

Current Management of Fungal Urinary Tract Infection and Funguria

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Outline

- Approach to candiduria
- Management of candiduria
 - Asymptomatic candiduria
 - Candiduria in ICU setting
 - *Candida* UTI and treatment

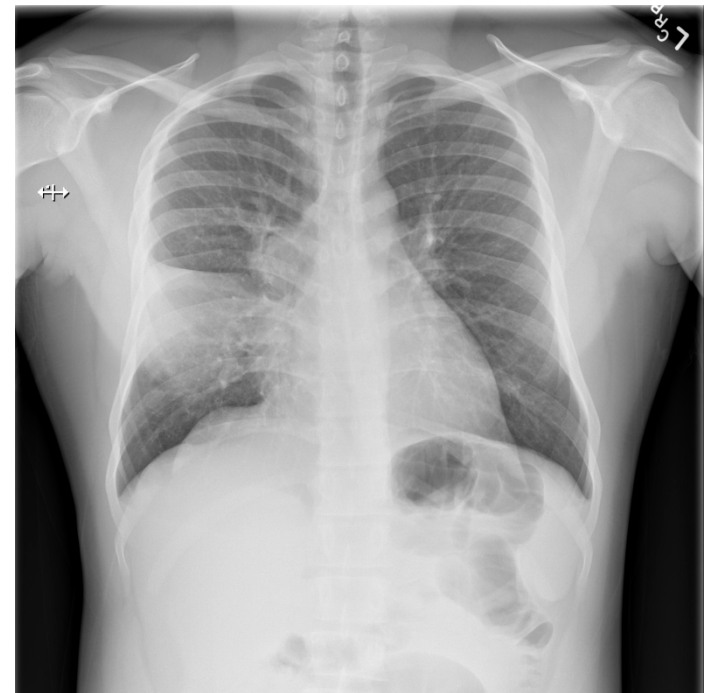
Case 1

- A 75-year-old female presented with fever and dyspnea for 3 days
 - Underlying disease : T2DM, HT, left MCA infarction
 - Status bed ridden
 - She was on Foley catheter due to neuropathic bladder
 - Last admission due to pneumonia 1 month ago
- PE:
 - T 39°C, BP 110/70 mmHg, P110/min, RR24/min
 - CVS: normal S1, S2, no murmur
 - RS: crepitation at right lower lung field
 - Abdomen: soft, not tender

Case 1

- Lab:
 - CBC: Hb 12 g/dL, Hct 36%
WBC 14,000 cell/cumm
(**N 90%**, L18, M 2%),
Plt 110,000 cell/cumm
 - BUN 25, Cr 1.2, Na 135,
K 4, Cl 100, HCO₃ 15
 - UA: pH 6, sp.gr. 1.020,
WBC 5-10, RBC 0-1,
leukocyte neg, nitrite neg,
yeast 2+
 - **Urine culture: *Candida albicans* < 10⁵ CFU/mL**

- CXR



Case 1

- Piperacillin/tazobactam was initiated for treatment of pneumonia.
- What should you do next
 - A. Start amphotericin B
 - B. Start fluconazole
 - C. Start an echinocandin
 - D. Change Foley catheter and repeat UA
 - E. Repeat UA and observe only

Candiduria

Candiduria

- Definition: unclear
 - Urine culture: *Candida* spp.
 - Microscopic visualization in urine
 - No diagnostic criteria (CFU cutoff): range 10^3 - 10^5 CFU/ml
- Most patients: asymptomatic
- Serendipitous finding in urine
- Common in hospitalized patient esp. ICU setting
- Epidemiology:
 - 16.5-40% in ICU
 - *Candida albicans* (>50%) > *C. glabrata* > *C. tropicalis*

Candiduria

Contamination

- Repeat UA or urine culture
- Clean-voided, midstream sample

Colonization

- Change catheter or device
- Repeat urine

Infection

- Symptoms?



Symptomatic vs. Asymptomatic Candiduria

- Lower tract infection
 - Dysuria
 - Urgency
 - Suprapubic discomfort
 - Stranguria
- Upper tract infection
 - Fever
 - Frank pain
- Patients with Foley catheter or unconscious: may have no symptom
- Urinalysis: pyuria?, yeast cell cast? CFU cut-off?



Risk factors of candiduria

- **Diabetes mellitus**
- Extremes of age
- Female sex
- **Prolonged hospitalization**
- **ICU admission**
- **Broad-spectrum antibiotics**
- Bladder dysfunction
- Urinary stasis
- Nephrolithiasis
- Renal transplantation
- **Instrumentation of the urinary tract**
- Concomitant bacteriuria
- Congenital abnormalities of the urinary tract
- Structural abnormalities of the urinary tract
- **Indwelling urinary tract devices**
- Bladder stones

Asymptomatic candiduria

Develop
candidemia?

Treat?



Natural History of Asymptomatic Candiduria

Prospective Multicenter Surveillance Study of Funguria in Hospitalized Patients

Carol A. Kauffman,¹ José A. Vazquez,² Jack D. Sobel,²
Harry A. Gallis,^{3,a} David S. McKinsey,⁴

From the ¹University of Michigan and Veterans Affairs Medical Center, Ann Arbor, Michigan; ²Wayne State University Medical

- Multicenter prospective surveillance study
- 861 patients: yeast in urine culture
- 530 (61.6%) patients → evaluate outcome
 - 117/155 (75%) resolved without treatment
 - Only 7 patients (1.3%) developed candidemia



Natural History of Asymptomatic Candiduria

- Most observational studies^{1,2}: candiduria does NOT commonly lead to candidemia (1.3-8%)
- Candiduria as a source of candidemia → urinary tract obstruction and have undergone urinary tract procedure³
- Marker for greater mortality⁴
 - BUT death not related to *Candida* infection
 - Likely a marker for severity of illness
 - Treatment did not improve outcome

¹Clinical Infectious Diseases 2000; 30:14–8

²Intensive Care Med. 2008 Feb;34(2):292-9

³Clin Infect Dis 1993; 17:662

⁴The Journal of infection. 2007;55(5):450–5.

Treatment of asymptomatic candiduria

- 316 asymptomatic candiduric hospitalized patient
- Randomized: fluconazole 200 mg vs placebo 14 days

Characteristic	Fluconazole (n = 159)	Placebo (n = 157)
Age (y)	70.2 ± 1.2	70.2 ± 1.1
Male	65 (41)	55 (35)
Female	94 (59)	102 (65)
White	122 (77)	118 (75)
Black	33 (21)	38 (24)
Diabetes mellitus	77 (45)	70 (45)
Recent antibiotics	144 (91)	146 (93)
Catheterized	89 (56)	88 (56)
Age (y)	71.6 ± 1.6	72.0 ± 1.5
Male	27 (30)	27 (31)
Female	62 (70)	61 (69)
Diabetic	36 (40)	35 (40)
Noncatheterized ^a	70 (44)	69 (44)
Age (y)	68.3 ± 1.8	67.7 ± 1.4
Male	38 (54)	28 (41)
Female	32 (46)	41 (58)
Diabetic	41 (59)	35 (51)

Treatment of asymptomatic candiduria

Analysis group	Fluconazole	Placebo	<i>P</i>
All enrolled patients (<i>n</i> = 316) ^a	79/159 (50)	46/157 (29)	<.001
Catheterized	35/89 (39)	18/88 (20)	.008
Uncatheterized	44/70 (63)	28/69 (41)	.01
Patients completing 14 days of therapy (<i>n</i> = 238)	75/118 (63)	42/120 (35)	<.0001
Catheterized	33/64 (52)	16/65 (25)	.002
Uncatheterized	42/54 (78)	26/55 (47)	.0015
Two-week follow-up ^a after therapy completed (<i>n</i> = 173) ^b	59/87 (68)	56/86 (65)	.7
Catheterized	27/44 (61)	22/39 (56)	.7
Uncatheterized	32/43 (74)	34/47 (72)	1.00

- Candiduria recurred 40%
- None of these patients developed candidemia



Management of asymptomatic candiduria

- **Recommendations**
- Elimination of predisposing factors eg. Foley catheter
- Treatment with antifungal agents is **NOT** recommended unless the patient high risk for dissemination
 - Neutropenic patients
 - Very low-birth-weight infants (<1,500 g)
 - Undergo urologic manipulation
 - Oral fluconazole, 400 mg daily, OR
 - AmB deoxycholate, 0.3–0.6 mg/kg daily
 - Several days before and after the procedure



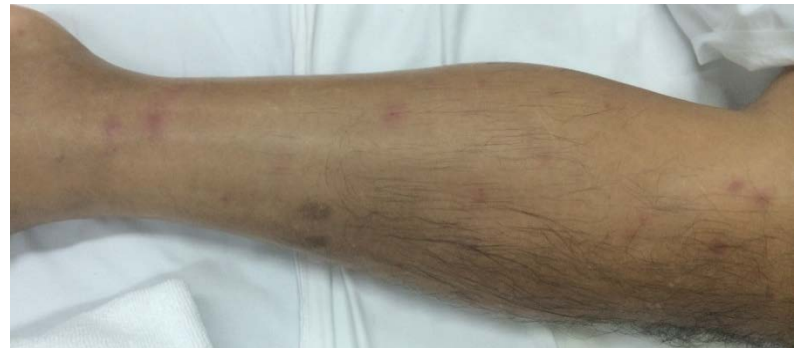
Case 2

- A 75-year-old male was admitted in the ICU with severe community acquired pneumonia
- He was complicated with ***Acinetobacter baumannii*** pneumonia and treated with intravenous colistin for 10 days and vancomycin was added for phlebitis
- 5 days later, he developed new onset fever with septic shock

Case 2

- PE:
 - V/S: T 39°C, BP 80/40 mmHg, P 120/min, RR 26/min (on ventilator)
 - Rt internal jugular CVC
 - CVS: unremarkable
 - RS: crepitation right lung (same as previous)
 - Abdomen: soft, not tender

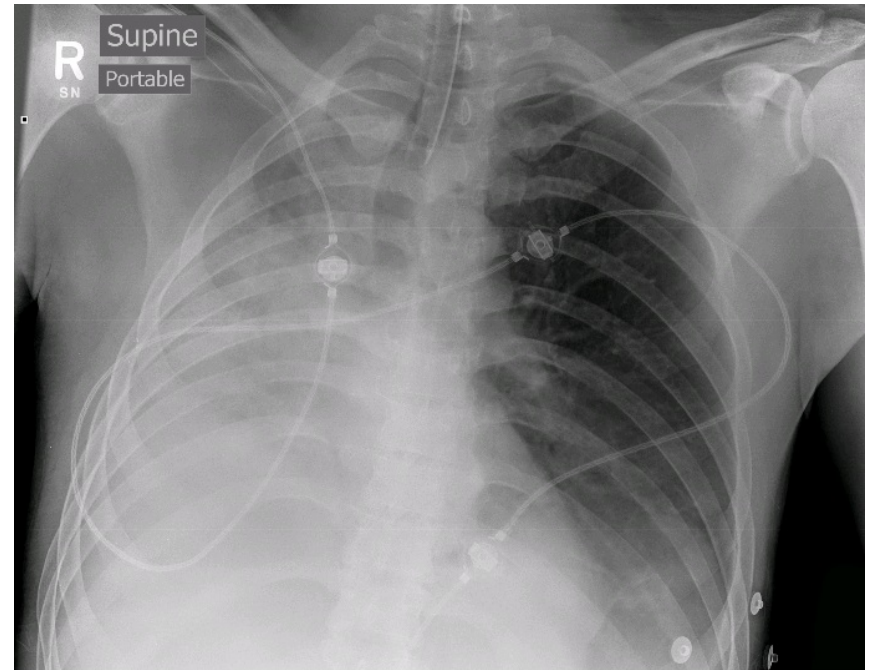
- Skin:



Case 2

- Lab:
 - CBC: Hb 10 g/dL, Hct 30.5% **WBC 15,000** cell/cumm (N 80%, L10, **band 10%**), Plt 120,000 cell/cumm
 - BUN 30, cr 1.3, Na 135, K 4, Cl 100, HCO3 13
 - UA: pH 6, sp.gr. 1.020, WBC 5-10, RBC 0-1, leukocyte neg, nitrite neg, **yeast 2+**

- CXR: same as 2 days ago



Case 2

- What should you do next
 - A. Start amphotericin B
 - B. Start fluconazole
 - C. Start an echinocandin
 - D. Change Foley catheter and repeat UA
 - E. Repeat UA and observe only

Candiduria in ICU Setting

- Evaluate possibility of disseminated candidiasis
- 46-80% of persons with candidemia → accompanying with candiduria
- However!!!
- Candiduria commonly found in hospitalized patients esp. in ICU
- Removing catheter → resolve 20-40% and reinserted of catheter can resolve in 20% of candiduria
- Correct risk factors eg. discontinue ATB if no indication

Candiduria and Candidemia

- In a large prospective study, only 7 (1.3%) of 530 patients who had candiduria and were followed for 12 weeks developed candidemia.¹
- A retrospective study, 11 (10.5%) of 105 patients with candiduria developed candidemia.²
- In a treatment trial that specifically enrolled asymptomatic or minimally symptomatic patients with candiduria, none of 316 patients developed candidemia.³
- In the presence of obstruction, candidemia can follow candiduria.^{4,5}

¹Saudi Med J 2006;27(11):1706-10, ²Clin Infect Dis 2001; 32(11):1602-7,

³Clin Microbiol Infect 2006;12(6): 538-43, ⁴Expert Rev Anti Infect Ther 2007;5(2):277-84,

⁵Drug Aging 1996;8(2):89-96

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Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome

- A 1-year prospective observational study in 24 adult ICUs
- 262 patients with nosocomial candidemia and/or candiduria
- The mean incidences of candidemia and candiduria were 6.7 and 27.4/1000 admissions, respectively.
- 8% of candiduric patients developed candidemia with the same species.

Predisposing Factors for Candidemia

- **Neutropenia**
- **Non-neutropenic host**
 - Prolonged broad spectrum antibiotics
 - Intravascular catheterization
 - ICU admission
 - Abdominal & thoracic surgery
 - Parenteral nutrition
 - Severe burn

NON-specific !!

Candida Scores

Leon score¹

- Non-neutropenic ICU patients

Criteria

- Multifocal *Candida* colonization
- Surgery
- TPN
- Severe sepsis (X 2)

- **Positive: Total score ≥ 3**
- **Sensitivity 81%**
- **Specificity 74%**

Ostrosky-Zeichner score²

Major criteria

- ICU stay ≥ 4 days and
- Systemic ATB therapy or Central venous catheter

Minor criteria

- TPN
- Any dialysis
- Any major surgery
- Pancreatitis
- Steroid use
- Immunosuppressive drug use
- Positive: 2 major + 2 minor criteria
- Sensitivity 34%
- Specificity 90%



Developing SiCAS-2 Local Score

Multivariate analysis (Non-neutropenic group)

	Coefficient	Standard Error	P value	RR	95% C.I.	
Candiduria	0.752	0.664	0.047	2.12	1.011	4.46
Parenteral nutrition	1.193	0.394	0.003	3.30	1.50	7.23
Solid tumor	1.312	0.451	0.005	3.71	1.49	9.26
Severe sepsis	2.324	0.383	<0.001	10.21	4.76	21.93

Siriraj Candidemia Assessment Score (SiCAS)

- **SiCAS-2 (Non-neutropenia)**
 - = 2(Parenteral nutrition)
 - + 2(Candiduria)
 - + 3(Solid tumor)
 - + 5(Severe sepsis) -5
- Positive: score ≥ 0

Cutoff value for SiCAS-2 with discriminatory power

Cutoff	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(≥ -5)	100.00	0.00	36.24	1.0000	
(≥ -3)	94.94	47.48	64.68	1.8077	0.1066
(≥ -2)	88.61	64.03	72.94	2.4633	0.1779
(≥ -1)	81.01	69.78	73.85	2.6811	0.2721
(≥ 0)	75.95	72.66	73.85	2.7781	0.3310
(≥ 2)	49.37	88.49	74.31	4.2888	0.5722
(≥ 3)	16.46	97.84	68.35	7.6245	0.8539
(≥ 4)	13.92	98.56	67.89	9.6772	0.8733
(≥ 5)	7.59	98.56	65.60	5.2785	0.9375
(≥ 7)	1.27	100.00	64.22		0.9873
(> 7)	0.00	100.00	63.76		1.0000



Empirical antifungal therapy in non-neutropenic patients

- Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites.

(strong recommendation; moderate-quality evidence).

- Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock.

(strong recommendation; moderate-quality evidence)

Case 2

- H/C: budding yeast
- Urine culture: *Candida albicans*

Treatment:

- Treat for candidemia (empirical and definite)
 - Echinocandin (AI)
 - Amphotericin B (liposomal or deoxycholate)
 - Fluconazole

Case 3

- A 39-year-old woman with type 2 diabetes mellitus developed urinary dysuria, frequency, urgency and pelvic discomfort without systemic features shortly after renal transplantation
- Her medication: mycophenolate mofetil, tacrolimus and prednisone
- PE:
 - V/S:T 36.8c, BP 130/80 mmHg, P 80/min, RR 18/min
 - Abdomen: mild tender at suprapubic area
 - Other: unremarkable

Case 3

- Lab:
 - CBC: Hb 12 g/dL, Hct 36% WBC 8,000 cell/cumm (N 60%, L135, M 5) Plt 120,000 cell/cumm
 - BUN 18, cr 1.3, Na 135, K 4, Cl 100, HCO₃ 24
 - UA: pH 6, sp.gr. 1.020, WBC 20-30, RBC 0-1, leukocyte neg, nitrite neg, **yeast 2+**
- Urine culture: ***C. albicans***

Case 3

- What should you do next
 - A. Start amphotericin B
 - B. Start fluconazole
 - C. Start an echinocandin
 - D. Change Foley catheter and repeat UA
 - E. Repeat UA and observe only

Symptomatic candiduria



Symptomatic candiduria

- Pathophysiology
 1. Ascending infection: lower tract → upper tract
 2. Hematogenous spreading to kidney
- Cystitis: dysuria, frequency, suprapubic discomfort
- Pyelonephritis: fever, frank pain
- Fungal ball (rare): oliguria, stranguria
- Rarely: prostatitis, epididymitis, orchitis

Treatment of symptomatic candiduria

Antifungal susceptibility

Adequate antifungal
concentration in urine

Antifungal treatment

- Cell membrane
 - Polyene antibiotics: Amphotericin B
 - Azole antifungals
 - Allylamine antifungals: terbinafine
- DNA/RNA Synthesis
 - Flucytosine
- Cell Division
 - Griseofulvin
- Cell Wall
 - Echinocandins

Azole antifungals

- Fluconazole
 - 80% excrete in the urine
 - High concentration in urine (10 time to plasma)
 - Active against most of *C. albicans* (most common cause of fungal UTI)
 - Drug of choice for *Candida* UTI
- Other azoles: minimal excretion of active compound in urine
 - Not useful for *Candida* UTI

Flucytosine

- 97% excrete in the urine
- High concentration in urine
- Good activity against many *Candida* species except *C. krusei*
- Side effect:
 - Bone marrow suppression
 - GI disturbance
 - Rash
 - hepatotoxicity



Amphotericin B

- AmB deoxycholate
 - Active against most of *Candida* species
 - High concentration in urine
 - Renal toxicity
- Lipid formulation: designed to decrease renal toxicity
 - Do not achieve levels in urine and kidney
 - Should not be used

Echinocandins

- Low concentrations (<2% of the dose) of active drug in urine
- Generally are ineffective in treating *Candida* UTI
- Case reports of successful treatment
 - Infection localized in kidney
 - Hematogenous spreading

Symptomatic *Candida* cystitis

- **Recommendations**
- For fluconazole-susceptible organisms
 - Oral fluconazole, 200 mg (3 mg/kg) daily for 2 weeks
- For fluconazole-resistant *C. glabrata*
 - AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7days OR
 - Oral flucytosine, 25 mg/kg 4 times daily for 7–10 days
- For *C. krusei*
 - AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7days
- Removal of an indwelling bladder catheter, if feasible, is strongly recommended

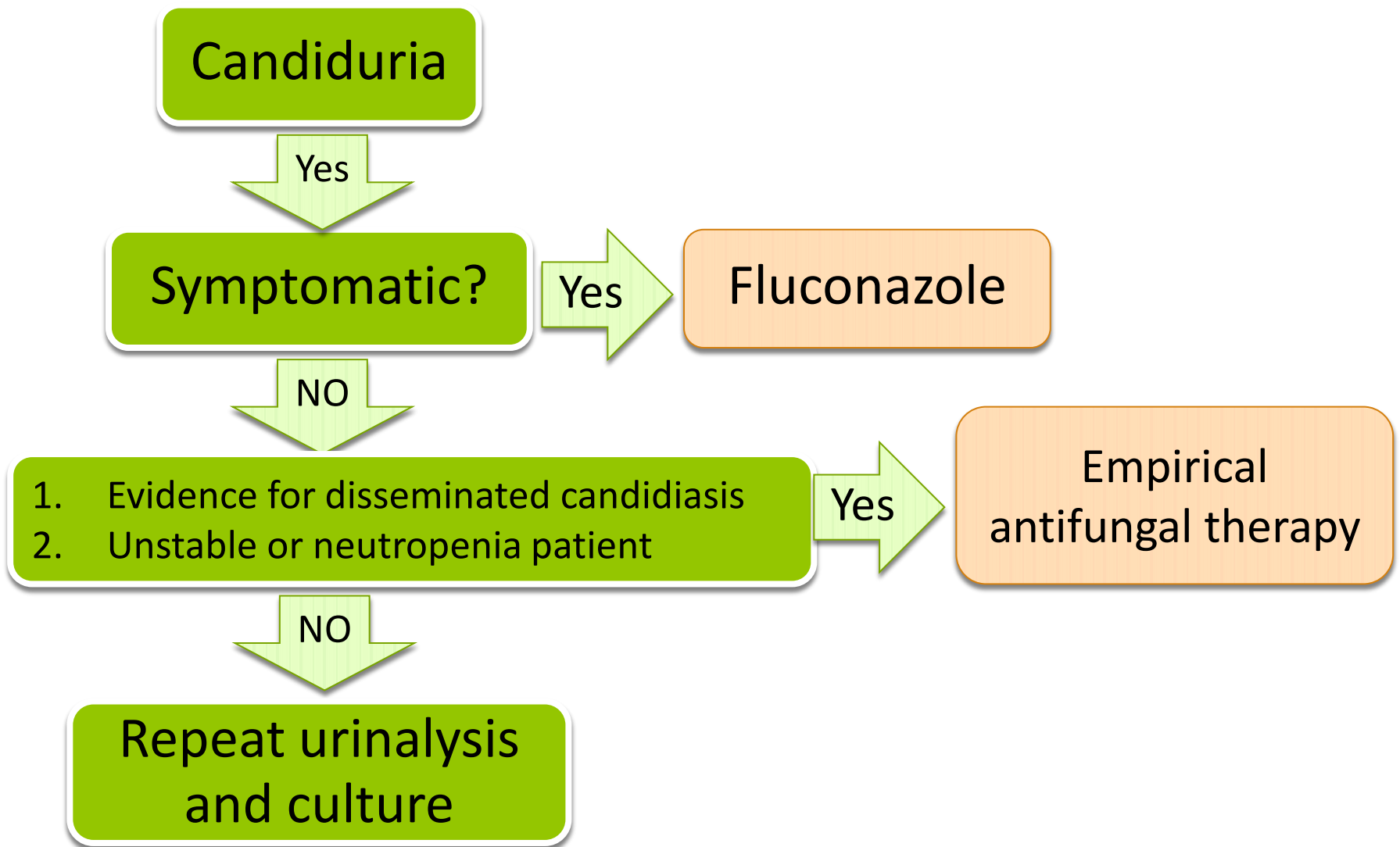
Symptomatic Ascending *Candida* Pyelonephritis

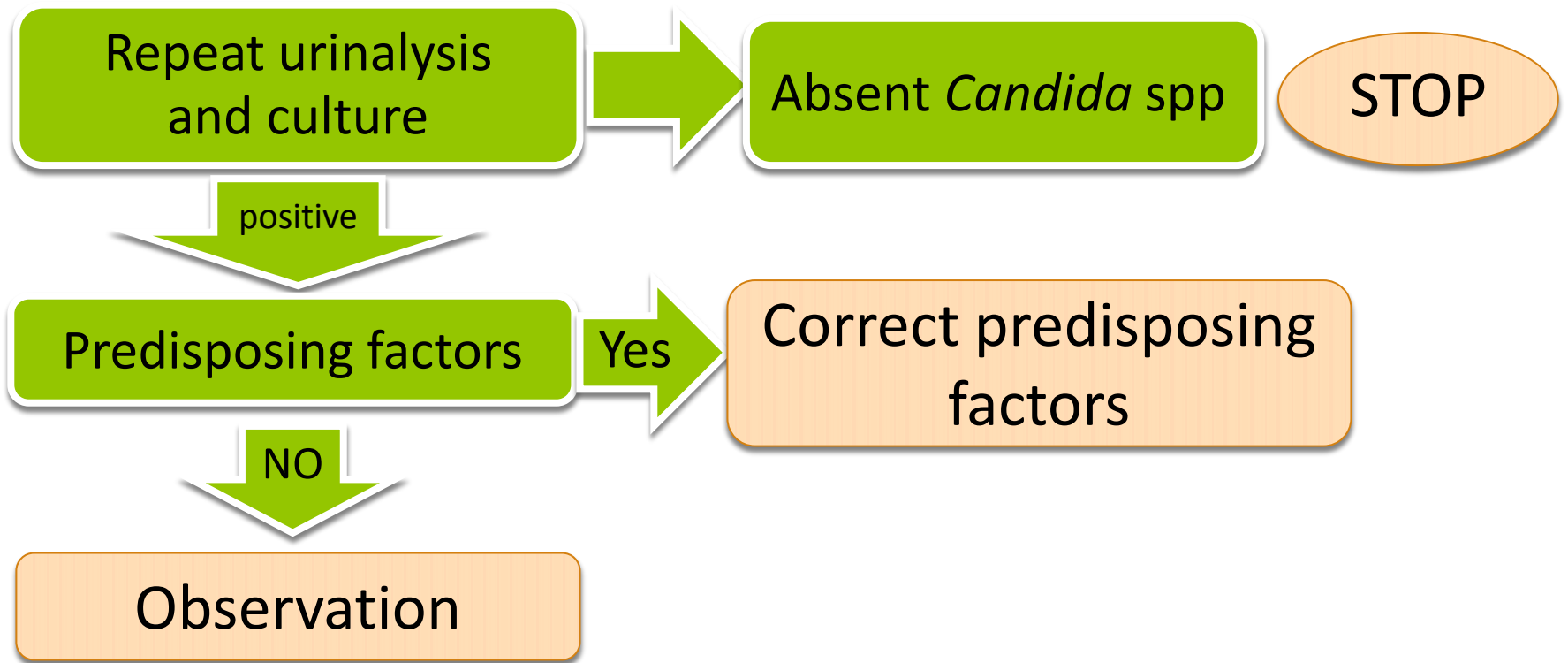
- **Recommendations**
- For fluconazole-susceptible organisms
 - Oral fluconazole, 200–400 mg (3–6 mg/kg) daily for 2 weeks
- For fluconazole-resistant *C. glabrata*,
 - AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days, with or without oral flucytosine, 25 mg/kg 4 times daily
 - Monotherapy with oral flucytosine, 25 mg/kg 4 times daily for 2 weeks
- For *C. krusei*
 - AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7day
- Elimination of urinary tract obstruction is strongly recommended
- For patients who have nephrostomy tubes or stents in place, consider removal or replacement, if feasible



Candida Urinary Tract Infection Associated With Fungus Balls

- **Recommendations**
- Surgical intervention is strongly recommended in adults
- Antifungal treatment
- Irrigation through nephrostomy tubes, if present, with AmB deoxycholate, 25–50 mg in 200–500 mL sterile water, is recommended





Thank you



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