

TITLE: CANDIDA INFECTIONS - TREATMENT GUIDELINES IN ADULT PATIENTS

GUIDELINES:

These are the 2011 Guidelines for the Treatment of *Candida* species infections in adult patients. These recommendations take into account drugs available on the New York-Presbyterian Hospital Formulary, susceptibility of *Candida sp.* to antifungal agents, hospital specific *Candida sp.* susceptibilities, toxicities and drug interactions of the antifungals, and cost. A patient's antifungal treatment history, history of positive fungal cultures, end-organ function, drug interaction potential, and level of immunosuppression corresponding to risk of non-*Candida* invasive fungal infections must always be taken into account. In addition, appropriate dosing for the patient's weight, end-organ function, site of infection, and drug interactions are essential to improving outcomes and limiting the selection of more resistant *Candida* species. Historically, lower dosing of fluconazole (100-200 mg daily) for systemic infections has been associated with an increase in the development of azole-resistant *Candida species*, such as *C. glabrata*.

Note: With few exceptions, all antifungal agents require approval from Infectious Diseases prior to use.

PURPOSE:

These guidelines are intended to optimize the use of antifungal therapy, but are not meant to replace clinical judgment.

APPLICABILITY:

Prescribers and pharmacists

PROCEDURE:

1. Usual Susceptibilities of *Candida sp.* to Antifungal Agents

<i>Candida sp.</i>	Fluconazole	Itraconazole	Voriconazole	Posaconazole	AmphoB	Caspofungin
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S to I
<i>C. glabrata</i>	S-DD to R	S-DD to R	S to S-DD	S to S-DD	S to I	S
<i>C. krusei</i>	R	S-DD to R	S to S-DD	S to S-DD	S to I	S
<i>C. lusitaniae</i>	S	S	S	S	S to R	S

Modified from Dodds Ashley et al. *Clin Infect Dis* 2006; 43: S28-39.

S=Susceptible

S-DD= Susceptible-dose dependent (increased MIC may be overcome by higher dosing – e.g. 12 mg/kg/day fluconazole)

I=Intermediate

R=Resistant

2. Breakdown of Candida species Isolated from Blood Cultures

NYP/C Milstein Hospital

	2005 n=59	2006 n=56	2007 n=58	2008 n=84	2009 n=50	2010 n=54
% <i>C. albicans</i>	46	41	42	31	46	31
% <i>C. glabrata</i>	30 ^a	25 ^b	38 ^c	39 ^d	22 ^e	43 ^f
% <i>C. parapsilosis</i>	10	23	12	11	16	15
% <i>C. tropicalis</i>	14	9	4	13	8	4
% <i>C. krusei</i>	--	2	--	--	2	--
% <i>Other</i>	--	--	--	5	6	8

a: FLU susceptibility: 17% S, 50% S-DD, 33% R

b: FLU susceptibility: 43% S, 50% S-DD, 7% R

c: FLU susceptibility: 32% S, 53% S-DD, 16% R

d: FLU susceptibility: 26% S, 32% S-DD, 42% R

e: FLU susceptibility: 50% S, 30% S-DD, 20% R

f: FLU susceptible: 30% S, 61% S-DD, 9% R, 7% unknown

NYP/WC

	2005 n=71	2006 n=62	2007 n=63	2008 n=75	2009 n=64	2010 n=74
% <i>C. albicans</i>	61	60	48	40	48	43
% <i>C. glabrata</i>	14 ^a	14.5 ^b	11.1 ^c	17.3 ^d	23 ^e	31 ^f
% <i>C. parapsilosis</i>	13	9.7	20.6	23	13	8
% <i>C. tropicalis</i>	7	9.7	12.6	13.3	9	8
% <i>C. krusei</i>	2	2	3	1	1.5	7
% <i>Other</i>	--	--	--	--	3	3

a: FLU susceptibility: 60% S, 0% S-DD, 40% R

b: FLU susceptibility: 44% S, 0% S-DD, 56% R

c: FLU susceptibility: 43% S, 14% S-DD, 43% R

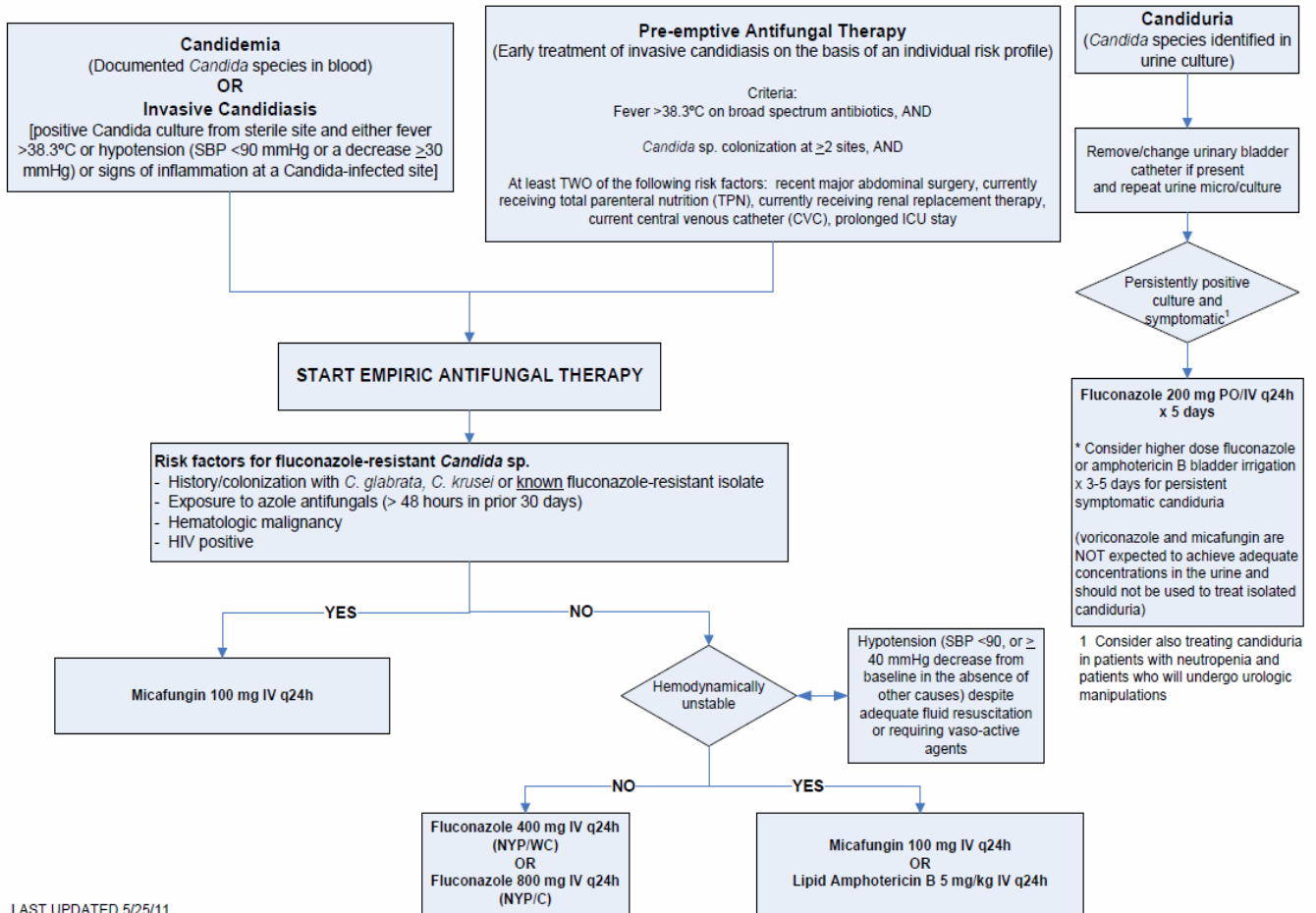
d: FLU susceptibility: 77% S, 0% S-DD, 23% R

e: FLU susceptibility: 53% S, 27% S-DD, 20% R

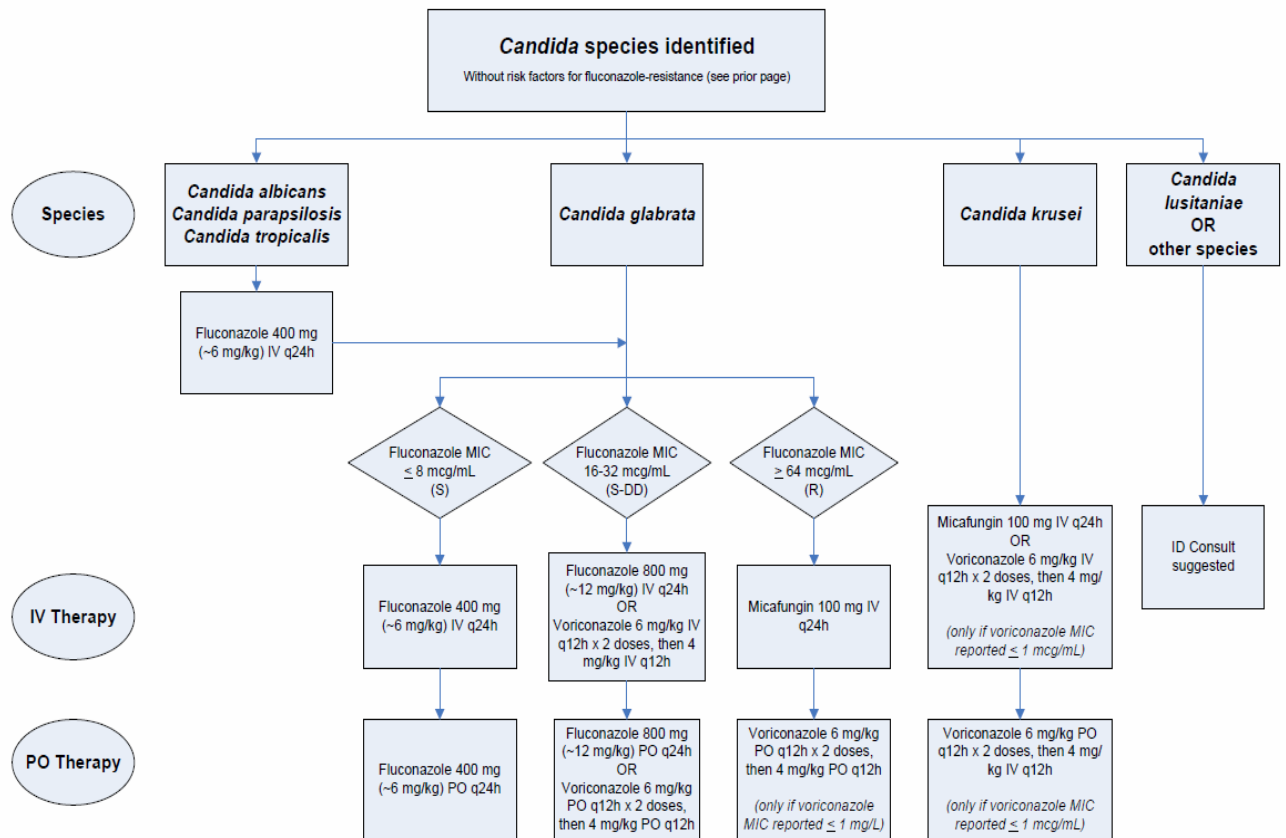
f: FLU susceptibility: 70% S, 17% s-DD, 13% R

3. Algorithm

Antifungal Therapy for the Treatment of Infections Caused by *Candida* species in Adult Patients



LAST UPDATED 5/25/11



PO THERAPY
 Oral therapy encouraged whenever possible. Most oral antifungal agents recommended above have very good oral bioavailability (>95%) and initiation of IV therapy is not always necessary unless patient is hemodynamically unstable and/or GI absorption can not be ensured. If IV therapy is initiated, the switch to oral or via tube administration is encouraged once the following criteria are met and there is an oral alternative. There is no need to re-load a patient with PO therapy, but just convert the maintenance therapy.

Criteria for oral or via tube administration:
 - GI absorption likely normal
 - Ability to receive oral dosage form (analogous to concomitant oral or via tube administration of any other meds)

4. Antifungal agents comparisons

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Amphotericin B products	Micafungin
Dosage forms	IV/PO	PO	IV/PO	PO	IV	IV
Oral bioavailability	>90%	55%	>95%	N/A	N/A	N/A
Effect of gastric pH	None	Decreased concentrations	None	? decreased with PPI	N/A	N/A
CSF penetration	Excellent (~80%)	Poor (<10%)	Good (40-60%)	N/A	N/A	Unknown, expected poor
Elimination route	Renal	Hepatic	Hepatic	Hepatic	Unknown	Hepatic
Renal dose adjustment	Yes ¹	No	No ²	No	No	No
Hepatic dose adjustment	No	Yes ³	Yes ⁴	No	No	No ⁵
Toxicities	Hepatotoxicity (high doses and prolonged therapy)	GI Hepatotoxicity Negative inotropic effects	Visual disturbances Hepatotoxicity Rash Hallucinations	GI Hepatotoxicity	Nephrotoxicity Infusion related reactions Electrolyte abnormalities	Phlebitis/ thrombophlebitis Elevated transaminases Histamine release reaction
Drug interaction potential	+	+++	+++	++	-	+
Induction/inhibition	Inhibits CYP3A4 and other CYP isoforms	Substrate and inhibitor of CYP3A4	Substrate and inhibitor CYP2C19>CYP2C9>CYP3A4	Inhibits 3A4	None	None

1 Fluconazole requires dose adjustment in renal dysfunction. For estimated CrCl <30mL/min or receiving hemodialysis or peritoneal dialysis, ½ the usual daily dose should be administered. For patients receiving continuous renal replacement therapy (CRRT), the usual dose should be administered.

2 Caution with use of IV formulation in patients with CrCl <50mL/min as cyclodextrin component accumulates (assessment of risk vs. benefit should be made)

3 Itraconazole has been associated with severe hepatotoxicity, including liver failure and death. Itraconazole use should be carefully monitored in patients with hepatic dysfunction.

4 Voriconazole requires dose adjustment in patients with hepatic dysfunction. For Child-Pugh Class A and B, reduce maintenance dose by ½ following usual loading dose. Use is not recommended in Child-Pugh Class C.

5 Micafungin pharmacokinetic data is unavailable for severe hepatic impairment

5. Cost comparisons of antifungal agents.

Approximate Antifungal Daily Costs - 2011

Antifungal	Approximate Cost/Dose	Usual Adult Dose	Approximate Cost/Day
Fluconazole 400 mg IV	\$8	400 mg IV q24h	\$8
Fluconazole 400 mg PO	\$1	400 mg PO q24h	\$1
Itraconazole 200 mg PO solution	\$19	200 mg PO q12h	\$38
Voriconazole 200 mg PO	\$45	200 mg PO q12h	\$90
Voriconazole 280 mg IV	\$184	280 mg IV q12h	\$368
Micafungin 100 mg IV	\$98	50 mg IV q24h	\$98
Amphotericin B conventional 70 mg IV	\$17	70 mg IV q24h	\$17
Amphotericin B Lipid (Abelcet®)	\$305	350 mg IV q24h	\$305
Posaconazole 400 mg PO	\$50	400 mg PO q12h	\$100

RESPONSIBILITY:

Joint Subcommittee on Anti-Infective Use

POLICY/GUIDELINE DATES:

Issued: April 2005

Reviewed: May 2010

Revised: May 2011

Medical Board Approval: