The Nebraska Medical Center Guidelines for Management of Invasive Candidiasis

Purpose
To provide a framework for initial evaluation and management of immunocompetent and immunocompromised patients with suspected, probable, or proven invasive candidiasis (IC) based on the recent 2009 Clinical Practice Guidelines by the Infectious Disease Society of America.[1] A summary of recommendations for the management of disseminated candidiasis in the neonatal population are also provided. The new guideline was updated to reflect newer antifungal agents, recent publications on the treatment of IC or suspected candidiasis as well as prophylaxis in high risk adult populations.

Definition
IC encompasses severe and invasive *Candida* infections that include candidemia, disseminated candidiasis, endocarditis, meningitis, endophthalmitis, and other deep tissue involvement. It excludes more superficial and less severe diseases such as oropharyngeal and esophageal candidiasis.[1]

Risk Factors
Risk factors for IC include: prolonged and broad-spectrum antibiotics, central venous catheters, total parenteral nutrition, renal replacement therapy, neutropenia, bone marrow transplant, hematologic malignancies, solid organ transplant (liver and kidney), premature birth, gastrointestinal surgery, burns, implanted prosthetic devices, immunosuppressive agents (including glucocorticoids, chemotherapy,and immunomodulators), and prolonged intensive care unit (ICU) stay.[1] Risk factors for non-albicans species include glucocorticosteroid use, central venous catheter placement, prior fluconazole therapy, and preexisting candiduria.[2,3]

An evaluation of systemic candidemia at TNMC was performed and a prediction rule created to help clinicians determine the likelihood of individual patients developing this infection. Pertinent risk factors identified included: 1) Currently receiving broad-spectrum antibiotics (**BSAbx**), defined as carbapenems, fluoroquinolones, 2nd, 3rd, and 4th generation cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, and tigecycline, 2) Presence of a central venous catheter (**CVC**), 3) Receipt of total parenteral nutrition (**TPN**), 4) Abdominal surgery within the last 7 days, 5) Steroid use, and 6) Length of stay (**LOS**) in the hospital. To calculate the risk of candidemia in an individual patient use the formula below and interpret as indicated. If the patient has the risk factor, then the value of that risk factor is 1 (i.e. Yes=1), if the patient does not have the risk factor, then the value is 0 (i.e. No=0). LOS should be entered as the exact number of days continuously hospitalized current assessment.

Prediction Rule = (1.54 x BSAbx) + (0.87 x CVC) + (0.92 x TPN) + (0.40 x Steroid) + (0.88 x Abdominal Surgery) + (0.04 x Pre-ICU LOS in days) =

Total < 2.45: No need for antifugals as probability of not developing candidemia 99.4% (NPV=99.4%)

Total ≥ 2.45: Consider antifungals on individual basis as probability of developing candidemia 4.7% (PPV 4.7%)

Recommended interpretation of the decision rule is if <2.45 no empiric antifungal is recommended as the risk for candidemia is exceedingly low. If result is ≥2.45 empiric therapy should be considered on an individual basis. The incidence level of candidemia in patients in this group does not meet the current guidelines standard of offering empiric therapy to patients who have a greater than 10% incidence of candidemia.[1] Thus, the decision rule is more useful in determining who would not benefit from empiric therapy.

Antifungal Selection
Selection of an antifungal agent should take into account history of recent azole exposure, history of antifungal intolerances, the dominant *Candida* species based on epidemiologic and institution-specific surveillance data, susceptibility data, severity of illness, relevant comorbidities, and evidence of involvement of the central nervous system (CNS), cardiac valves, and/or visceral organs. Early antifungal initiation is critical to successful treatment outcomes. Empiric or prophylactic use of antifungals may reduce morbidity, mortality, and length of stay in critically ill patients, but widespread use of antifungals must be balanced against the risk of toxicity, costs, and emergence of resistance.[1]

Currently, the prevalence of IC among adult ICU patients at TNMC is < 2%; thus, routine fungal prophylaxis in non-neutropenic ICU patients is **not** recommended at TNMC.

Susceptibility testing of *Candida* species is performed at TNMC on yeast isolates from sterile sites including blood, cerebrospinal fluid, synovial fluids, pleural fluids, and pericardial fluids. *Candida* species grow rather rapidly and can usually be identified within 3-5 days. Therapy should be guided by susceptibility testing results when available. In the absence of such results, Table 1 (see below) can be used.

Pharmacologic Considerations[1, 4-5] – There are 4 major antifungal categories (polyenes, triazoles, echinocandins, flucytosine). TNMC formulary antifungals are discussed briefly below.

1. Polyenes (amphotericin B deoxycholate and lipid amphotericin B formulations)[1,4]

    - Antifungal category of choice for use in pregnant individuals with IC.

    - AmB-d (amphotericin B deoxycholate) – The most common adverse effects include nephrotoxicity, infusion-related reactions (chills, rigors, hypotension), and potassium and magnesium wasting.

    - LFAmB (lipid amphotericin B formulation) – Three formulations exist with similar spectra to AmB-d (see Table 1 below) but with less nephrotoxicity and higher costs. The TNMC formulary agent is liposomal Amphotericin B (AmBisome®). LFAmB formulations possess different pharmacological properties and adverse events and should not be interchanged without careful consideration.

2. Triazoles (fluconazole, itraconazole, voriconazole, posaconazole)[1,4] – Triazoles have varied activity against *Candida* (see Table 1 below). All triazoles have good oral bioavailability, and the oral formulations are preferred when possible. Fluconazole is the only azole with clinically significant urinary concentrations. All inhibit CYP450 to varying degrees, and careful evaluation for drug-drug interactions is warranted. Generally, avoid in pregnancy due to risks of fetal malformations.

    - Fluconazole is well absorbed orally (~90% bioavailability), is unaffected by food and gastric pH, and among all triazoles, has the greatest penetration into cerebrospinal fluid (CSF) and vitreous body with concentrations at least 50% of serum. Fluconazole urine concentrations reach 10-20 times serum concentrations. Adjust dose for creatinine clearance <50mL/min.

    - Itraconazole is generally reserved for mucosal candidiasis, and little data exist for IC. GI absorption differs for capsule versus solution. Acid-reducing agents decrease absorption of the capsule, while food and acidic beverages (such as carbonated drinks and cranberry juice) enhance absorption. Oral solution is better absorbed on an empty stomach. Renal elimination is minimal (active drug <0.03%; inactive metabolite 40%).

    - Voriconazole is effective for mucosal and IC, but is primarily used for step-down oral therapy for fluconazole-resistant, voriconazole-susceptible strains of *C. krusei* and *C. glabrata.* Voriconazole has good oral bioavailability, CSF (~50% of serum), and vitreous penetration. Oral bioavailability is not affected by gastric pH but is decreased when consumed with food. IV voriconazole is complexed to a cyclodextrin molecule, and should not be used if the CrCl is < 50 mL/min due to risk of accumulation of this molecule. Renal elimination of unchanged drug is insignificant, and thus dosage adjustment for renal insufficiency is not necessary. Voriconazole is the only triazole to require dosage reduction for mild-to-moderate hepatic impairment. Serum levels can vary widely between patients due to common polymorphisms in the primary metabolic enzyme. Drug-drug interactions are frequent and need careful consideration when beginning, altering, or discontinuing treatment. Contraindicated in pregnancy.

    - Posaconazole does not have an indication for treatment of primary candidiasis but demonstrates *in vitro* activity similar to that of voriconazole. Clinical data are inadequate to make evidence-based recommendation for treatment other than oropharyngeal candidiasis. Available only as oral suspension with high bioavailability especially when small doses are given frequently and administered with fatty foods and in acidic environments. Major excretion pathway is feces (~77%) with minimal urinary elimination (~14%). Therefore, dosage adjustment

is not necessary in renal impairment. However, due to variability in posaconazole exposure in patients with creatinine clearance <20mL/min, patients should be monitored for breakthrough fungal infections.[6]

3. Echinocandins (caspofungin, anidulafungin, micafungin)[1,4-5] The TNMC formulary echinocandin is micafungin. Due to lack of data, these agents are generally avoided in pregnancy.

    - All agents are available parenterally only, dosed once daily, and do not require renal dose adjustment. Caspofungin requires dosage adjustment for moderate hepatic impairment (Child-Pugh class B). Echinocandins undergo nonenzymatic degradation and are not metabolized by the CYP450 system, although caspofungin undergoes phase II metabolism. Echinocandins have negligible distribution into CSF and urine.

    - Have a broad spectrum of activity and are similar to each other with respect to *in vitro* activity against *Candida* sp (see Table 1), with micafungin and anidulafungin having similar MICs that are generally lower than the MIC of capsofungin. *C. parapsilosis* has demonstrated less *in vitro* susceptibility to the echinocandins suggesting it may be less responsive to these drugs. However, the clinical significance of this finding is still unknown.

    - Echinocandins are generally well tolerated. Adverse drug reactions are less frequent with micafungin and anidulafungin compared with caspofungin. Phlebitis (3.5-25% of patients) and elevated liver enzyme levels (1-15%) occur more often with caspofungin compared with micafungin and anidulafungin (< 8%)

4. Flucytosine has broad antifungal activity against most *Candida* species except *C. krusei.*[1,4] Available orally only with good bioavailability. Most (>90%) is excreted unchanged in the urine, and dosage adjustment is necessary for renal dysfunction. Flucytosine is primarily used in combination with amphotericin B for invasive diseases such as meningitis or endocarditis and is rarely administered alone due to rapid emergence of resistance. Occasionally, flucytosine may be used for urinary tract infections when there are no other alternatives. Contraindicated in pregnancy.

Table 1. Spectra of Activity Against *Candida* Species of Various Antifungals [1,10]

	Fluconazole	Voriconazole	Posaconazole	Itraconazole	Echinocandins	Amphotericin	Flucytosine
C. albicans	S	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S to R	S	S
C. tropicalis	S	S	S	S	S	S	S
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
C. krusei	R	S	S	S-DD to R	S	S to I	I to R
C. lusitaniae	S	S	S	S	S	S to R	S
C. dubliniensis	S	S	S	S	S	S	S
C. guilliermondii	S	S	S	S	S to I	S to I	S
I= intermediately susceptible; R= resistant; S= susceptible; S-DD= susceptible dose-dependent							

Monitoring [7-9]

- Therapeutic drug monitoring for itraconazole and voriconazole is recommended with extended treatment courses (e.g., ≥4 weeks) to ensure adequate absorption, monitor changes in dosages, monitor the addition of an interacting agent, and assess adherence. Timing of drug sampling for these agents is ill-defined. This is further complicated by nonlinear pharmacokinetics exhibited by itraconazole and voriconazole, making use of the half-life less applicable in determining the time of drug sampling. Therefore, multiple samples are needed to ensure effective and nontoxic concentrations are maintained.
    - Itraconazole blood concentrations vary widely and are generally higher (~30%) with solution than capsule formulation; however, wide inter-patient variability exists.
    - Itraconazole can be measured by high-performance liquid chromatography (HPLC) or bioassay. The results of bioassay are 2-10 times higher than those of HPLC because the bioassay measures both itraconazole and its active metabolite, hydroxyitraconazole. Determination of total antifungal activity by HPLC requires a separate assay for itraconazole and hydroxyitraconazole. The sum of itraconazole and its metabolite should be used in assessing drug levels.

- Itraconazole levels should only be drawn after steady-state is achieved, which takes ~2 weeks due to its long half-life. The long half-life results in serum concentrations which vary little and allows for blood collection at any time in relation to drug administration.
- Voriconazole nonlinear pharmacokinetics and genetic differences in metabolism account for observable intra-patient and inter-patient variability. Although the reported half-life of voriconazole is ~6 hours, this varies greatly depending on dose administered. Therefore, the recommendation is to obtain levels after 7 days of therapy to ensure steady state is reached. Drug toxicity has been observed at higher concentrations as well as reduced clinical response at lower concentrations.
- The upper limit desired therapeutic level for voriconazole is currently 6mg/L, however this is unknown for itraconazole

- If flucytosine is used in infants, careful drug monitoring is recommended as clearance is directly proportional to the glomerular filtration rate (GFR). Very low birth weight infants may accumulate high plasma concentrations due to immaturity.
- Turnaround time for HPLC and liquid chromatography-mass spectrometry (LC-MS) is up to 1 week.

Table 2: Summary of desired reference ranges for antifungal monitoring[7-9]

Drug	Lab assay	Desired trough levels		When to obtain levels
		Prophylaxis (mg/L)	Treatment (mg/L)	
Itraconazole	Bioassay	>0.5	>1-2	1-2 weeks
Voriconazole	HPLC and LC-MS	0.5-6	1-6	1 week
Flucytosine		N/A	Peak (2hrs post dose): 50-100mg/L Trough: 25-50mg/L	≥2 weeks
LC-MS: Liquid chromatography-mass spectrometry; HPLC : High-performance liquid chromatography				

Length of therapy[1]

Without obvious metastatic complications, duration of antifungal therapy for IC is 2 weeks (3 weeks for neonates) after documented clearance of *Candida* species from the bloodstream and resolution of symptoms.

Table 3: Treatment Guidelines; All dosages are based on normal renal/hepatic function.[1,10]

Proven/Suspected Candidiasis Treatment			
	Preferred General Initial Therapy	**Alternative Therapy**	**Definitive Therapy/Notes**
CANDIDEMIA			
Treatment Candidemia Nonneutropenic Patient	• Fluconazole for less critically ill & without recent (≤3 months) azole exposure. • Micafungin for patients with moderately severe to severe illness or with recent azole exposure. • Transition from micafungin to fluconazole for isolates likely susceptible (*C. albicans)* if patient clinically stable. • Catheter removal strongly recommended	• Amphotericin B deoxycholate for intolerance or limited availability of preferred antifungals. AmBisome® may be used if needed due to toxicities associated with amphotericin B deoxycholate. • Voriconazole effective for candidemia but offers little advantage over fluconazole. Recommended as step-down therapy for selected cases of candidiasis due to susceptible *C. krusei* or *C. glabrata.* Generally reserved for aspergillosis.	• Infectious Disease (ID) consult recommended. • *C. glabrata*: micafungin preferred. o Transition to fluconazole or voriconazole not recommended without confirmation of isolate susceptibility. o If initially received fluconazole or voriconazole with clinical improvement and negative follow-up cultures, continuation of azole to therapy completion is reasonable. • *Candida parapsilosis:* fluconazole preferred. o If initially received micafungin with clinical improvement and negative follow-up cultures, continuation is reasonable. • *C. krusei:* micafungin, Abelcet®, or voriconazole preferred. • *C. lusitaniae*: fluconazole or micafungin preferred over amphotericin • **Document fungus clearance from bloodstream** • **Treat for 2 weeks AFTER documented clearance from bloodstream and resolution of symptoms** • **Ophthalmology evaluation/fundoscopic examination for all patients** • Consider trans-esophageal echocardiogram if blood cultures are persistently positive.
Treatment Candidemia Neutropenic Patient	• Micafungin recommended for most. • Catheter removal strongly recommended.	• Fluconazole reasonable for less critically ill without recent azole exposure. • Voriconazole if additional mold coverage needed.	
CANDIDIASIS			
Empiric Treatment Suspected Invasive Candidiasis in Nonneutropenic	• Similar to proven candidemia. Avoid azoles if recent exposure. • Consider for the critically ill with risk factors for IC and no other known cause of fever based on clinical assessment, serologic markers for IC, and/or culture data from nonsterile sites.	• Amphotericin B deoxycholate for intolerance or limited availability of preferred antifungals. AmBisome® may be used if needed due to toxicities associated with amphotericin B deoxycholate.	• **See above for prediction rule for invasive candidiasis** • Infectious Disease (ID) consult recommended.
Empiric Treatment Suspected Invasive Candidiasis in Neutropenic	• Micafungin • AmBisome ® • Voriconazole	• Fluconazole: Do not use if recent azole exposure. • Itraconazole: Do not use if recent azole exposure. • Amphotericin B deoxycholate effective but carries higher risk of toxicity.	• Infectious Disease (ID) consult recommended.
Neonatal Disseminated Candidiasis Treatment	• Amphotericin B deoxycholate (1mg/kg daily) • Fluconazole (12mg/kg daily) • Treat for 3 weeks. • IV catheter removal strongly recommended.	• AmBisome® if urinary tract involvement excluded. • Micafungin should be used with caution and limited to situations in which resistance or toxicity precludes use of other agents.	• Infectious Disease (ID) consult recommended. • Lumbar puncture and ophthalmology evaluation recommended with sterile body fluid and/or urine cultures positive for *Candida* species. • Imaging of genitourinary tract, liver and spleen should be

			performed if results of sterile body fluid cultures are persistently positive.
Chronic disseminated	• Stable patients: Fluconazole • Severely ill: Amphotericin B deoxycholate 0.5-0.7mg/kg daily or AmBisome®, then switch to fluconazole once stable	• Micafungin then step down to fluconazole	• Infectious Disease (ID) consult recommended. • Transition from amphotericin or micafungin to fluconazole is preferred after several weeks of treatment. • Duration of treatment: until lesions resolved (usually months) • Treatment should be continued through periods of immunosuppression (chemotherapy or transplant).
CNS	• AmBisome® ± flucytosine for several weeks, then fluconazole daily	• Fluconazole (if patient cannot tolerate AmBisome®)	• Infectious Disease (ID) consult recommended. • Treat until signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. • Remove intraventricular devices if possible.
Endocarditis	• AmBisome® ± flucytosine • Amphotericin B deoxycholate 0.6-1mg/kg daily ± flucytosine • Micafungin	• Stable patients with susceptible organisms and negative blood culture: step down to fluconazole	• Infectious Disease (ID) consult recommended. • Valve replacement, including prosthetic valves, strongly recommended. • If valvular replacement not feasible, chronic suppression with fluconazole is recommended.
Pericarditis, myocarditis, suppurative thrombophlebitis	• AmBisome® • Fluconazole • Micafungin	• If AmBisome® or micafungin used: step down to fluconazole once stable	• Infectious Disease (ID) consult recommended. • Several months of therapy is usually warranted for pericarditis or myocarditis. Pericardial window or pericardiectomy recommended. • At least 2 weeks of treatment after 1st negative blood culture is recommended for suppurative thrombophlebitis. Adjunctive surgical incision and drainage or vein resection is recommended for thrombophlebitis.
Osteomyelitis	• Fluconazole • AmBisome® for several weeks, then fluconazole	• Micafungin • Amphotericin B deoxycholate	• Infectious Disease (ID) consult recommended. • Transition from amphotericin or micafungin to fluconazole is preferred after several weeks of treatment. • Duration: 6-12 months • Surgical debridement often necessary.
Septic arthritis	• Fluconazole • AmBisome® for several weeks, then fluconazole	• Micafungin • Amphotericin B deoxycholate	• Infectious Disease (ID) consult recommended. • Transition from amphotericin or micafungin to fluconazole is preferred after several weeks of treatment. • Duration: 6 weeks • Surgical debridement for all cases and removal of infected prosthesis is recommended in most cases.
Endopthalmitis	• Amphotericin B deoxycholate 0.7-1mg/kg + flucytosine • Fluconazole	• AmBisome® • Voriconazole • Micafungin	• Infectious Disease (ID) consult recommended. • Surgical intervention is desired for patients with severe disease or vitreitis. • Duration: at least 4-6 weeks with resolution of infection based on serial ocular exams. • Diagnostic vitreal aspiration required if etiology unknown.

Candida from respiratory secretions	• Rarely indicates invasive candidiasis and should not be treated.		• *Candida* pneumonia and lung abscess are very uncommon, however colonization of bronchial tree is common in patients on ventilator. • Diagnosis of *Candida* pneumonia requires histopathological confirmation.
Candiduria: asymptomatic	• Treatment is generally not indicated with few exceptions noted below. • Neutropenic and neonates: manage as per invasive candidiasis outlined above • Urologic procedures: fluconazole 200- 400 mg (3–6 mg/kg) daily for several days before and after procedure	• Urologic procedures: Amphotericin B deoxycholate 0.3–0.6 mg/kg daily for several days before and after the procedure	• Remove urinary catheter if present. • Treat only high risk patients: neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. • If persistent or recurrent, image kidneys and collecting system to exclude abscess, fungus ball, or urologic abnormality.
Candiduria: symptomatic	• Complicated by disseminated candidiasis: treat as described for candidemia. • Cystitis: o Fluconazole susceptible: Fluconazole 200 mg (3 mg/kg) PO daily for 2 weeks • Pyelonephritis: o Fluconazole-susceptible: fluconazole PO 200–400 mg (3–6 mg/kg) daily for 2 weeks • Fungus balls o Surgical intervention strongly recommended in non-neonates. o Fluconazole 200–400 mg (3–6 mg/kg) daily o Treat until symptoms resolved and urine cultures no longer yield *Candida* species.	• Cystitis: o Fluconazole resistant: Amphotericin B deoxycholate IV 0.3–0.6 mg/kg IV daily for 1–7 days OR flucytosine for 7–10 days • Pyelonephritis: o Fluconazole-resistant: Amphotericin B deoxycholate IV 0.5–0.7 mg/kg daily ± flucytosine OR flucytosine for 2 weeks. • Fungus ball: o Amphotericin B deoxycholate IV 0.5–0.7 mg/kg daily ± flucytosine o Adjunct to systemic therapy: amphotericin B deoxycholate 50 mg/L of sterile water irrigation.	• Remove urinary catheter if present. • Amphotericin B deoxycholate bladder irrigation, although not recommended, may be useful for fluconazole-resistant *C. glabrata* or *C. krusei.* • Fluconazole is mainstay. No other currently available azole is useful, because of minimal excretion of active drug into urine. • Echinocandins are not useful because of minimal excretion into urine. • Alternatives are oral flucytosine, systemic amphotericin B deoxycholate, and bladder irrigation with amphotericin B deoxycholate. • Avoid lipid amphotericin B formulations.
Peritonitis[11-13]	• Micafungin (preferred if critically ill) • Fluconazole	• Amphotericin B deoxycholate ± flucytosine	• Infectious Disease (ID) consult recommended. • **Use of antifungals for empiric therapy of peritonitis usually not warranted.** Consider in the setting of recurrent peritonitis following recent antibiotic treatment for bacterial peritonitis. • Peritoneal dialysis catheter removal with temporary hemodialysis is strongly recommended. • If *C. parapsilosis* is isolated, fluconazole preferred. • If *C. glabrata* is isolated, micafungin is preferred until fluconazole susceptibility can be confirmed.

ADULT DOSING (unless otherwise specified above) All doses are for normal renal/hepatic function.

• Fluconazole: loading dose 12mg/kg [800mg], then 6mg/kg [400mg] IV/PO daily • Itraconazole 200mg [3mg/kg] PO q12hr—acidic environment enhances absorption of capsule • Voriconazole: 6mg/kg [400mg] q12hr x 2 doses, then 3mg/kg [200mg] q12hr thereafter IV/PO	• Micafungin: 100mg IV q24hr • Amphotericin B deoxycholate (conventional): 0.5-1 mg/kg IV daily • Liposomal amphotericin B (AmBisome®): 3mg/kg IV daily (doses up to 5mg/kg/day are allowed only for NICU patients) • Flucytosine: 25 mg/kg PO QID

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