Management bundles for invasive candidiasis

- **Inclusion criteria:** Non-neutropenic patients of older than 17 years old treated with anti-fungals for invasive candidiasis. Bundle A is indicated for candidemia, and bundle B is indicated for empirical therapy

Definitions

- **Compliance with the bundles:** Compliance with the bundles is defined as evidence that all key bundle elements are completely fulfilled. Compliance is evaluated in patients who survive more than 7 days after initiation of antifungal therapy
- **Clinical response:** Clinical response is judged 7-14 days after the end of all treatment courses, and treatment is considered to be successful if all attributable signs and symptoms associated with candidemia have resolved. Treatment is considered to have failed if there is unresponsive infection after at least 5 days of therapy, or if relapse occur. In patients with treatment failure of initial antifungals or unacceptable adverse events necessitating a change of initial antifungal therapy, overall treatment was judged to be successful if a favorable clinical response was obtained with alternative therapy.
- **Mortality:** mortality is evaluated 28 days after the start of antifungal therapy.

Appropriate selection and dosing of antifungals in the bundles

Antifungals	Appropriate indication	Standard dosing
Echinocandins	Patients with moderately severe to severe illness	Caspofungin: loading dose of 70 mg, then 50 mg daily, Micafungin: 100-150 mg daily
	Infection due to *Candida glabrata* and *C. krusei*	
	Patients with candidemia in whom CVCs cannot be removed	
	Consider poor ocular penetration in ocular candidiasis	
Fluconazole	Patients who are less critically ill and who have no recent azole exposure.	Loading dose of 800 mg, then 400 mg daily
	Infection due to *C. parapsilosis* and *C. albicans*	
	Transition to fluconazole in clinically stable patients with infection due to *C. albicans*	
Voriconazole	Alternative therapy	6 mg/kg b.i.d. for two doses, then 3-4 mg/kg b.i.d
	Step-down oral therapy	
	Limitation of intravenous formulation in renal impairment	
	Consider therapeutic drug monitoring	
Itraconazole	Alternative therapy	200 mg b.i.d. for 2 days, then 200 mg daily
	Limitation of intravenous formulation in renal impairment	
Liposomal amphotericin B	Patients with severe sepsis/septic shock	2.5-5.0 mg/kg daily
	Infection due to *C. glabrata*, *C. krusei* and *C. guilliermondii*	
	Patients with candidemia in whom CVCs cannot be removed	
Amphotericin B deoxycholate	Recommendation against use due to substantial renal and infusion-related toxicity	–
Flucytosine	Combination use with other antifungals	25 mg/kg q.i.d.

Abbreviation: CVCs, central venous catheters

Bundle A（candidemia）

Phase	Elements of the bundles（□：Key elements）	Achievement of the elements	
		Patients with CVCs placement	Patients without CVCs placement
Bundles at the start of therapy	1. Removal of existing central venous catheters (CVCs) within 24 h of diagnosis	□	
	2. Initial appropriate selection of antifungals	□	□
	3. Initial appropriate dosing of antifungals	□	□
Bundles after initiation of therapy	4. Ophthalmologic examinations	□	□
	5. Follow-up blood cultures until clearance of candidemia	□	□
	6. Assessment of clinical efficacy on the 3rd to 5th day to consider necessity of alternative therapy to consider alternative therapy	□	□
	7. Appropriate choice of alternative antifungals	□	□
	8. At least 2 weeks of therapy after documented clearance of *Candida* from bloodstream and resolution of attributable symptoms	□	□
	9. Step-down oral therapy	□	□

Isolated candida spp:

□ *C. albicans*, □ *C.glabrata*, □ *C.parapsilosis*, □ *C.tropicalis*, □ *C.krusei*, □ *C.guilliermondii*, □ other（ ）, □ yeast without identification of Candida sp

Ocular candidiasis:

□ YES, □ NO, □ unknown

Organ involvement:

□ YES, □ NO [□osteomyelitis, □ endocarditis, □ central nervous system infections, □ other（ ）]

Antifungal therapy

Primary therapy: □F-FLCZ/FLCZ, □VRCZ, □ITCZ, □MCFG, □CPFG, □L-AMB, □other（ ）
Alternative therapy： □F-FLCZ/FLCZ, □VRCZ, □ITCZ, □MCFG, □CPFG, □L-AMB, □other（ ）

Patients characteristics

1. Central venous catheters: □ YES, □ NO
2. □total parenteral nutrition, □steroid use, □immunosuppressive therapy, □anticancer therapy, □surgery, □＞65 y, □chronic renal failure/dialysis, □malignant tumor, □malnutrition, □prolonged ICU stay, □ventilator use, □severe severity(APACHE II score>15, etc.), □diabetes, □organ transplantation, □ heart disease, □ liver cirrhosis/chronic hepatic dysfunction

Clinical outcomes

1. Compliance of the bundles（achievement of all key elements）; □ YES, □ NO
2. Clinical efficacy（7-14 d after end of treatment）：□success, □failure, □indeterminant
3. Mortality（28 d after initiation of therapy）：□death, □alive

Bundle B（empirical therapy）

Phase	Elements of the bundles（ ☐：Key elements）	Achievement of the elements
Bundles at the start of therapy	1.Positive for risk factors of invasive candidiasis	☐
	2. Two sets of blood cultures obtained prior to anti-fungal administration	☐
	3. Surveillance cultures for *Candida*	☐
	4. Measurement of β-D-glucan	☐（ pg/mL） Test kit（ ）
	5. Therapy based on serologic markers or *Candida* species colonization at ≥2 non-sterile sites	☐ （☐serological test, ☐*Candida* colonization≥2 sites）
	6. Initial appropriate selection of antifungals	☐
	7. Initial appropriate dosing of antifungals	☐
Bundles after initiation of therapy	8. Assessment of clinical efficacy on the 3rd to 5th day to consider necessity of alternative therapy or discontinuation of antifungal therapy	☐
	9. Step-down oral therapy for patients with favorable clinical course	☐

Site of candida isolation :

☐sputum, ☐intraperitoneal fluid, ☐urine, ☐stool, ☐vascular catheter（negative for blood culture), ☐ other（), ☐none

Isolated *Candida* spp：

☐ *C. albicans* , ☐ *C.glabrata* , ☐ *C.parapsilosis* , ☐ *C.tropicalis* , ☐ *C.krusei* , ☐ *C.guilliermondii* , ☐other（), ☐ yeast without identification of Candida sp

Antifungal therapy

Primary therapy: ☐F-FLCZ/FLCZ, ☐VRCZ, ☐ITCZ, ☐MCFG, ☐CPFG, ☐L-AMB, ☐other（ ）
Alternative therapy: ☐F-FLCZ/FLCZ, ☐VRCZ, ☐ITCZ, ☐MCFG, ☐CPFG, ☐L-AMB, ☐other（ ）

Risk factors associated with invasive candidiasis :

☐broad spectrum antibiotics, ☐placement of central venous catheters, ☐total parenteral nutrition, ☐steroid use, ☐immunosuppressive therapy, ☐anticancer therapy, ☐abdominal surgery, ☐＞65 y, ☐chronic renal failure/dialysis, ☐malignant tumor, ☐malnutrition, ☐prolonged ICU stay, ☐ventilator use, ☐ H_2antagonist/proton pump inhibitor, ☐severe severity（APACHE II score>15, etc）, ☐extensive burn injury, ☐necrotic pancreatitis, ☐perforation of the digestive tract, ☐diabetes, ☐organ transplantation, ☐vaginal candidiasis, ☐*Candid*a colonization
（Other factors affect clinical outcomes ; ☐ heart disease, ☐ liver cirrhosis/chronic hepatic dysfunction）

Clinical outcomes

1. Compliance of the bundles（achievement of all key elements）; ☐ YES, ☐ No
2. Clinical efficacy（7-14 d after end of treatment）：☐success, ☐failure, ☐indeterminant
3. Mortality（28 d after initiation of therapy）：☐death, ☐alive