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Principles in the Evaluation and Treatment of Candiduria in Adults

The isolation of yeast cells from urine is a common occurrence in hospitalized patients. However, clinicians are often confused by the current data on how best to evaluate and treat this finding since funguria can represent such disparate conditions as benign *Candida* colonization of a catheterized, immunocompetent patient or fungal sepsis in a neutropenic patient.¹ Additionally, available treatment options for asymptomatic candiduria do not uniformly result in lasting sterilization of the urine.^{2,3} Treatment guidelines for infections due to *Candida* species were recently published by the Infectious Diseases Society of America.⁴ The key recommendations of these practice guidelines for the evaluation and management of candiduria are presented here to help identify those patients at particular risk for progressive disease as well as those patients who might not need antifungal therapy.

Microbiology

Candida species are the most frequently identified yeast cells in urine samples submitted for culture. A prospective surveillance study of 861 hospitalized patients with candiduria revealed that *C. albicans* was the most commonly isolated yeast and was found in 52% of cases.⁵ The next most commonly isolated yeasts in this study were *C. glabrata* (16%), *C. tropicalis* (8%) and *C. parapsilosis* (4%). Morphologically similar under many conditions, the various *Candida* species can be distinguished from each other in the microbiology laboratory. Exact species identification may be appropriate in certain clinical situations since different *Candida* species often demonstrate distinctive patterns of antifungal susceptibility (Table 1).

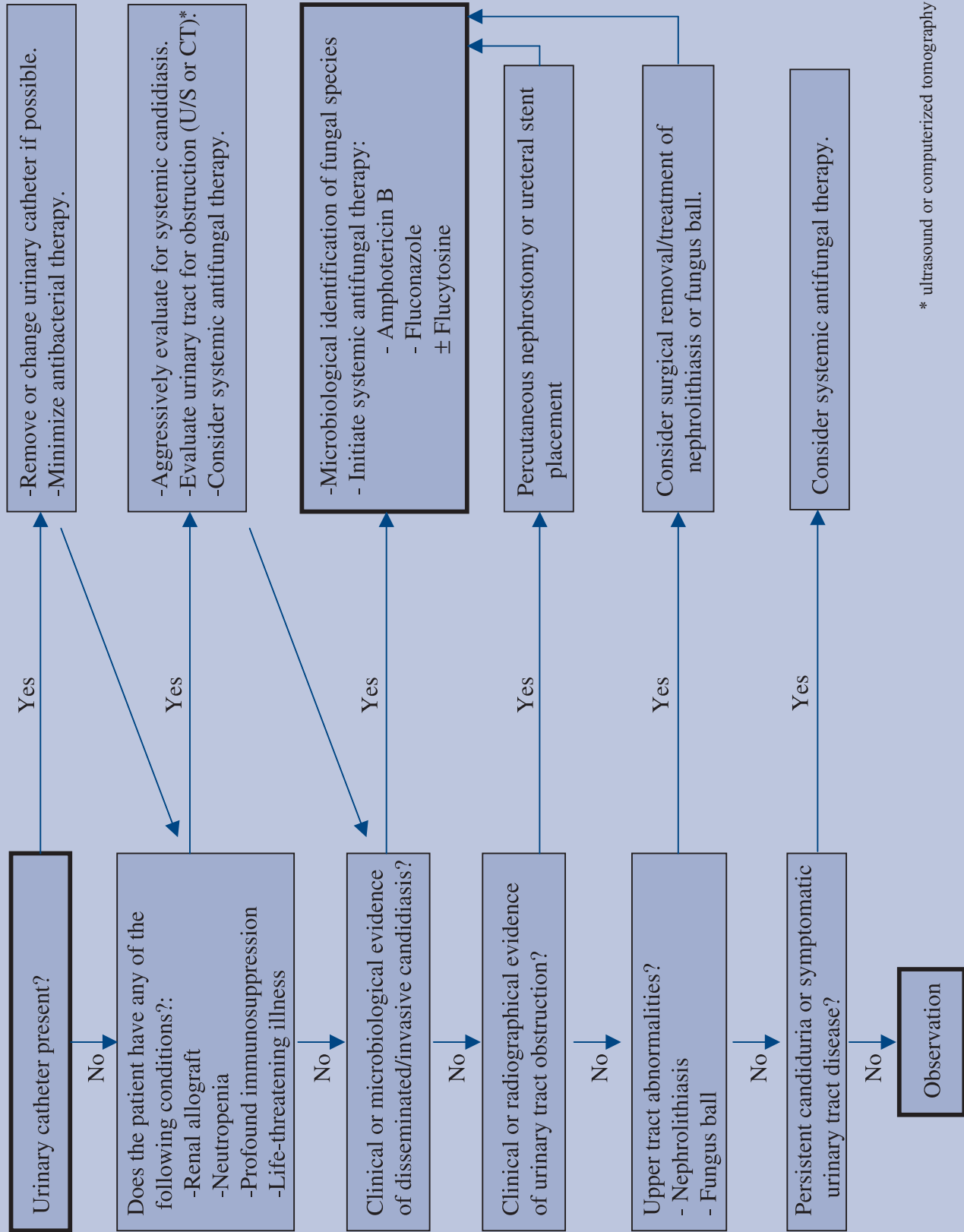
Frequent *Candida* Species Isolated from Urine and General Patterns of Susceptibility.

S = generally susceptible at appropriate doses. I = intermediate susceptibility.
R = generally resistant. (Rex et al, 2000).

Fungal species	Antifungal susceptibility	
	Fluconazole	Amphotericin B
<i>Candida albicans</i>	S	S
Non-<i>albicans</i> <i>Candida</i>		
<i>C. glabrata</i>	S to R	S to I
<i>C. tropicalis</i>	S	S
<i>C. parapsilosis</i>	S to R	S
<i>C. krusei</i>	R	S to I
<i>C. lusitanae</i>	S	S to R

Table 1

Proposed Flowchart for the Evaluation and Management of Asymptomatic Candiduria.



* ultrasound or computerized tomography

Figure 1

Acquisition of Candiduria

Most cases of candiduria occur in hospitalized patients having some form of urinary drainage devices. The pathophysiology of most candiduria cases is thought to be retrograde migration via bladder catheters of *Candida* species inhabiting the genital and perineal areas. In various studies, more than 80% of patients with candiduria had some form of bladder catheterization.^{5,6} Conditions that increase the rates of genital *Candida* colonization, such as diabetes mellitus, antibiotic use and female sex, are known risk factors for candiduria.^{5,6,7} *Candida* species rarely ascend the ureters and cause kidney involvement but may do so in the setting of mechanical obstructions and ureteral stents. Rarely, candiduria results from a fungal bloodstream infection with subsequent renal involvement.⁸

“The pathophysiology of most candiduria cases is thought to be retrograde migration via bladder catheters of *Candida* species inhabiting the genital and perineal areas.”

When to Treat Candiduria

There is general agreement that any patient with candiduria and objective evidence of parenchymal involvement of the urinary tract should be treated with systemic antifungal therapy.⁴ Additionally, candiduria may be the only microbiologic evidence of systemic candidiasis, especially among neutropenic or renal transplant patients and neonates. One study reported that 42% of neonates with candiduria had either a fungus ball or abscess involving the kidneys.⁹ Therefore, candiduria should prompt an aggressive evaluation in these patient populations for generalized candidal infection with blood cultures and imaging studies of the abdomen. Most experts agree that asymptomatic candiduria in these high-risk populations should be treated empirically pending the outcome of further studies.

However, most cases of candiduria are found in patients who have no particular symptoms localizing infection to the urinary tract and who do not have risk factors for invasive renal disease such as profound immunosuppression or anatomic genitourinary abnormalities. In these patients, candiduria is

“...most cases of candiduria are found in patients who have no particular symptoms localizing infection to the urinary tract...”

almost never indicative of a systemic or invasive mycosis but, rather, of lower urinary tract colonization in the setting of urinary instrumentation. Controversy exists over the efficacy of antifungal therapy for candiduria in this setting since the natural history of this condition is incompletely understood. Clearly, asymptomatic candiduria resolves spontaneously in

many cases. However, the value of prospectively identifying those patients that might benefit from aggressive intervention is not known. One study, which followed 155 patients with candiduria who received no treatment for their condition, found that 76% had spontaneous resolution of the candiduria over time.⁵ Alternatively, treating all episodes of candiduria is unwarranted since neither local nor systemic therapies consistently result in prolonged sterilization of the urine.^{3,10} Such an approach may result in both toxicities in the patient and further antifungal resistance among these important pathogens.

The decision not to treat patients with asymptomatic candiduria often raises the concern for the potential development of systemic infection. Complications such as ascending involvement of the kidney or candidemia have been found to be very rare (<2%) in patients with no urinary structural abnormalities whose initial presentation was one of asymptomatic candiduria. Definable risk factors for developing candidemia as a result of candiduria were assessed

Key Recommendations for Candiduria.

(Rex et al, 2000)

- 1) Asymptomatic candiduria rarely requires therapy.
- 2) Candiduria may be the only microbiological evidence of disseminated candidiasis.
- 3) Candiduria should be treated in the following patient groups:
 - symptomatic patients
 - neutropenic patients
 - low-birth weight infants
 - patients with renal allografts
 - patients with urologic manipulations
- 4) Short-course therapy is not recommended. Therapy for 7-14 days is more likely to be successful.
- 5) Removal of foreign devices in the urinary tract may help to clear candiduria. If complete removal is not possible, replacement with new devices may be beneficial.
- 6) For systemic treatment of candiduria, the following drug doses have been used in most clinical trials.
 - fluconazole, 200 mg/d PO or IV for 7-14 days
 - amphotericin B 0.3-1.0 mg/kg/d IV for 1-7 days
 - flucytosine 25 mg/kg/q.i.d PO may be useful in combination with another systemic agent, especially in infections due to non-*albicans* *Candida* species
- 7) Bladder irrigation with amphotericin B may transiently clear funguria but is rarely indicated; it may be used as a diagnostic tool for evaluating upper tract involvement.
- 8) Relapse of funguria is frequent, even after systemic therapy. Chronic urinary catheterization is a significant risk factor for recurrence.
- 9) Persistent candiduria in immunocompromised patients may indicate urinary obstruction or upper tract disease and should be pursued aggressively.

Table 2

in a retrospective study.¹⁰ These investigators identified 249 patients with candidemia and found 26 likely had a urinary source. The majority of patients who developed blood-stream infection as a result of candiduria had a structural abnormality of the urinary tract (88%) or urinary obstruction (73%). In this study, candidemia resulting from a urinary source was usually of short duration, often resolving spontaneously, in contrast to candidemia from an intravascular source. However, 2 deaths among these patients were felt to be directly attributable to systemic *Candida* infection from a urinary source.

Recent recommendations for the treatment of candidiasis adopted by the Infectious Diseases Society of America outline those patients who should be treated for asymptomatic candiduria (Table 2). Populations in whom asymptomatic candiduria should aggressively be treated include neutropenic patients, low birth weight infants, and renal allograft recipients. Other populations at risk in which systemic antifungal therapy should be strongly considered for candiduria include patients without current or recent instrumentation of the urinary tract, patients with obstructive uropathy, and critically ill patients in intensive care units. Occult candidemia should also be considered in febrile patients with candiduria and no other clear source of infection.

“Currently available systemic regimens may be beneficial for treating or preventing the systemic complications of candiduria in susceptible patient populations.”

Treatment of Candiduria

Several studies have prospectively evaluated the efficacy of available therapies for asymptomatic candiduria. Leu and Huang compared the efficacy in candiduria of placebo, oral fluconazole, a single intravenous dose of amphotericin B, and local bladder irrigation with various concentrations of amphotericin B solutions.² Approximately 40% of untreated patients demonstrated resolution of funguria at 1 week by simply minimizing antibiotics and removing or changing urinary catheters. Among treated patients, amphotericin B local administration resulted in effective early clearance of funguria (82% to 87% clearance at 1 day) but the effect did not last since only 43% to 68% of patients displayed sustained microbiologic resolution at 7 days. Systemic therapy with oral fluconazole or single dose intravenous amphotericin B resulted in 1-week urine culture clearance rates of 77% and 72%, respectively.

Recently, Sobel et al. prospectively evaluated the efficacy of fluconazole versus placebo in fungal eradication of 316 asymptomatic or minimally symptomatic hospitalized patients

with candiduria.³ Higher early rates of fungal clearance were observed in patients treated with fluconazole (50%) than with placebo (29%) ($P < .001$). This effect did not last. There was no significant difference in the eradication rates 2 weeks after treatment was discontinued in the fluconazole or placebo groups.

The consensus of these and previous studies is that both local and systemic therapies fail to result in sustained clearance of funguria. Currently available systemic regimens may be beneficial for treating or preventing the systemic complications of candiduria in susceptible patient populations. Therefore, systemic therapy for candiduria should likely be limited to patients at an increased risk for developing invasive or systemic infection caused by *Candida*. Based on recent expert recommendations,⁴ a working plan for evaluating and managing asymptomatic candiduria is proposed (Fig. 1).

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