Research Article

Risk factors for early invasive fungal disease in critically ill patients

Gurmeet Singh, Ceva Wicaksono Pitoyo, Dita Aditianingsih[1], Cleopas Martin Rumende

Abstract

Background: The incidence of invasive fungal disease (IFD) is increasing worldwide in the past two to three decades. Critically ill patients in Intensive Care Units are more vulnerable to fungal infection. Early detection and treatment are important to decrease morbidity and mortality in critically ill patients. **Objective:** Our study aimed to assess factors associated with early IFD in critically ill patients. **Materials and Methods:** This prospective cohort study was conducted in critically ill patients, from March to September 2015. Total number of patients (74) in this study was drawn based on one of the risk factors (human immunodeficiency virus). Specimens were collected on day 5–7 of hospitalization. Multivariate analysis with logistic regression was performed for factors, with $P < 0.25$ in bivariate analysis. **Results:** Two hundred and six patients were enrolled in this study. Seventy-four patients were with IFD, majority were males (52.7%), mean age was 58 years (range 18–79), mean Leon's score was 3 (score range 2–5), majority group was nonsurgical/nontrauma (72.9%), and mean fungal isolation was positive on day 5. *Candida* sp. (92.2%) is the most frquently isolated fungal infection. Urine culture yielded the highest number of fungal isolates (70.1%). Mortality rate in this study was 50%. In multivariate analysis, diabetes mellitus (DM) ($P = 0.018$, odds ratio 2.078, 95% confidence interval 1.135–3.803) was found as an independent factor associated with early IFD critically ill patients. **Conclusion:** DM is a significant factor for the incidence of early IFD in critically ill patients.

Keywords: *Candida*, critically ill, diabetes mellitus, early invasive fungal disease, risk factor

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.194007

Quick Response Code:

Introduction

Invasive fungal disease (IFD) is a disease where fungus is obtained from blood cultures or from other body parts that are normally sterile accompanied by signs of infection. The incidence of IFD is on the rise over the last two to three decades, especially in health-care facilities, representing one of the important infectious complications in hospitalized patients. Critically ill patients are more susceptible to this disease, particularly in Intensive Care Unit (ICU), due to the complexity of their underlying disease.

Majority of the fungi causing IFD is the *Candida* sp. In the US, a national study on sepsis epidemiology from 1979 to 2000 reported that the incidence of sepsis induced by fungal infection increased by 207%.[1] In 2006, the Health Protection Agency estimated more than 5000 cases of invasive *Candida* infections occurring in the UK every year and about 40% of them are found in ICU. Epidemiological survey on six sentinel hospitals in the UK reported that 45% of *Candida* infections in blood

From:
Department of Internal Medicine, Respirology and Critical Illness Division, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, [1]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Correspondence:
Dr. Gurmeet Singh, Jl. Diponegoro No. 71, Central Jakarta 10430, Indonesia.
E-mail: gurmeetsingh10@yahoo.com

How to cite this article: Singh G, Pitoyo CW, Aditianingsih D, Rumende CM. Risk factors for early invasive fungal disease in critically ill patients. Indian J Crit Care Med 2016;20:633-9.

occur in ICU as fungal infection can be found in every group of patients in ICU.[2]

The risk factors for fungemia and candidiasis sepsis include comorbidities of severe diseases, variety of surgical interventions, catheter and intravascular invasive instruments, broad-spectrum antibiotics, parenteral nutrition, trauma and malnutrition-associated immunosuppression, and intra-abdominal or intrathoracic infections. Furthermore, intravenous cannulation, tracheostomy, urinary catheterization, pneumonia, endotracheal intubation, diabetes mellitus (DM), organ failure, and human immunodeficiency virus (HIV) are the risk factors for IFD.[3]

Data about IFD in Indonesia are still scarce, and many overseas studies show that most fungal isolation is found on day 9 of the treatment.

Materials and Methods

Study population

Two-hundred and fifty-two critically ill patients treated in ICU/High Care Unit (HCU) and common ward from March to September 2015 were included in the study. The inclusion criteria were patients aged ≥18 years with IFD risk factor based on *Candida* score as shown in Table 1.[4] Exclusion criteria included patient/family who refused to take part in the research, passed away, or discharged before sampling (treatment day 5–7), incomplete medical record, and patient on antifungal therapy before specimen collection.

Methods

Candida score[4] was used for detecting invasive candidiasis in critically ill patients. On treatment day 5–7, laboratory examination was conducted by taking blood sample (maximum 20 ml), body fluid (10 ml ascites fluid, 10 ml pleural fluid, 10 ml pericardial fluid, 2 ml cerebrospinal fluid), respiratory specimen (sputum, endotracheal aspiration, bronchoalveolar lavage [BAL]), urine (50 ml), pus, fine needle aspiration, central venous catheter (CVC), and drainage fluid/surgical tissue specimen. Blood and body fluid specimen were collected under aseptic condition in BACTEC culture vial. Other body fluids and blood specimens were processed in Microbiology Division, Clinical Pathology Department. BAL fluid was processed in Parasitology Department. Cytology and histopathology specimens were processed in Pathology Anatomy Department. Sampling technique was done according to the operational standards of Prevention and Control of Nosocomial Infections.

This research gained ethical approval (No 182/UN2.F1/ETIK/2015) from the Ethical Research Committee of Universitas Indonesia. All data were kept confidential by the researchers.

Data analysis

This is a prospective cohort study. Samples were taken using consecutive sampling. We define patients with IFD if they meet criteria as shown in Table 2.[5] Primary data were processed using computer program SPSS 20 (Armonk, NY: IBM Corp.). Numerical data are presented as mean and standard deviation. Bivariate and multivariate analyses were performed on risk factors for IFD.

Results

Clinical characteristic

In total, 252 patients treated in the hospital (ICU, HCU, and common ward) were analyzed. A total of 206 patients fulfilled the inclusion criteria and 46 patients were excluded from the study as shown in Figure 1. Majority of the patients were male. The median age was 58 years (range, 18–79 years). Median Leon score was 3 (range score, 2–5). Nonsurgical/trauma comprised

Table 1: *Candida* score

Variable	Score
Multifocal *Candida* colonization	1
Surgery	1
Total parenteral nutrition	1
Severe sepsis	2

Table 2: Diagnostic criteria for fungal infection

Diagnostic criteria for fungal infection
Blood
Candida sp. found in blood culture
C. neoformans found in blood culture
Ascites fluid
Candida sp. found in ascitic fluid culture
Pleural fluid
Any type of fungus found in pleural fluid culture
CSF
India ink preparation positive for *C. neoformans*
Cryptococcus antigen detected
Any type of fungus found in CSF culture
Endotracheal aspiration
Aspergillus sp. found in endotracheal aspiration culture
BAL
Aspergillus sp. found in BAL culture
Urine
Candida sp. found in urine culture with candiduria $>10^4$ colony forming units/ml
Pus
Any type of fungus found in pleural pus culture
Fine needle aspiration
Any type of fungus found in fine needle aspiration

BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid; *C. neoformans*: *Cryptococcus neoformans*

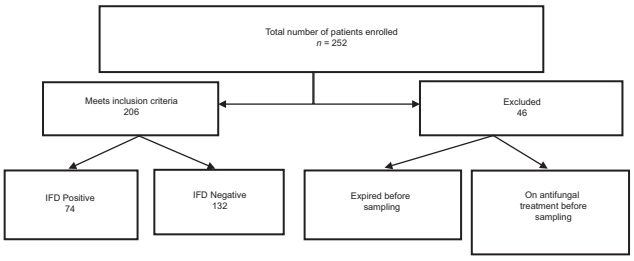

Figure 1: Study design

72.9% (n = 54) of high-risk population with IFD. Median positive fungal isolation was day 5. Mortality rate was 50% (n = 37). The clinical characteristics of patients are summarized in Table 3.

Fungal distribution

Candida sp. was found in 71 (92.2%) patients, and 6 (7.7%) were infected by non-*Candida* sp. Among the 71 patients with *Candida*, 25 (32.4%) had *Candida albicans* and 46 (59.7%) had non-albicans *Candida* infection. In addition, 31 (40.2%) were confirmed as *Candida tropicalis*, 6 (7.7%) as *Candida parapsilosis*, 5 (6.4%) as *Candida krusei*, and 4 (5.1%) were undifferentiated. The distributions are detailed in Table 4.

Fungal colonization of urine specimens was detected in 54 (70.1%) patients, followed by blood specimens in 12 (15.5%) patients. From urine specimens, 23 (29.8%) patients had *C. albicans*, 30 (38.9%) had non-albicans *Candida*, and 1 (1.2%) had *Trichosporon asahii* infection. Among 30 patients detected with non-albicans *Candida*, 23 (38.9%) had *C. tropicalis*, 3 (3.8%) had *C. krusei*, 3 (3.8%) had *C. parapsilosis* infection, and 1 (1.2%) was undifferentiated. The distributions are detailed in Table 5.

Factors affecting incidence of early invasive fungal disease

Twelve variables were analyzed as factors related with IFD. In bivariate analysis, DM (P < 0.25) and mechanical ventilator (P < 0.25) were significantly associated with early IFD. Multivariate analysis showed DM as a risk factor for early IFD. The descriptions are given in Tables 6 and 7.

Discussion

In this study, most patients were male (52.7%), similar to a study by Singh *et al*.[5] and a South Indian study where the percentage of males were 61.2% and 71.2%, respectively. Gender is not a predisposing factor of IFD. Patient's age in this study was between 18 and 79 years (oldest) with mean age of 58.0 years, similar with a study from India where the age range was between 18 and 80 years, with mean age of 43.5 years.[5] The average *Candida* score was 3, with most patients from the nonsurgical/trauma group (72.9%), similar to Singh *et al*.[5] As mentioned by León *et al*.,[4] early IFD detection could be performed in critically ill patient with *Candida* score >3.

Fungal isolates were mostly positive on day 5 of the treatment with 50% mortality. In this study, 43 patients died before day 5 of the treatment, so specimen sampling could not be done. Studies by Singh *et al*.[5] and Greece reported that most fungal isolates are positive on day 9, while another study from India reported that it is positive on day 15. The mortality rate in this study is not much different from other studies. Paswan *et al*.,[6]

Table 3: Clinical characteristic of patients with positive early invasive fungal disease (n=74)

Patient characteristics	Results
Gender, *n* (%)	
Male	39 (52.7)
Female	35 (47.29)
Age (year), median (minimum-maximum)	58 (18-79)
Leon score, median (minimum-maximum)	3 (2-5)
Diagnosis, *n* (%)	
Trauma	0
Surgery	
Digestif	8 (10.8)
Thoracic and cardiovascular	3 (4.0)
Cardiovascular	2 (2.7)
Urology	2 (2.7)
Obstetrics and gynecology	2 (2.7)
Neurology	2 (2.7)
Orthopedic	1 (1.3)
Medical	54 (72.9)
Fungal isolation, median (minimum-maximum)	5 (5-7)
Mortality, *n* (%)	
Survive	37 (50)
Died	37 (50)

Table 4: Fungal species distribution

Fungal species	Mortality		Total, *n* (%)
	Survive	Died	
Candida			71 (92.2)
Candida albicans	10	15	25 (32.4)
Non-albicans *Candida*	25	21	46 (59.7)
C. tropicalis	19	12	31 (40.2)
C. parapsilosis	2	4	6 (7.7)
Candida krusei	2	3	5 (6.4)
Undifferentiated *Candida* sp.	2	2	4 (5.1)
Non-*Candida*			6 (7.7)
T. asahii	1	0	1 (1.2)
Actinomyces	1	0	1 (1.2)
C. laurentii	1	0	1 (1.2)
Cryptococcus sp.	0	1	1 (1.2)
Zygomycosis	0	1	1 (1.2)
Other mycosis	1	0	1 (1.2)

C. tropicalis: Candida tropicalis; C. parapsilosis: Candida parapsilosis; C. krusei: Candida krusei; T. asahii: Trichosporon asahii; C. laurentii: Cryptococcus laurentii

Table 5: Fungal distribution based on culture specimen

Specimen	Fungal infection, *n* (%)	Fungal species	
		Isolate	Total, *n* (%)
Urine	54 (70.1)	*Candida* albicans	23 (29.8)
		Non-albicans *Candida*	30 (38.9)
		C. tropicalis	23 (29.8)
		C. krusei	3 (3.8)
		Undifferentiated *Candida* sp.	3 (3.8)
		C. parapsilosis	1 (1.2)
		T. asahii	1 (1.2)
Blood	12 (15.5)	Non-albicans *Candida*	11 (14.2)
		C. parapsilosis	5 (6.4)
		C. tropicalis	3 (3.8)
		C. krusei	2 (2.5)
		Undifferentiated *Candida* sp.	1 (1.2)
		Non-*Candida* fungi	1 (1.2)
Tissue	4 (5.1)	*C. tropicalis*	3 (3.8)
		Actinomyces	1 (1.2)
		Zygomycosis	1 (1.2)
Ascites	2 (2.5)	*C. albicans*	1 (1.2)
		C. tropicalis	1 (1.2)
Pleural effusion	1 (1.2)	*C. albicans*	1 (1.2)
CSF	1 (1.2)	*Cryptococcus* sp.	1 (1.2)
Endotracheal aspiration	1 (1.2)	*C. laurentii*	1 (1.2)
Pus	1 (1.2)	*C. tropicalis*	1 (1.2)
BAL	0		0
Surgical drainage	0		0
Total			77

C. tropicalis: *Candida tropicalis*; *C. parapsilosis*: *Candida parapsilosis*; *C. krusei*: *Candida krusei*; *T. asahii*: *Trichosporon asahii*; *C. laurentii*: *Cryptococcus laurentii*; *C. albicans*: *Candida albicans*; BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid

Leleu *et al*.,[7] Gudlaugsson *et al*.,[8] and Zaoutis *et al*.[9] reported a mortality rate of 61.2%, 31%, 38%, and 44%, respectively. For patients with high IFD risk, early diagnosis and therapy are essential to achieve a better end result, including reduced morbidity and mortality.[3]

Candida sp. was the most common fungus isolate (92.2%) found. Aggressive use of intravascular equipment and poor hand-washing techniques can cause nosocomial transmission.[6] Among non-albicans *Candida*, *C. tropicalis* was the most found fungal isolate (40.2%), similar to studies by Singh *et al*.,[5] 85.2%, Resultanti *et al*.,[10] 29.4%, and Paswan *et al*.,[6] 49%, while different results were obtained in India and the USA where *Candida guilliermondii* and *Candida glabrata* were the most common fungi isolated, respectively.[6,10,11]

In general, *Candida* sp. is a commensal organism found on mucosal surface, but it can cause severe infection and death.[12] Although *C. albicans* is the most common mucocutaneous infection causing fungus, the incidence caused by non-*C. albicans* sp. is increasing. Some factors such as severe immunosuppression, prematurity, broad-spectrum antibiotic usage, and empirical antifungal therapy can be associated with this change. *Candida* adhesion to host epithelial cells is an important step in pathogenesis of infection.[12] *Candida* adhesion with host cell, host cell protein, or competition with other microbes can prevent and decrease clearance rate by host cell's defense mechanism. *C. albicans* is a species with high adherence to buccal epithelial cell. This is similar with the report from Mane *et al*.[13] *C. tropicalis*, *C. glabrata*, and *Candida dubliniensis* are usually located in the buccal epithelial cell.

This study analyzes 12 factors associated with early IFD in critically ill patients. From bivariate analysis, the significant factors found are DM and mechanical ventilation. On multivariate analysis, only DM was significant. In this study, malignancy is not found as significant risk factor of IFD, similar with the Singh *et al*.'s[5] study. Contrastingly, a study conducted in India reported malignancy as a risk factor of IFD.[5] This might be due to fungal isolations being looked for on day 5–7. Neutropenia is still regarded as the main problem in most immunocompromised patients.[14] Patients with neutropenia for more than 7 days have a higher risk for bacterial and fungal infection. *Candida* infection was more common during neutropenia or 2 weeks postneutropenia, whereas *Aspergillus* infection tends to occur during neutropenia or 3 weeks postneutropenia. *Zygomycosis* is less common than *Candida* or *Aspergillus* infection but is found in long-term neutropenia.

In this study, the number for IFD in critically ill patients with DM was 41.9% (31 patients), seen as

Table 6: Bivariate analysis for early invasive fungal disease (*n*=206)

Variable	Invasive fungal disease (%)	Noninvasive fungal disease (%)	*P*	RR (95% CI)
Malignancy				
Yes	17 (23)	38 (28.8)	0.365	0.819 (0.52-1.27)
No	57 (77)	94 (71.2)		
DM				
Yes	31 (41.9)	34 (25.8)	0.017	1.564 (1.09-2.23)
No	43 (58.1)	98 (74.2)		
CVC				
Yes	51 (68.9)	84 (63.6)	0.444	1.166 (0.78-1.73)
No	23 (31.1)	48 (36.4)		
Parenteral nutrition				
Yes	18 (24.3)	34 (25.8)	0.820	0.952 (0.62-1.46)
No	56 (75.7)	98 (74.2)		
Broad-spectrum antibiotic				
Yes	71 (95.9)	129 (97.7)	0.466	0.710 (0.31-1.61)
No	3 (4.1)	3 (2.3)		
Postmajor surgery				
Yes	20 (27)	35 (26.5)	0.936	1.017 (0.67-1.53)
No	54 (73)	97 (73.5)		
Steroid therapy				
Yes	14 (18.9)	27 (20.5)	0.791	0.939 (0.58-1.50)
No	60 (81.1)	105 (79.5)		
Renal replacement therapy				
Yes	13 (17.6)	23 (17.4)	0.979	1.006 (0.62-1.62)
No	61 (82.4)	109 (82.6)		
Mechanical ventilator				
Yes	30 (40.5)	67 (50.8)	0.159	0.766 (0.52-1.11)
No	44 (59.5)	65 (49.2)		
Tracheostomy				
Yes	3 (4.1)	9 (6.8)	0.416	0.683 (0.25-1.85)
No	71 (95.9)	123 (93.2)		
HIV				
Yes	4 (5.4)	7 (5.3)	0.975	1.013 (0.45-2.26)
No	70 (94.6)	125 (94.7)		
Severe sepsis				
Yes	72 (97.3)	129 (97.7)	0.847	0.896 (0.30-2.66)
No	2 (2.7)	3 (2.3)		

CVC: Central venous catheter; HIV: Human immunodeficiency virus; DM: Diabetes mellitus; CI: Confidence interval

Table 7: Multivariate analysis for early invasive fungal disease

Variable	*P*	OR	95% CI
DM	0.018	2.078	1.135-3.803
Mechanical ventilation	0.061	0.561	0.307-1.026

DM: Diabetes mellitus; OR: Odds ratio; CI: Confidence interval

a significant factor from bivariate and multivariate analyses. Different results were obtained in various studies. This might be because control of blood sugar level in Indonesia is not yet optimal. Some studies reported that in the glycosylated hemoglobin (HbA1C) level <8.0%, the T-CD4 lymphocyte response and function are not compromised. Proportional increase in HbA1C among diabetic patients can trigger glycation in immunoglobulin which may jeopardize the biological function of antibodies.[15] This study did not evaluate HbA1C further.

CVC is not a significant risk factor of IFD among critically ill patients. Similar results were found in studies by Paswan *et al*.[6] and Chow *et al*.[16] However, Fraser *et al*.[17] and Blumberg *et al*.[18] reported that CVC is a risk factor for IFD in critically ill patients. This difference might be caused by varying methods of CVC insertion.[19] Insertion and care of patients with CVC were in accordance with standard guidelines.

This study did not find a significant association between parenteral nutrition and IFD. Incidence of IFD in patients who received parenteral nutrition is 24.3% (n = 18). Contrastingly, studies by Chow *et al*.,[16] Fraser *et al*.,[17] and Blumberg *et al*.[18] reported that parenteral nutrition is a risk factor of IFD. This difference might be caused by early enteral nutrition in our study.

Among patients receiving broad-spectrum antibiotics, 95.9% had fungal infection. Studies from Pittet *et al*.,[20] Wey *et al*.,[21] and a large study involving 3000 ICU patients in US and Brazil reported that type and duration of antibiotic treatment affect IFD.[22] The use of broad-spectrum antibiotics may be related to the underlying surgical and medical condition. We did not

find a significant association between broad-spectrum antibiotic use and IFD in critically ill patients. Duration of administration and type of antibiotic are not documented in this research though specific analysis may reveal significant differences.

Incidence of IFD among patients with postmajor surgery and steroid therapy was 27% (20 patients) and 18.9% (14 patients), respectively. A study from Chow *et al*.[16] and multicenter study in Spain reported postmajor surgery as a risk factor in IFD. Angele and Faist[23] reported that injury, trauma, and blood loss cause suppression of cellular immunity associated with increased susceptibility to wound infection and sepsis.

A study from Paswan *et al*. reported that steroid therapy was not a significant risk factor for IFD in critically ill patients.[6] Steroid is an effective treatment for skin diseases which suppresses the immune system, thus allowing fungal infection.[24] In this study, postmajor surgery and steroid therapy were not significant risk factors for IFD. The type of surgery, number of surgery, and steroid dosage in septic shock and other such conditions such as chronic obstructive pulmonary disease were not documented though specific analysis may reveal significant differences.

IFD incidence in patients with renal replacement therapy is 17.6% (13 patients). In this study, renal replacement therapy was not found as a significant factor for IFD, similar to studies by Singh *et al*.,[5] Paswan *et al*.,[6] Fraser *et al*.,[17] and Pittet *et al*.[20] In contrast, Chow *et al*.[16] and multicenter studies in US and Brazil reported renal replacement therapy as a significant risk factor for IFD in critically ill patients. This may be caused by differences in the studies' approach. Chow *et al*.[16] reported that renal replacement therapy is a risk factor of IFD because they associated this with the length of therapy. Although unclear, immune deficiency among end-stage renal disease patient might be associated with metabolic disorder and nutritional status in uremic condition.

In bivariate analysis, the relative risk (RR) of mechanical ventilation in IFD was 0.766 (confidence interval 95% 0.52–1.11 *P* - 0.159). However, in multivariate analysis, no significant association was found, similar to studies by Singh *et al*.,[5] Paswan *et al*.,[6] and Chow *et al*.[16] Contrastingly, Fraser *et al*.[17] reported that mechanical ventilation is a significant risk factor of IFD. Longer mechanical ventilation may increase the risk of infection. Body defense mechanism in critically ill patients changes due to the underlying diseases and medical devices used. Similarly, when they are intubated, the tube keeps the vocal cords open which increases risk of aspiration.[25] Long-term mechanical ventilation is not recorded in this study though specific analysis may reveal significant differences.

In this study, tracheostomy was not a significant factor for IFD in critically ill patients, similar to findings by Singh *et al*.,[5] Paswan *et al*.,[6] Chow *et al*.,[16] and Fraser *et al*.[17] This might be because fungal isolation was done in day 5–7 of the treatment, whereas tracheostomy is usually done in patients on mechanical ventilation for more than 2 weeks. In this study, four from seven HIV patients had IFD; however, no significant association was found between HIV and IFD, similar with studies by Paswan *et al*.,[6] Singh *et al*.,[5] and Chow *et al*.[16] A suppressed immune system could be ineffective against all kinds of infection, allowing fungal growth.[24]

There was no significant association between severe sepsis and IFD in this study. This is similar to findings by Singh *et al*.,[5] Paswan *et al*.,[6] Fraser *et al*.,[17] and Pittet *et al*.[20] although differs from Chow *et al*.[16] and a multicenter study in Spain, who reported a significant association. The usage of mechanical ventilation (>3 days), APACHE score, coinfection of positive and negative Gram bacteria, and the usage of urine catheter (>3 days) are not documented in this research though specific analysis may reveal a different result.

Conclusion

DM is a significant risk factor of early IFD in critically ill patients, justifying administration of early antifungal therapy. In addition, further research is needed to evaluate critically ill patients with high-risk factor of early IFD by performing serial fungal culture.

Acknowledgment

We would like to extend our appreciation to each person involved in the completion of this paper. Our special thanks go to Nidya Parasayu and Stephanie Gita Wulansari for their support and contributions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Yang SP, Chen YY, Hsu HS, Wang FD, Chen LY, Fung CP. A risk factor analysis of healthcare-associated fungal infections in an intensive care unit: A retrospective cohort study. BMC Infect Dis 2013;13:10.

2. Muskett H, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D. Risk factors for invasive fungal disease in critically ill adult patients: A systematic review. Crit Care 2011;15:R287.
3. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. Ann Intensive Care 2011;1:37.
4. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, *et al.* A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med 2006;34:730-7.
5. Singh T, Kashyap AK, Ahluwalia G, Chinna D, Sidhu SS. Epidemiology of fungal infections in critical care setting of a tertiary care teaching hospital in North India: A prospective surveillance study. J Clin Sci Res 2014;3:14-25.
6. Paswan AK, Raju DC, Singh DK, Dubey RK, Mishra PK. An observational study of the risk factors and incidence of invasive fungal infections in ICU patients. Anaesth Pain Intensive Care 2013;17:136-40.
7. Leleu G, Aegerter P, Guidet B; Collège des Utilisateurs de Base de Données en Réanimation. Systemic candidiasis in intensive care units: A multicenter, matched-cohort study. J Crit Care 2002;17:168-75.
8. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, *et al.* Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172-7.
9. Zaoutis TE, Prasad PA, Localio AR, Coffin SE, Bell LM, Walsh TJ, *et al.* Risk factors and predictors for candidemia in pediatric intensive care unit patients: Implications for prevention. Clin Infect Dis 2010;51:e38-45.
10. Resultanti. Risk factor for candidemia in non-neutropenia septic patients [master's thesis]. Jakarta, Indonesia: Universitas Indonesia; 2015.
11. Leroy G, Lambiotte F, Thévenin D, Lemaire C, Parmentier E, Devos P, *et al.* Evaluation of "*Candida* score" in critically ill patients: A prospective, multicenter, observational, cohort study. Ann Intensive Care 2011;1:50.
12. Deorukhkar SC, Saini S, Mathew S. Non-albicans *Candida* infection: An emerging threat. Interdiscip Perspect Infect Dis 2014;2014:615958.
13. Mane A, Pawale C, Gaikwad S, Bembalkar S, Risbud A. Adherence to buccal epithelial cells, enzymatic and hemolytic activities of *Candida* isolates from HIV-infected individuals. Med Mycol 2011;49:548-51.
14. Donowitz GR, Maki DG, Crnich CJ, Pappas PG, Rolston KV. Infections in the neutropenic patient – New views of an old problem. Hematology 2001;1:113-39
15. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab 2012;16 Suppl 1:S27-36.
16. Chow JK, Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg DA, *et al.* Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit Care Med 2008;36:1993-8.
17. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: Epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992;15:414-21.
18. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, *et al.* Risk factors for candidal bloodstream infections in surgical intensive care unit patients: The NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 2001;33:177-86.
19. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, *et al.* Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 2011;39 4 Suppl 1:S1-34.
20. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994;220:751-8.
21. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. A matched case-control study. Arch Intern Med 1989;149:2349-53.
22. Ferrara JJ, MacDougall C, Gallagher JC. Empiric antifungal therapy in patients with febrile neutropenia. Pharmacotherapy 2011;31:369-85.
23. Angele MK, Faist E. Clinical review: Immunodepression in the surgical patient and increased susceptibility to infection. Crit Care 2002;6:298-305.
24. Swierzewski JJ. Update 99: Fungal Infection Risk Factors. Lyme Disease Prevention Tips; 13 August, 2015. Available from: http://www.healthcommunities.com. [Last accessed on 2015 Oct 29].
25. Alp E, Voss A. Ventilator associated pneumonia and infection control. Ann Clin Microbiol Antimicrob 2006;5:7.