Expert Panel Recommendations on the Clinical Practice Guidelines for the Diagnosis and Management of Invasive Candidiasis in Indonesia

Anna Rozaliyani[1-3*], Erni Juwita Nelwan[4,5], Mardiastuti Wahid[6], Dita Aditianingsih[7], Mulya Rahma Karyanti[8], Siti Pratiekauri[9], Adityo Susilo[4,5], Fathiyah Isbaniah[1,3], Heidy Agustin[1,3], Yulia Rosa Saharman[6], Robiatul Adawiyah[2,3,9], Findra Setianingrum[2,3], Vera Irawany[7], Rudyanto Sedono[7], Debbie Latupeirissa[8], Nina Dwi Putri[8], Winda Sofvina[3,9], Mulyati Tugiran[2,3]

[1]The Indonesian Society of Respirology (*Perhimpunan Dokter Paru Indonesia*, PDPI), Jakarta, Indonesia.
[2] The Department of Parasitology, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[3]The Indonesian Pulmonary Mycoses Centre (IPMC), Jakarta, Indonesia.
[4]The Indonesian Society of Tropical Medicine and Infectious Diseases (*Perhimpunan Kedokteran Tropis dan Penyakit Infeksi Indonesia*, PETRI), Jakarta, Indonesia.
[5]The Indonesian Internist Association (*Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia,* PAPDI), Indonesia.
[6]The Indonesian Society for Clinical Microbiology (*Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia*, PAMKI), Jakarta, Indonesia.
[7] The Indonesian Society of Anaesthesiology and Intensive Therapy (*Perhimpunan Dokter Anesthesiology dan Terapi Intensif Indonesia*, PERDATIN), Jakarta, Indonesia.
[8]The Indonesian Pediatrics Society (*Ikatan Dokter Anak Indonesia*, IDAI), Jakarta, Indonesia.
[9]The Indonesian Society for Medical Specialist in Clinical Parasitology (*Perhimpunan Dokter Spesialis Parasitologi Klinik Indonesia*, PDS ParK), Jakarta, Indonesia.

Corresponding Author:
Anna Rozaliyani, MD, PhD. The Department of Parasitology, Faculty of Medicine Universitas Indonesia. Jl. Salemba Raya 6, Jakarta 10430, Indonesia. Email: anna.rozaliyani@ui.ac.id.

ABSTRACT

Invasive candidiasis (IC) ranks among the primary causes of deadly fungal infections. The frequency of IC rises alongside increasing number of patients with altered immune systems, critically ill, chronic diseases, and various medical procedures. The disease causes high morbidity and mortality, as well as prolonged stay and increases hospital costs. The diagnosis and management of IC in Indonesia is still a challenge. Laboratory facilities in identifying pathogenic fungi and susceptibility tests to antifungals are still limited. Clinical awareness and financial support from health policymakers are also insufficient. Early diagnosis is essential for proper treatment to reduce morbidity and mortality rates. Initiated by the Indonesian Pulmonary Mycoses Centre (IPMC), several expert representatives from six medical professional organizations in Indonesia have agreed to set up a meeting series to prepare a joint draft on the diagnosis and management of IC. The expert panel aimed to achieve a consensus on the clinical practice guidelines for diagnosing and treating IC in Indonesia.

Keywords: *diagnosis, expert panel, invasive candidiasis, management.*

INTRODUCTION

Fungal infection or mycosis is an important infection that can be life-threatening. The serious and dangerous clinical spectrum of mycosis is known as invasive mycosis. Invasive candidiasis (IC) is a type of invasive mycosis due to *Candida* spp. It is frequently found in patients with certain predisposing factors and altered immune systems, including critically ill patients treated in the Intensive Care Unit (ICU). The incidence of IC is estimated to reach 700,000 cases worldwide, with a mortality rate of 40-98%.[1–3]

The World Health Organization (WHO) released a list of fungal priority pathogens (FPPL) in October 2022 to increase awareness of mycoses, including its link to problems related to fungal resistance to antifungal agents. The list of priority pathogens should be encouraged by policymakers at national and global levels to provide better access to diagnosis and management for mycosis patients. The fungi are divided into 3 groups: namely critical priority, high priority, and medium priority. *Candida auris* and *Candida albicans* are included in the critical priority group, while *Candida glabrata, Candida parapsilosis, and Candida tropicalis* are included in the high-priority group. Meanwhile, *Candida krusei* is included in the medium priority group.[4]

The diagnosis and management of IC in Indonesia is still a challenge. Morbidity and mortality also become crucial issues and a major burden of public health menace. Diagnostic facilities for IC are very limited in Indonesia, including clinical awareness, access to antifungal agents, and health financing support.[5] Some expert representatives from six medical professional organizations in Indonesia have agreed to set up a meeting series to prepare a joint draft on the diagnosis and management of IC. The expert panel aimed to achieve a consensus on the clinical practice guidelines for diagnosing and treating IC in Indonesia.

METHODS

Expert Panel

The expert panel held a meeting series from August 2022 to February 2023, initiated by the Indonesian Pulmonary Mycoses Centre. The meetings invited a panel of experts from six professional organizations in Indonesia: The Indonesian Society of Respirology (*Perhimpunan Dokter Paru Indonesia*, PDPI), The Indonesian Internist Association (*Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia*, PAPDI)/The Indonesian Society of Tropical Medicine and Infectious Diseases (*Perhimpunan Kedokteran Tropis dan Penyakit Infeksi Indonesia*, PETRI), The Indonesian Society of Anaesthesiology and Intensive Therapy (*Perhimpunan Dokter Anesthesiology dan Terapi Intensif Indonesia*, PERDATIN), The Indonesian Pediatrics Society (*Ikatan Dokter Anak Indonesia*, IDAI), The Indonesian Society for Clinical Microbiology (*Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia*, PAMKI), The Indonesian Society for Medical Specialist in Clinical Parasitology (*Perhimpunan Dokter Spesialis Parasitology Klinik Indonesia*, PDS Park), and the expert from the Department of Parasitology, Faculty of Medicine Universitas Indonesia. The expert panel agreed to achieve a consensus on the clinical practice guidelines to aid the diagnosis and treatment of IC in Indonesia.

Evidence Evaluation

The expert panel carefully discussed and analyzed some international guidelines and the latest literature on the diagnosis and management of IC. The draft was prepared based on the critical review and adhered to the principles of evidence-based medicine. The sources of evidence were the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG) Consensus Group (2008, 2020, 2021),[6–8] the Infectious Diseases Society of America guideline (2016),[9] the Australasian Antifungal Guidelines Steering Committee (2021),[10] the European Society of Clinical Microbiology and Infectious Diseases (2012, 2019),[11,12] the European Conference on Infection in Leukemia (2017, 2020).[13,14] The epidemiology data, clinical relevance, and applicability of the evidence for invasive *Candida* infections in Indonesia were also explored and discussed. The review process was carried out in stages on

the initial draft, followed by group discussions, until an agreement was reached in the form of a consensus regarding IC.

Levels of Recommendation

The recommendations were constructed based on the quality of evidence, the diagnostic options that can be implemented considering the limited facilities in Indonesia, the affordability of treatment access, etc. The task force followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scheme of levels of evidence and recommendation grades (**Table 1**). GRADE has four levels of strength of recommendation: high, moderate, low, and very low. Furthermore, the panel also recommended a three-tier quality of evidence: Level I, II, and III.[15]

Guideline Development

The discussions were recorded at the meeting and written up as a manuscript draft. The working group writing committee drafted the first version of the manuscript, which was sent to the other group members for their critical review. The draft was reviewed, edited, and commented on the outline and manuscript drafts until a final version was reached and approved by all members. The panel agreed on several recommendations based on the best scientific evidence.

EPIDEMIOLOGY OF INVASIVE CANDIDIASIS

Incidence

Invasive candidiasis frequently occurs in hospitals, including a *Candida* bloodstream infection (candidemia) as the most common form of IC. Various studies in many countries have reported an increased incidence of IC[1,2] The incidence of candidemia in Europe was estimated at 79 cases per day, 3.88 per 100,000 population, with a mortality rate of 37%.[3] The incidence of IC in Australia increased from 1.81 to 2.41 cases per 100,000 population in 2001 and 2015.[16] Increased incidence of candidemia in Switzerland was reported from 2.96 per 100,000 cases in 2009–2013 to 4.20 in 2014–2018.[17] The incidence of candidemia also increased from 0.43 to 1.33 cases per 1,000 hospitalizations between 2013-2018 in Korea.[18]

Candidemia is a major cause of invasive mycoses in hospitalized children. The highest incidence was reported in neonates and infants <1 year old.[19] In 2015, the incidence of candidemia in neonates in the United States reached 11.8 per 100,000 births, while in infants was 17.5 cases per 100,000 in 2015. The incidence of IC in the pediatric population was 0.8 cases per 100,000 in 2014.[20] The overall IC mortality rate in pediatric patients ranges from 10–14.4%, while it was 22% in neonates.[21]

Table 1. Definition of the recommendation's strength and evidence quality[15]

The strength of recommendation	Grade	Definition
	A	Strongly recommended for use
	B	Moderately support a recommendation for use
	C	Marginally support a recommendation for use
	D	Not recommended to use
The quality of evidence	Level	
	I	Evidence from ≥ 1 well-designed randomized controlled trial
	II	Evidence from ≥ 1 well-designed clinical trial; from cohort or case-control analytical studies; from multiple case series
	III	Evidence from the opinion of respected authorities, based on clinical experience, descriptive case studies, or expert committee reports

Table 2. Invasive candidiasis/candidemia in Indonesia

Population	Location	Year	Incidence (%)	References
Critically ill patients	Cipto Mangunkusumo Hospital, Jakarta	2011-2014	117 cases	22
	Cipto Mangunkusumo Hospital Jakarta	2012-2014	12,3	23
	Hasan Sadikin Hospital, Bandung	2016-2017	3,5	24
Sepsis patients	National Brain Center Hospital, Jakarta	2017-2020	13,7	25
Critically ill children	Cipto Mangunkusumo Hospital, Jakarta	2013-2014	8,3	26
Sepsis neonates	Cipto Mangunkusumo Hospital, Jakarta	2001-2003	62,9	27

Epidemiological data on IC and candidemia are still lacking in Indonesia, both in adults and children because the data is only reported from the referral hospitals in Jakarta and Bandung (**Table 2**). The incidence of candidemia in Indonesia was estimated at 10 cases per 100,000 population yearly, while in adults' data vary widely depending on the patient population.[5]

The Etiology

The primary pathogen responsible for IC is C. albicans, but in recent decades, non-*Candida-albicans Candida* (NCAC) species have emerged as causes of candidemia.[28] The total proportion of IC due to *C. albicans* has decreased from 57.4% to 46.4% during the 1997-2016 surveillance period based on SENTRY program data.[29] The distribution of NCAC species can be differentiated based on patient characteristics. *Candida parapsilosis* is associated with candidemia in neonates and young adults. *Candida glabrata, C. tropicalis*, and *C. krusei* were isolated from blood cultures of elderly patients (>65 years) with risk factors, for example, abdominal surgery, solid tumors, hematological malignancies, organ transplantation, and long-term corticosteroid therapy.[28] *Candida glabrata* and *C. krusei* were reported to be the most common causative agents of candidemia in patients with hematological malignancies.[30] Studies at Cipto Mangunkusomo Hospital, Jakarta showed that *C. albicans* is the predominant species of IC (34.72%), followed by *C. tropicalis* (33%), and *C. parapsilosis* (14%).[23] Another study in the neonatal population showed that the most common cause of candidemia was *C. tropicalis* (48.5%).[31]

Risk Factors

Candida spp. is a typical microorganism in the human body, e.g. in the mouth, gastrointestinal tract, and vagina. However, Candida spp. can cause superficial infections to deadly systemic infections in certain conditions.[32] The degree of IC severity depends on the presence or absence of risk factors or predispositions to IC, including prolonged use of broad-spectrum antibacterial therapy, length of ICU stays, use of central venous catheters, receipt of parenteral nutrition, neutropenia, use of immunosuppressive agents, implantable prosthetic devices, and renal replacement therapy. Underlying diseases or comorbidities should also be carefully evaluated, as well as drugs, and host genetic factors.[33–36]

Underlying Diseases or Comorbidities

Several diseases might become the risk factors for IC, including malignancy, kidney failure, diabetes mellitus, neutropenia, and lymphopenia.[36] Acute leukemia, lymphoma, and myelodysplastic syndrome are the most common conditions associated with candidemia. Hematological malignancies and aplastic anemia also increase the risk of *Candida* infection (90%). Invasive candidiasis is also associated with immunodeficiency conditions, e.g, sepsis, stroke, cancer, chemotherapy recipients, patients living with HIV/AIDS, stem cell/organ transplant recipients, graft versus host disease (GVHD) patients, as well as neonates.[37,38]

Nosocomial Infections

The increasing cases of IC in hospitalized patients is associated and in line with the use of broad-spectrum antibiotics, immunosuppressant drugs, and long-term care, including in the ICU, as in critically ill patients. The main risk factors for IC in ICU patients include the use of broad-spectrum antibiotics, *Candida colonization,* use of central venous catheters, and administration of total parenteral nutrition. The risk of IC also increases in hemodialysis patients.[34,39,40]

Critically ill patients in the ICU are more susceptible to *Candida* infections through contamination from the hospital environment, health workers, invasive medical equipment (venous or urinary catheters, endotracheal tubes, drain tubes, etc.), or the potential for biofilm formation on those devices. [35,41,42]

Biofilm can trigger *Candida* resistance to antifungal agents by reducing the ability of drug penetration, as well as facilitating the development of persister cells which have various resistance mechanisms to reduce the effectiveness of antifungal agents. The incidence of *C. auris* infection in hospitals should specifically consider relevant risk factors, including travel history from endemic countries.[41,43,44]

Medications

Prolonged usage of systemic, broad-spectrum antibiotics, immunosuppressants, corticosteroids, and chemotherapy might increase the risk for IC.[34,36] Long-term antibiotic therapy can increase *Candida* colonization, change the composition of the microbiota in the body, and increase the risk of *Candida* resistance to antifungal agents.[35,44]

Genetics

Host genetic risk factors also influence, particularly the Dectin-1 receptor, a CD82 variant associated with the risk of candidemia and reduced cytokine production. Mutations in CARD9 are associated with autosomal recessive inheritance of host susceptibility to invasive infections by *Candida* spp.[36]

PATHOGENESIS

Candida is a commensal organism in the gastrointestinal tract, the skin, and the urinary tract. Candida is detected in 50-70% of healthy human mucosa. In patients with certain risk factors and/or altered immune systems, *Candida* colonization may occur as an initial consequence of microbiota dysbiosis (**Figure 1**). *Candida* colonization induces a resistance immune response. In cellular immunity, the production of T-helper cells increases. Monocytes activate the inflammatory response through the phagocytosis and cytokine production. Polymorphonuclear cells, including neutrophils, destroy fungi through opsonization processes, oxidative and non-oxidative mechanisms. The immune response dysregulation will increase fungal growth, thereby increasing the risk of candidemia and IC. Deep-seated candidiasis is most often associated with intra-abdominal invasion. Gastrointestinal or hepatobiliary surgery becomes the risk factor, as the intestinal mucosal barrier damage leads *Candida* to spread directly to the abdominal cavity and enter the bloodstream. [39,45–47]

The basic mechanism of *Candida* pathogenicity is its ability to adapt to the host environment and physiological barriers. Fungi are typically thermophilic, thriving best at room temperature. Candida albicans is capable of forming hyphae at temperatures over 35°C and surviving at 40°C, establishing this fungi as a leading cause of candidiasis. The ability to survive at high temperatures is used as a basis for distinguishing *C. albicans* from other species (NCAC).[2,39]

External and internal protective factors, including gut self-regulation, are necessary for maintaining *Candida* commensalism. The internal factors, including the intestinal mucosal barrier, are composed of goblet cells (producers

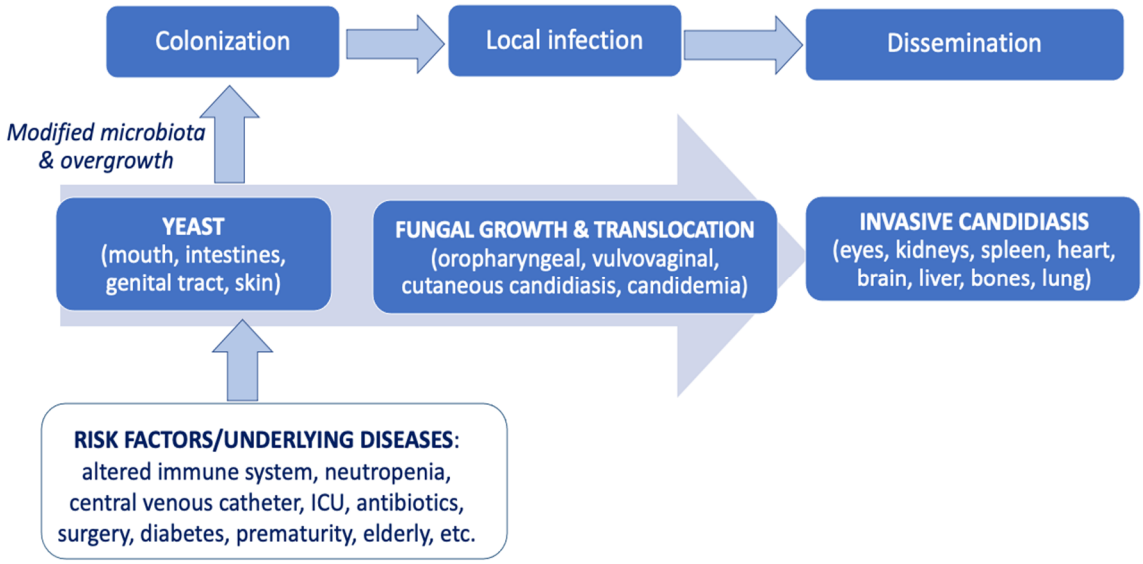


Figure 1. Various risk factors or underlying diseases play an important role in developing invasive candidiasis. Changes in the microbiota due to certain risk factors result in the overgrowth of *Candida* species and colonization. The altered immune system, especially neutropenia, as well as invasive procedures that damage the natural barrier of the skin or mucosa, such as intravascular catheters, gastrointestinal surgery, and chemotherapy-associated mucositis, facilitate local invasion, candidemia, and invasive candidiasis (adapted from Lass Florl, et al.)[48]

of mucus), paneth cells (producers of anti-microbial peptides/AMPs), and gastrointestinal microbiota. The mucus layer and intestinal epithelial cells control the translocation and composition of *Candida* yeast cells (non-pathogenic form). External factors, including a healthy diet that supports the growth of intestinal microbiota, chemical conditions, nutrition, and physiological factors, also influence the balance of microbiota. If hyphae are dominant, *Candida* can cause mucosal infections and kill epithelial cells, activating c-Fos and the release of inflammatory mediators/cytokines. This can be triggered by irrational use of antibiotics, unhealthy diet, cytostatic therapy, decreased intestinal mucus secretion, dysbiosis of the gastrointestinal microbiota, and others.[49–51]

DIAGNOSIS OF INVASIVE CANDIDIASIS

Rapid and accurate diagnosis of IC is important to support the appropriate antifungal administration. Early diagnosis can be challenging because fungal cultures have low sensitivity, often leading to delays in definitive treatment. The gold standard for IC diagnosis is the fungal culture or histopathological examination from the sterile site. The diagnosis of IC is intricate; therefore, relying solely on laboratory findings is insufficient to establish the diagnosis. For this reason, the terms proven, probable, or possible IC were introduced.[52,53]

Probable IC is based on the assessment of specific host factors (e.g. neutropenia, organ transplantation, immunosuppressive therapy, etc), clinical manifestations, and mycological evidence that comprises culture and microscopic analysis, and also non-culture-based tests, e.g. antigen detection. Possible invasive candidiasis is no longer defined.[52,53] The expert panel agreed to use the recent definition of IC from the EORTC/MSG 2020 [7] as part of the standard definition (**Table 3**).

Table 3. Definition of proven and probable invasive candidiasis[7]

Diagnosis	Criteria
	Microscopic analysis or culture from sterile materials
PROVEN	- Blood culture positive (yield yeast) OR - Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells of *Candida* OR - Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site AND clinical or radiological abnormality consistent with an infectious disease process
	Host factors
PROBABLE	- Recent history of neutropenia <0.5 × 10^9 neutrophils/L (<500 neutrophils/mm^3 for >10 days) temporally related to the onset of invasive fungal disease - Hematologic malignancy - Receipt of an allogeneic stem cell transplant - Solid organ transplant recipient - Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days - Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte- specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 day - Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, CARD9 deficiency, STAT-1 gain of function, or severe combined immunodeficiency) - Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
	Clinical features
	At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks: - Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or meningeal enhancement - Progressive retinal exudates or vitreal opacities on ophthalmologic examination
	Mycological evidence
	ß-D-glucan (Fungitell) ≥80 ng/L (pg/mL) detected in at least 2 consecutive serum samples provided that other etiologies have been excluded

Clinical Manifestations

Candidiasis is the most common fungal infection, both superficial and invasive. Many organs and body systems are at risk of developing IC through bloodstream infections. In the cardiovascular system, infective endocarditis possibly occurs. The source of infection might be intracardiac or intravascular implants that cause biofilm. The gastrointestinal, hepatosplenic, and genitourinary tract organs are also susceptible to IC, with symptoms in the form of abscesses. The nervous system and osteoarticular (the most common form is vertebral osteomyelitis), respiratory system (e.g. *Candida* lung abscess), and visual system (e.g. endophthalmitis) are also not clear from the threat of *Candida* infection.[39,54,55]

Laboratory Tests

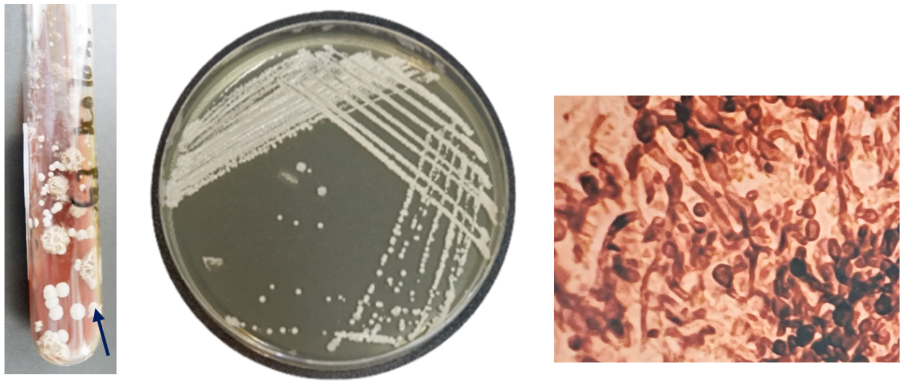
Species identification can be established after examining cultures on certain media, semi-automatic or automatic methods, and molecular methods. Specimen handling is very important as an initial part of the diagnosis of IC (**Table 4**). Identifying *Candida* spp. from clinical material takes 24-96 hours. This has an impact on delays in the initiation of early treatment.[56–58]

Figure 2 documented the culture of *Candida* on Sabouraud Dextrose Agar media and histopathological preparations. The development and validation of diagnostic tests other than non-culture is the most important need in the diagnosis of IC and candidemia. Laboratory tests other than non-culture-based are more sensitive and faster than blood culture, but cannot determine the identification to the species level or antifungal susceptibility testing. The *Candida* PCR test has not been standardized yet. The most important task in increasing laboratory capacity to diagnose IC is to incorporate tests other than non-culture into an effective and cost-effective management strategy so that the quality of IC management can be improved.[56–58]

The possibility of IC can be predicted by using the *Candida* score, Ostrosky-Zeichner clinical prediction rule, or other scoring systems.[60] The *Candida* score study at Cipto Mangunkusumo Hospital was developed based on risk factors in ICU patients. The results of the study showed that the predictor factors for candidemia were: length of stay 8-14 days (score 1), length of stay >14 days (score 2), severe sepsis (score 3), and

Table 4. Specimen type, clinical material, optimal volume, and delivery need to be considered in making a diagnosis of invasive candidiasis.[59]

No	Clinical material	Optimal volume	Shipping (container, time, temperature)
1	Blood (adult)	20-30 mL	- Inoculated culture bottles (usually in Bactec) - Lysis-centrifugation blood culture tubes or aerobic blood culture bottles - Blood syringe/tube without preservatives - Stored for 2 hours at room temperature
2	Blood (children, neonates)	Based on body weight - < 1 kg: 2mL - 1,1-2 kg: 4 mL - 2,1-12,7 kg: 6 mL - 12,8-36,3 kg: 20 mL - >36,3 kg: 40-60 mL	- Inoculated culture bottles (usually in Bactec) - Stored for 2 hours at room temperature
3	Sterile body fluid (aspirates/ fluid from liver, peritoneal, pleural, cerebrospinal, pericardial, etc.	10-50 mL	Sterile container, stored for 2 hours at room temperature or if > 2 hours, stored at 4°C (for 2-24 hours)
4	Tissue	Sufficient	- Sterile container, keep the tissue moist (add a few drops of 0.9% NaCl), avoid formalin. - Stored for 1 hour at room temperature, or at 4°C if >1 hour
5	Swab	Sufficient	- Swab kit/ equipment - Stored for 2 hours at room temperature
6	Clinical material from endophtalmitis patient	Sufficient	- Sterile container - Stored for 2 hours at room temperature
7	Abses/purulent aspirates		- Sterile container - Stored for 2 hours at room temperature
8	Cases of aneurysm vascular infection and vascular graft	Tissue biopsy/ resected vascular	- Sterile container - Stored for 2 hours at room temperature



A B C

Figure 2. *Candida* isolated from blood culture in *Sabouraud Dextrose Agar*; 2.2. *Candida* sub-culture in *Sabouraud Dextrose Agar* plate; 2.3. Histopathology of *Candida* from the organ tissue (Courtesy of Parasitology Laboratory, Faculty of Medicine Universitas Indonesia)

surgery (score 1), with a cut-off score of 3.5. This *Candida* score can be used as a guide for starting empirical therapy at Cipto Mangunkusumo Hospital.[61] However, the role of the *Candida* score as a diagnostic method for IC in pediatric patients is still limited.[62]

In critically ill patients, delaying antifungal therapy due to waiting for culture results is associated with a poor prognosis.[58] In ICU patients, the BDG test shows a sensitivity and specificity of 81% and 61%. The assay has been used to guide pre-emptive antifungal therapy, with a positive predictive value of 30%.[63] The PCR test is the main component of molecular methods, used to amplify DNA from clinical material. The use of PCR is still limited for research purposes due to the lack of standardization in various countries.[56–58] Fungal susceptibility testing uses methods based on the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[43,56] In Indonesia, the commonly used device to identify and conduct the susceptibility test is Vitek which is CLSI and EUCAST-based.

Recommendation:

- Isolation and identification of *Candida* spp. from clinical material culture should be performed using Sabouraud dextrose agar medium with the addition of antibiotics. A blood volume of 20-30 mL is recommended if the diagnosis suggests possible candidemia. Blood cultures should be repeated if candidemia is present. The aim is to monitor disease progression and determine the duration of therapy (strong recommendation, level II evidence).
- Direct microscopic examination of sterile samples should be performed, in addition to fungal culture to diagnose IC (strong recommendation, level II evidence).
- Susceptibility testing should be carried out routinely on clinically significant isolates grown from sterile samples, and for which clinicians and mycologists have been consulted, particularly if there has been previous use of antifungal drugs, or when there are species intrinsically associated with resistance, e.g. *Candida glabrata* isolated in culture. The susceptibility testing of invasive isolates should be reviewed periodically, to anticipate whether there are changes in the susceptibility profile and clinical management. (strong recommendation, level II evidence).

The expert panel agreed that there must be national guidelines approved by various medical professionals in Indonesia for an adequate diagnosis of IC. The guideline should be applied wherever possible based on clinical and laboratory data, by optimal use of local resources and expert advice. The panel also realized that the availability of diagnostic facilities in Indonesia is still limited for fungal infections. However, every effort should be optimized to diagnose infections at the species level. The local laboratory should be empowered and collaborate with reference laboratories to improve IC diagnostic quality.

TREATMENT OF INVASIVE CANDIDIASIS

Once a diagnosis of IC has been made, providing adequate treatment is very crucial, considering that delayed treatment is associated with increased mortality. Excessive or insufficient administration of antifungal therapy has the potential to cause drug toxicity and fungal resistance. To overcome these challenges, an initial treatment strategy was developed using the following scheme: prophylactic, empiric, pre-emptive, and targeted therapy (**Table 5**).[35,64,65]

Principles for Selection of Antifungal Therapy

The serious illnesses and problems of IC patients need careful consideration in choosing antifungal therapy. The patient's clinical condition, previous exposure to antifungal, risk of fungal colonization, local epidemiology, infection sites, organ dysfunction, accompanying therapy, and the need for therapeutic drug monitoring (TDM) are factors that should be considered in selecting appropriate treatment.[35]

The antifungal group is divided based on its mechanism of action: echinocandins, triazoles, amphotericin B, and the new group. Echinocandins have fungicidal activity against almost all *Candida* species by changing the structure of the fungal cell membrane. Echinocandins inhibit the biosynthesis of 1,3-β-D-glucan, a component of *Candida* cell membranes. Echinocandins are recommended therapy of IC in critically ill or unstable patients, who have been previously exposed to antifungal agents and have proven resistance to azoles, for almost all *Candida* species. Drugs included in this group are caspofungin, anidulafungin, and micafungin.[2,9,39]

Table 5. Strategy for administering antifungal therapy in invasive candidiasis[35]

Strategy of therapy	Definition
Prophylaxis	Antifungal prescription to prevent infection in risks patient
Empirical	Antifungal prescription in response to the signs and symptoms in ICU or critically ill patients with risk factors (possible diagnosis)
Pre-emptive	Antifungal prescription in response to positive non-culture or radiology-based tests (probable diagnosis)
Targeted	Antifungal prescription in response to microbiology test evidence in proven invasive candidiasis

Table 6. Risk factors associated with candidemia and antifungal treatment[65]

Patients at risk/ risk factors	Candida spp.	Therapy
All patients	*Candida albicans*	- Echinocandins (1) - Fluconazole, 800 mg then 400 mg (2) - Liposomal amphotericin B, 3–5 mg/kg/day (3)
ICU patients Neonates Vascular catheter	*Candida parapsilosis*	- Echinocandins (1) - Fluconazole, 800 mg then 400 mg (2)
Older age Diabetes Cancer Hematological malignancies Stem cell transplantation Azole prophylaxis	*Candida glabrata*	Fluconazole and voriconazole are not recommended for frequent azole resistance - Echinocandins (1) - Liposomal amphotericin B, 3–5 mg/kg/day (3)
Corticosteroid therapy Hematological malignancies Stem cell transplantation	*Candida tropicalis*	- Echinocandins (1) - Fluconazole, 800 mg then 400 mg (2) - Liposomal amphotericin B, 3–5 mg/kg/day (3)
Corticosteroid therapy Hematological malignancy Stem cell transplantation Azole prophylaxis	*Candida krusei*	Fluconazole is not recommended for frequent azole resistance - Echinocandins (1) - Liposomal amphotericin B, 3–5 mg/kg/day (3) - Voriconazole (4)
Diabetes Cancer Hematological malignancy ICU/invasive procedure	*Candida auris*	- Echinocandins (1)

Notes: (1) anidulafungin: loading dose 200 mg, then 100 mg daily, micafungin: 100 mg daily; (2) In stable patients without previous exposure to azoles; (3) If isolates are not susceptible to azoles and echinocandins or in the presence of organ involvement; (4) 6 mg/kg q12h × 2 doses (load) then 3–4 mg/kg q12h.

Fluconazole, itraconazole, voriconazole, Posaconazole (not available in Indonesia), and isavuconazole belong to the triazole group. These drugs are fungistatic by inhibiting the biosynthesis of ergosterol, a component of the fungal cell wall, and inhibiting the cytochrome P450 enzyme. The azole group can be used as an alternative to IC initial therapy. Because all azole groups have decreased activity against C. *glabrata* and *C. krusei*, for these two species, the amphotericin B group is used as an alternative to echinocandins. The mechanism of action of amphotericin B is that it binds to the ergosterol component in the fungal cell wall, resulting in leakage and disruption of the balance of the composition of the fungal cell wall which causes the death of the fungus (fungicidal properties).[2,39,65]

A new and quite promising antifungal drug group has now passed phase 2 and 3 clinical trials for the treatment of invasive candidiasis, namely rezafungin. It has a structure similar to an echinocandin with a longer half-life, so the interval between doses is longer (7 days). Other drugs such as Ibrexafungerp oral is a glucan synthase inhibitors, while Fosmanogepix is a guanosine monophosphate inhibitor and has activity against all pathogenic *Candida* species, except *C. krusei*. A new drug, ATI-2307 works by inhibiting mitochondria and is expected to provide an alternative to antifungal drugs amidst the emergence of resistance to echinocandins. The choice of antifungal therapy for candidemia must consider various factors, as summarized in **Table 6**.[35,65]

Optimal IC management still affords many challenges, including the high cost of treatment, fungal resistance to antifungal therapy, the timing of starting and stopping antifungal therapy, etc. Critically ill patients in the ICU might suffer from severe sepsis and unstable hemodynamic conditions, the use of organ support devices including mechanical ventilation, renal replacement therapy(RRT), extracorporeal membrane oxygenation (ECMO), etc.[35,65]

Recommendation

- Prophylactic and pre-emptive therapy is not recommended for ICU patients. Empirical antifungal therapy may be considered in patients with septic shock, multi-organ failure, and *Candida* colonization in at least 2 extra-intestinal organs (moderate recommendation, level III evidence).
- Prophylaxis with fluconazole is recommended for very low birth weight infants admitted to units with a high incidence of IC (strong recommendation, level II evidence).
- If there are cases of *C. auris* in the hematology/oncology or ICU population, infection control and prevention are necessary, including isolation, screening of close contacts, and environmental cleaning (moderate recommendation, level III evidence).

CONCLUSION

The expert panel has developed and approved national guidelines on diagnosing and managing invasive candidiasis for medical professionals in Indonesia. The guidelines should be implemented based on sufficient clinical and laboratory data. Local laboratories must be empowered and collaborate with reference laboratories to improve the quality of IC diagnostics. Early diagnosis is very important for adequate management so that morbidity and mortality rates can be reduced. Direct microscopic examination of sterile samples should be conducted, including histopathological examination and fungal culture from sterile sites as the gold standard for IC diagnosis. The choice of antifungal treatment is performed by considering clinical condition, previous exposure to antifungal, risk of fungal colonization, local epidemiology, infection sites, organ dysfunction, accompanying therapy, and the need for therapeutic drug monitoring (TDM).

ACKNOWLEDGMENTS

The expert panel would like to thank all colleagues who has supported this joint activity, from the initial step to completion, including heads of medical professional organizations, research assistants, and all related partners.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest relevant to the content of the article.

CONTRIBUTORS

All authors contributed to the design and interpretation of the data and to further drafts.

REFERENCES

1. Denning DW. Global incidence and mortality of severe fungal disease. Lancet Infect Dis. 2024;S1473-3099(23)00692-8.
2. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nat Rev Dis Primers. 2018;4:1–20.
3. Koehler P, Stecher M, Cornely OA, et al. Morbidity and mortality of candidaemia in Europe: an epidemiologic. Clin Microbiol Infect. 2019;25:1200–12.
4. WHO. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022.
5. Wahyuningsih R, Adawiyah R, Sjam R, et al. Serious fungal disease incidence and prevalence in Indonesia. Mycoses. 2021;64:1203–12.
6. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813–21.
7. Donnelly PJ, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020;71:1367–76.
8. Bassetti M, Azoulay E, Kullberg BJ, et al. EORTC/MSGERC Definitions of invasive fungal diseases: summary of activities of the Intensive Care Unit working group. Clin Infect Dis. 2021;72:S121–7.
9. Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2015;62:409–17.
10. Chang CC, Blyth CC, Chen SCA, et al. Introduction to the updated Australasian consensus guidelines for the management of invasive fungal disease and use of antifungal agents in the haematology/oncology setting, 2021. Intern Med J. 2021;51:3–17.
11. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18:19–37.
12. Martin-Loeches I, Antonelli M, Cuenca-Estrella M, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med. 2019; 45:789–805.
13. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017; 102:433–44.
14. Groll AH, Pana D, Lanternier F, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. Lancet Oncol. 2021;22: e254–69.
15. Piggott T, Morgan RL, Cuello-Garcia CA, et al. Grading of recommendations assessment, development, and evaluations (GRADE) notes: extremely serious, GRADE's terminology for rating down by three levels. J Clin Epidemiol. 2020;120:116–20.
16. Chapman B, Slavin M, Marriott D, et al. Changing epidemiology of candidaemia in Australia. J Antimicrob Chemother 2017;72:1103-8.
17. Adam K manuel, Osthoff M, Lamoth F, et al. Trends of the epidemiology of candidemia in Switzerland : A 15-Year FUNGINOS Survey. Open Forum Infect Dis. 2021;8:1–9.
18. Kim JH, Suh JW, Kim MJ. Epidemiological trends of candidemia and the impact of adherence to the candidemia guideline: Six-year single-center experience. J Fungi. 2021;7:1-7.
19. Walsh TJ, Katragkou A, Chen T, Salvatore CM, Roilides E. Invasive candidiasis in infants and children: Recent advances in epidemiology, diagnosis, and treatment. J Fungi. 2019;5:1-8.
20. Benedict K, Roy M, Kabbani S, et al. Neonatal and pediatric candidemia: results from population-based active laboratory surveillance in four US locations, 2009-2015. J Pediatric Infect Dis Soc. 2018;7:e78-85.
21. Lausch KR, Schultz Dungu KH, Callesen MT, et al. Pediatric candidemia epidemiology and morbidities: a nationwide cohort. Pediatric Infect Dis J. 2019;38: 464–9.
22. Mursinah M, Ibrahim F, Wahid M. *Candida* profile causes candidemia and pattern of sensitivity to antifungals in critically ill patients at Cipto Mangunkusuno Hospital. Indones J Biotech Med. 2016;5:105-11.
23. Kalista KF, Chen LK, Wahyuningsih R, Rumende CM. Karakteristik klinis dan prevalensi pasien kandidiasis invasif di Rumah Sakit Cipto Mangunkusumo. Jurnal Penyakit Dalam Indonesia. 2017;4:56-60.
24. Maulana HR, Sumardi U, Koesoemadinata RC. Prevalensi kandidiasis invasif di unit perawatan intensif Rumah Sakit Hasan Sadikin Bandung. Jurnal Penyakit Dalam Indonesia. 2019;6:8-10.
25. Rinawati W, Kumalawati J, Bardosono S, Immanuel S, Sukartini N, Indrasari ND. Invasive candidiasis among high prevalence neurological patients. J Infect Dev Ctries. 2022;16:871–80.
26. Indrawan DK, Pudjiadi AH, Latief AL. Insidens kandidemia di Paediatric Intensive Care Unit Rumah

Sakit Dr. Cipto Mangunkusumo. Sari Pediatri. 2017;18:182-5.
27. Rozaliyani A. Kandidemia pada neonatus dan profil resistansi *Candida* spp. terhadap derivat azol (thesis). Jakarta: Universitas Indonesia; 2004.
28. Quindós G. Epidemiology of candidaemia and invasive candidiasis. A changing face. Rev Iberoam Micol. 2014;31:42–8.
29. Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty years of the SENTRY antifungal surveillance program: results for *Candida* species from 1997 – 2016. Open Forum Infect Dis. 2019; 6: S79–94.
30. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive candidiasis: *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. Cancer. 2008;112:2493-9.
31. Wahyuningsih R, Rozaliyani A, Jannah S, Amir I, Prihartono J. Kandidemia pada neonatus yang mengalami kegagalan terapi antibiotik. Majalah Kedokt Indones. 2008;58:110–5.
32. Tan TY, Tan AL, Tee NWS, Ng LSY, Chee CWJ. The increased role of non-albicans species in candidaemia: Results from a 3-year surveillance study. Mycoses. 2010;53:515–21.
33. Soriano A, Honore PM, Puerta-Alcalde P, et al. Invasive candidiasis: current clinical challenges and unmet needs in adult populations. J Antimicrob Chemother. 2023;78:1569-85.
34. Thomas-Rüddel DO, Schlattmann P, Pletz M, Kurzai O, Bloos F. Risk factors for invasive *Candida* infection in critically ill patients: a systematic review and meta-analysis. Chest. 2022;161:345–55.
35. Logan C, Martin-Loeches I, Bicanic T. Invasive candidiasis in critical care: challenges and future directions. Intensive Care Med. 2020;46:2001–14.
36. Riera FO, Caeiro JP, Angiolini SC, et al. Invasive candidiasis: update and current challenges in the management of this mycosis in South America. Antibiotics. 2022;11:1–16.
37. Alves J, Palma P, Azevedo D, et al. Candidemia in the patient with malignancy. Hosp Pract. 2018;46:246–52.
38. Berkow EL, Lockhart SR. Fluconazole resistance in *Candida* species: a current perspective. Infect Drug Resist. 2017;10:237–45.
39. McCarty TP, White CM, Pappas PG. Candidemia and invasive candidiasis. Infect Dis Clin North Am. 2021; 35:389–413.
40. Krcmery V, Barnes AJ. Non-albicans *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance. J Hosp Infect. 2002;50:243–60.
41. Nishida R, Eriguchi Y, Miyake N, et al. Breakthrough candidemia with hematological disease: results from a single-center retrospective study in Japan, 2009-2020. Med Mycol. 2023;61:1-8.
42. Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Azole antifungal resistance in *Candida albicans* and emerging non-albicans *Candida* species. Front Microbiol. 2016;7:2173-6.
43. Keighley C, Cooley L, Morris AJ, et al. Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. Intern Med J. 2021;51: 89–117.
44. Worth LJ, Harrison SJ, Dickinson M, van Diemen A, Breen J, Harper S, et al. *Candida auris* in an Australian health care facility: importance of screening high risk patients. Med J Australia. 2020;212:510-15.
45. Drummond RA, Desai J V, Ricotta EE, et al. Article Long-term antibiotic exposure promotes mortality after systemic fungal infection by driving lymphocyte dysfunction and systemic escape of commensal bacteria: long-term antibiotic exposure promotes mortality after systemic fungal infection. Cell Host Microbe. 2022;30:1020-33.
46. Yapar N, Pullukcu H, Avkan-Oguz V, et al. Evaluation of species distribution and risk factors of candidemia: A multicenter case-control study. Med Mycol. 2010; 49:26–31.
47. Keighley C, Chen SCA, Marriott D, et al. Candidaemia and a risk predictive model for overall mortality: a prospective multicentre study. BMC Infect Dis. 2019; 19: 1–10.
48. Lass-Flörl C, Kanj SS, Govender NP, Thompson GR, Ostrosky- Zeichner L, Govrins MA. Invasive candidiasis. Nat Rev Dis Primers. 2024;10:1–18.
49. Tong Y, Tang J. *Candida albicans* infection and intestinal immunity. Microbiol Res. 2017;198:27–35.
50. Kumamoto CA, Gresnigt MS, Hube B. The gut, the bad and the harmless: *Candida albicans* as a commensal and opportunistic pathogen in the intestine. Curr Opin Microbiol. 2020;56:7–15.
51. Martins N, Ferreira ICFR, Barros L, Silva S, Henriques M. Candidiasis: Predisposing factors, prevention, diagnosis and alternative treatment. Mycopathologia. 2014;177:223–40.
52. Clancy CJ, Nguyen MH. Diagnosing invasive candidiasis. J Clin Microbiol. 2018; 56: 1–9.
53. Barantsevich N, Barantsevich E. Diagnosis and treatment of invasive candidiasis. Antibiotics. 2022; 11:718-15.
54. Kullberg BJ, Arendrup MC. Invasive Candidiasis. In: Campion EW, editor. New Eng J Med. 2015;373: 1445–56.
55. Kotey FC, Dayie NT, Tetteh-Uarcoo PB, Donkor ES. *Candida* bloodstream infections: changes in epidemiology and increase in drug resistance. Infect Dis. 2021;14:1-5.
56. Pitarch A, Nombela C, Gil C. Diagnosis of invasive candidiasis: from gold standard methods to promising leading-edge technologies. Curr Top Med Chem. 2018; 18:1375–92.
57. Sabino R, Wiederhold N. Diagnosis from tissue: histology and identification. J Fungi. 2022;8:1–8.

58. Hage CA, Carmona EM, Epelbaum O, et al. Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice: An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2019;200:535–50.
59. Miller JM, Binnicker MJ, Campbell S, et al. A Guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67:e1–94.
60. Juneja D, Jain R, Singh O, Borah AK. Candida Score: a Predictor of mortality in patients with candidemia. J Assoc Physicians India. 2022;70:11–2.
61. Mursinah, Ibrahim F, Wahid MH. Risk factors and scoring systems for patients with candidemia at a tertiary hospital in Jakarta, Indonesia. Acta Med Indones. 2016;48:193–9.
62. Ratridewi I, Juwita N, Putera MA, Nugroho S. Peran skor *Candida* sebagai metode diagnostik kandidiasis invasif terhadap neutropenia berat pada anak dengan keganasan. Sari Pediatri. 2021;22:351-5.
63. Mikulska M, Giacobbe DR, Furfaro E, et al. Lower sensitivity of serum (1,3)-β-D-glucan for the diagnosis of candidaemia due to *Candida parapsilosis*. Clin Microbiol Infect. 2016;22:646.e5-8.
64. Uneno Y, Imura H, Makuuchi Y, Tochitani K, Watanabe N. Pre-emptive antifungal therapy versus empirical antifungal therapy for febrile neutropenia in people with cancer. Cochrane Database Syst Rev. 2022;11:1-10.
65. Tortorano AM, Prigitano A, Morroni G, Brescini L, Barchiesi F. Candidemia: evolution of drug resistance and novel therapeutic approaches. Infect Drug Resist. 2021;14:5543–53.