating renal candidiasis because the failure of this form has been reported [54].

The treatment approaches to *Candida* prostatitis have not been determined because *Candida* prostatitis is uncommon and the current approaches are based on individual case reports not from randomized controlled trials. Fluconazole has been used on susceptible organisms and is recommended at 400 mg per day for four weeks because the drug does not accumulate in the prostate. On the other hand, the achieved concentrations might not be sufficient to eradicate some strains [51]. Amphotericin B is a commonly used antifungal agent for *Candida* prostatitis. In many reports, surgical drainage for an abscess and resection of prostate tissue are important for therapy [55,56]. For the successful treatment of *Candida* prostatitis, surgical intervention combined with the use of drugs, such as fluconazole or amphotericin B, is required. Similar to *Candida* prostatitis, most *Candida* epididymo-orchitis patients require surgical drainage of an abscess and/or orchiectomy for treatment in combination with fluconazole or amphotericin B [57,58].

3. Treatment of Complications

Rare but serious complications of *Candida* UTI, such as emphysematous pyelonephritis and papillary necrosis, almost always require nephrectomy. Drainage should be

performed if a perinephric abscess is detected.

A fungus ball should be treated with medical therapy and surgical or radiological interventions. Systemic therapy is effective because these luminal aggregates of hyphae and necrotic tissues often result from systemic candidiasis or deeply disseminated parenchymal infection. Fluconazole is the mainstay of therapy. Although antifungal agent therapy can result in spontaneous disruption and passage of the hyphal mass filament and debris, it is not sufficient to eliminate the fungus ball completely [59]. An invasive procedure is almost always required to relieve the obstruction and remove the mass. If access to the renal pelvis through nephrostomy tubes is available, local irrigation with amphotericin B or fluconazole can be considered [60,61]. Intermittent saline irrigation, percutaneous endoscopic disruption and drainage, and percutaneous irrigation with streptokinase can also be performed to facilitate the breakdown and passage of fungus balls [62,63].

4. Antifungal Agent

The selection of an appropriate antifungal agent must consider the antifungal susceptibility of the organism and the ability of the antifungal agent to achieve the adequate concentrations in the urine.

Oral fluconazole, which is excreted into the urine as an active drug and achieves high urine levels, is the agent of choice for the treatment of *Candida* UTI [48]. Most *Candida* species are susceptible to fluconazole, including *C. albicans*, which is the most commonly cultured *Candida*, and fluconazole is effective for infections of both the upper and lower urinary tract. In particular, *C. glabrata* is often resistant to fluconazole, and *C. krusei* is uniformly resistant to fluconazole. Unlike fluconazole, the other azole agents, such as itraconazole, posaconazole, and voriconazole, are metabolized in the liver, and urinary excretion is either minimal or absent. Therefore, except for fluconazole, the other azole agents are not recommended for the treatment of *Candida* UTI.

If fluconazole is ineffective, intravenous amphotericin B deoxycholate may effective in treating *Candida* UTI and is the treatment of choice for UTI from *C. glabrata* or *C. krusei*. The recommended dose is 0.3 to 1.0 mg/kg per day for 5 to 7 days, but even a single-dose with 0.2 to 1.0 mg/kg has been shown to be effective [64]. The lipid formulations of amphotericin B, which show reduced nephrotoxicity, do not show adequate concentrations in the urine, and failure of these formulations has been reported [54].

Flucytosine is also valuable in treating fluconazole-resistant *C. glabrata*-induced UTI. Flucytosine achieves high concentrations in the urine and is active against many isolated *C. glabrata*. On the other hand, *C. krusei* is not susceptible to flucytosine. The recommended dose is 25 mg/kg every six hours daily for 7 to 10 days and 14 days for cystitis and upper UTI, respectively [48,51]. Nevertheless, this dosage is associated with the likelihood of bone marrow toxicity; thus, a lower dosage of 25 mg/kg every eight hours daily is preferred, but this dosage should be adjusted according to the level of creatinine clearance [23]. Complete blood cell counts and close monitoring of the patients for rash, diarrhea, or other gastrointestinal complaints are necessary. Hepatotoxicity is associated with flucytosine in up to 41% of patients.

CONCLUSIONS

Candiduria is observed predominantly in a nosocomial setting and is an uncommon finding in healthy people. On the other hand, patients with specific risk factors are vulnerable to *Candida* UTI. The optimal therapy for *Candida* UTI remains uncertain. Interventions for eliminating the predisposing factors, such as aggravating infections, should be implemented regardless of whether drug therapy is used. Decisions regarding the use of drug therapy, including the choice of agent, method of administration, and treatment duration, should be based on the medical condition of the patient and local epidemiology.

In elderly people, *Candida* UTI has become an increasingly important problem. Antifungal agent administration must be used with caution because elderly patients are usually already taking a number of medications and the risk of drug-drug interactions is more likely. When a therapeutic regimen is planned, comorbidities and multidrug use should be considered. Elderly patients can be colonized more easily by pathogenic fungi and have an increased incidence of *C. glabrata* infection, which has higher rates of mortality and resistance to fluconazole.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article

was reported.

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AUTHOR CONTRIBUTIONS

S.O.Y. participated in the study design. S.J.K. participated in data collection and wrote the manuscript. J.H.R. and Y.B.K. participated in coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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