Research Article

BJMP 2013;6(1):a618

Risk factors for candida blood stream infection in medical ICU and role of colonization – A retrospective study

Setu Patolia, Eneh Kennedy, Mehjabin Zahir, Swati Patolia, Neerja Gulati, Dharani Narendra, Rakesh Vadde, Saurav Pokharel, Frances M. Schmidt, Danilo Enriquez and Joseph Quist

Abstract

Candida blood stream infection (candidaemia) is one of the most serious hospital acquired infections with high morbidity and mortality rates in the Intensive Care Unit (ICU). A number of risk factors have been identified in a variety of studies. ICU patients are frequently colonised with Candida species. The role of Candida colonisation as a causal factor for candidaemia remains controversial. Our objective for the study was to evaluate the risk factors for candidaemia and to evaluate the role of colonisation to predict candidaemia. We evaluated a total of 1483 patients aged over 18 years who stayed in ICU for more than 7 days. We collected various data about risk factors for candidaemia. A total of 56 patients (3.77%) developed candidaemia. We collected demographic and risk factor data including Candida colonisation of the urinary and respiratory tract. Binary logistic regression with forward likelihood ratio method model was used to analyse these risk factors. In our study, total parenteral nutrition (odds ratio (OR)- 3.274, 95% confidence interval (CI) 1.263-8.486), presence of central venous line (OR- 1.895, CI 1.032-3.478), previous or current antibiotic use (OR 3.268, CI 1.532-6.972), respiratory tract colonisation (OR 2.150, CI 1.078-4.289) and urinary tract colonisation (OR 3.508, CI 1.926-6.388) were significant risk factors for Candida blood stream infection (BSI). Based on the model, we calculated the candidaemia risk score and based on the receiver operative curve analysis, a score more than 2 would be associated with a higher risk of candidaemia. Candida species isolated in the respiratory tract or urine were similar to that found in Candida BSI (Kappa coefficient for agreement of 0.83 and 0.47 respectively). So, it can be concluded that Candida colonisation of the respiratory tract and/or urine is a significant risk factor for Candida BSI along with the other risk factors.

Keywords: Candidemia, Risk factors, Central Venous line, Colonization.

Abbreviations: ICU- intensive care unit,OR- odds ratio,CI- confidence interval,BSI- blood stream infection,HIV- Human immunodeficiency virus,IDSA- Infectious Disease Society of America,COPD- Chronic obstructive pulmonary disease,DM- Diabetes Mellitus,ESRD- End stage renal disease, TPN- Total parenteral nutrition.

Introduction:

Candida species is a leading cause of nosocomial infections and the most common fungal infection in intensive care units. Candida infection ranges from invasive candidal disease to blood stream infections (candidaemia). The incidence of Candida infection has been rising over the past two decades, particularly with the use of immunosuppressive drugs for cancer and HIV[1,2,3] , and most of these infections occur in ICU settings.[4] Candida infection is associated with high mortality and morbidity. Studies have shown that mortality attributable to candidaemia ranges from 5 to 71% depending on the study.[5,6,7]Candidaemia is also associated with longer length of hospital stay and higher cost of care.

Early recognition of Candida BSI has been associated with improved outcome. Candida sepsis should be suspected in a patient who fails to improve and has multiple risk factors for invasive and bloodstream Candida infection. A variety of risk factors identified for candidaemia include previous use of antibiotics, sepsis, immunosupression, total parenteral nutrition, central venous line, surgery, malignancy and neutropaenia. Patients admitted to ICU are frequently colonised with Candida species. The role of colonisation in Candida blood stream infection and invasive candidal disease has always been debated. Few studies support the use of presumptive antifungal treatment in ICU based on colonisation and number of sites colonised by Candida. The NEMIS study has raised doubt about this approach of presumptive treatment. The Infectious Disease Society of America (IDSA) 2009 guidelines identify Candida colonisation as one of the risk factors for invasive candidiasis, but warn about the low positive predictive value of the level of Candida colonisation. [8] We conducted a retrospective cohort study in our medical ICU to identify risk factors for Candida blood stream infections including the role of Candida colonisation.

Hospital and Definitions:

This study was conducted at Interfaith Medical Center, Brooklyn, New York. It is a 280 bed community hospital with 13 medical ICU beds. A case of nosocomial Candida blood stream infection was defined as a growth of Candida Species in a blood culture drawn after 48 hours of admission. Cultures in our hospital are routinely done by the Bactec Method – aerobic and anaerobic cultures. Cultures are usually kept for 5 days at our facility and if yeast growth is identified, then species identification is done. In our ICU it is routine practice to do endotracheal culture and urine culture for all patients who are on mechanical ventilator supports and failing to improve. In

patients who are not mechanically ventilated, it is routine practice to send sputum culture and nasal swabs to identify MRSA colonisation.

Study Design:

This study was a retrospective cohort study. We retrospectively reviewed all patients' charts admitted to our medical ICU from 2000 to 2010 which stayed in the ICU for more than 7 days, irrespective of their diagnosis. Data were collected for demographics – age and sex. Data were also collected for risk factors for candidaemia – co-morbidities (HIV, cancer, COPD, diabetes mellitus, end-stage renal failure (ESRF)), presence or absence of sepsis, current or previous use of antibiotics, presence of central venous lines, steroid use during ICU stay, requirement of vasopressor support and use of total parenteral nutrition (TPN). Culture results for Candida including species identification were obtained for blood, urine and endotracheal aspirates.

Statistical Methods:

Patients were divided in two groups based on presence or absence of Candida BSI. Demographic data and risk factors were analysed using the chi square test to look at the difference between the two groups. Endotracheal aspirates and sputum cultures were combined to create a group with Candida respiratory tract colonisation. Binary logistic regression with forward likelihood ratio method was used to create models. Different models were generated for risk factors. Interactions between antibiotic use, steroid use, vasopressor support and sepsis were analysed in different models. Interactions between urine cultures and endotracheal aspirates/sputum cultures were also analysed by a different model. The model with the lowest Akaike information criterion (AIC) was chosen as the final model. The candidaemia risk score was calculated based on this final model to predict the risk of Candida BSI. Receiver operating curve (ROC) analysis was used to select the best cut-off value for the candidaemia risk score. Candida species in urine and endotracheal aspirates were compared with Candida species in blood culture using the kappa test. Data were analysed using SPSS statistical analysis software version 18.

Study Results:

A total of 1483 patients were included in the study. 56 patients (3.77%) had a blood culture positive for Candida species. Table 1 demonstrates demographic characteristics of the study population. There were no significant differences in the both groups for age, sex, diabetes mellitus, COPD, HIV, cancer and ESRF. As demonstrated in the table, 82.1% of patients in candidaemia groups recently used or were taking antibiotics as compared to 39.6% of patients in groups with no candidaemia. The P value was significant for this difference. Similarly, 71.4% of patients in the group with candidaemia had sepsis as compared to 30.6% in the other group with a P value of 0.000. Use of vasopressor (severe septic shock) was different between two groups – 23.2% and 10.1%, P value of 0.004. Steroid use, central lines and total parenteral nutrition use was higher in the candidaemia group as compared to the group without candidaemia. Similarly the rate of positive Candida cultures in urine and endotracheal aspirates was higher in the candidaemia group as compared to the group without.

Table 1: Demographic characteristic of study population

Characteristic	Candidaemia (total 56) N (% of candidaemia)	No candidaemia (total 1427) N (% of no candidaemia)	Chi Square
Age >65 years	34 (60.7%)	676(47.40%)	0.06
Male sex	27 (48.2%)	694(48.6%)	0.530
Diabetes mellitus	22 (39.3%)	506(35.5%)	0.325
COPD	1(1.8%)	75(5.3%)	0.206
HIV	9 (16.1%)	253(17.7%)	0.458
Cancer	4(7.1%)	99(6.9%)	
ESRF	11(19.6%)	251(17.6%)	0.401
Previous or current antibiotic use	46 (82.1%)	565(39.6%)	0.00
Sepsis	40(71.4%)	436(30.6%)	0.000
Vasopressor support (Septic shock)	13(23.2%)	144(10.1%)	0.004
Steroid use	27(48.2%)	431(30.2%)	0.004
Central line	30(53.6%)	267(18.7%)	0.000
Total parenteral nutrition	7(12.5%)	29(2.0%)	0.000
Candida in endotracheal aspirate/sputum culture	13(23.2%)	112(7.8%)	0.000
Candida in urine culture	34(60.7%)	262(18.4%)	0.000

Table 2 shows that 57.1% of Candida BSI were caused by C. Albicans, 30.4% by C. Glabrata and 12.5% by C. Parapsilosis. This incidence rate of species is similar to that found in other studies. Table 3 shows the two models with the lowest AIC value. The only difference between these two models was antibiotic use- previous or current use of antibiotics compared to current use of antibiotic in sepsis. Table 4 shows that when multifocal site positivity (urine and endotracheal culture) were used in the model, the AIC value increased significantly. This means that when multifocal sites were used in place of individual sites for the model, good amounts of information were lost and this model did not have good predictive value as compared to the model where individual sites are used for prediction of candidaemia. The model with lowest AIC was chosen as the final model. Binary logistic regression analysis with forward conditional analysis showed that only TPN, central venous line, previous or current antibiotic use,

endotracheal aspirate culture positivity for Candida species and urine culture positive for Candida species were included in a statistical significant model. The final model had a P value of 0.000. Odds ratio with 95% confidence intervals and respective P values for all these risk factors are shown in Table 5. Age greater than 65 years, sex, sepsis or septic shock, co-morbidities and steroid use were not significant risk factors for candidaemia.

From this model, the candidaemia risk score calculated would be: Candidaemia risk score = 1.184 for previous or current antibiotic use + 0.639 for presence of central venous line + 1.186 for total parenteral nutrition + 0.760 for positive endotracheal culture for Candida + 1.255 for positive urine culture for Candida.

Table 6 shows the relationship between the Candida strain identified in endotracheal/sputum culture to that in blood culture. Similarly, Table 7 shows the relationship between the Candida strain identified in urine culture and that in blood culture. Strains identified in endotracheal aspirate culture had a very high value for the Kappa test and urine culture had a moderate value for agreement by the Kappa test. Thus, it can be inferred that Candida strain identified in blood culture was very similar to that identified in urine or endotracheal culture.

Table 2: Candida strains responsible for Candida blood stream infection

Species in the blood culture	Number (%)
Candida Albicans	32(57.1%)
Candida Glabrata	17 (30.4%)
Candida Parapsilosis	7 (12.5%)

Table 3: Models with lowest two AIC

Variables	-2 log likelihood	AIC
Previous or current antibiotic use CVP line Total parenteral nutrition Endotracheal culture Urine culture	394.822	406.822
CVP line Total parenteral nutrition Endotracheal culture Urine culture Current antibiotic use in sepsis	395.730	407.73

Table 4: Model with 2 sites positive for Candida

Variables	-2 log likelihood	AIC
Sepsis CVP line Total parenteral nutrition Endotracheal and urine culture	407.920	417.92

Table 5: Odds ratio with 95% confidence interval for risk factors for candidaemia

Effect	Co efficient (•)	Odds ratio	95 % Confidence limit		P value
			Lower	Upper	
TPN	1.186	3.274	1.263	8.486	0.015
CVP line	0.639	1.895	1.032	3.478	0.039
Antibiotic Use	1.184	3.268	1.532	6.972	0.002
Endotracheal/ sputum culture	0.760	2.150	1.078	4.289	0.030
Urine	1.255	3.508	1.926	6.388	0.000

Table 6: Endotracheal aspirate culture in candidaemic patients

Endotracheal/Sputum Culture	Blood Culture		Kappa Test For Agreement
	C. Albicans	C. Glabrata	
C. Albicans	9	0	0.83
C.Glabrata	0	3	
C. Tropicalis	0	1	

Table 7: Urine cultures in candidaemic patients

Urine culture	Blood culture			Kappa Test for the agreement
	C. Albicans	C. Glabrata	C. Tropicalis	
C. Albicans	15	5	1	0.47
C. Glabrata	1	10	0	
C. Krusei	1	1	0	

Discussion

Candida is the most common nosocomial fungal infection in the ICU. Candidaemia accounts for approximately 5-8% of nosocomial BSI in the hospitals in the US.[9,10,11] It accounts for approximately 50-75% of the cases of invasive fungal infection in the ICU[12,13] and its rate varies from 0.2-1.73 per 1000 patient days.[9,14,15] In a study done by Theoklis et al., candidaemia was associated with a mean 10.1 day increase in length of stay and a mean $39,331 increase in hospital charges.[16] A study of 1,765 patients in Europe found that Candida colonisation was associated with increased hospital length of stay and increase in cost of care by 8000 EUR.[17] ICU patients are at increased risk of infection because of their underlying illness requiring ICU care, immunosuppressant use, invasive or surgical procedures and nosocomial transfer of infections. A number of risk factors have been identified in different studies. In a matched case-control trial, previous use of antibiotic therapy, Candida isolated at other sites, haemodialysis and presence of a Hickman catheter were associated with increased risk of candidaemia.[13] Similarly age of more than 65

years, steroid use, leucocytosis and prolonged ICU stays were risk factors for Candida BSI in 130 cases.[18] Surgery, steroids, chemotherapy and neutropaenia with malignancy are the other identified risk factors.[19]

Candida BSI has a very high mortality rate. The attributable mortality varies from 5-71% in different studies.[5,12,16,20] Even with treatment, there is high mortality as demonstrated in a study by Oude Lashof et al where out of 180 patients treated for candidaemia, 33% died during treatment and 55% completed treatment without complications.[21] Risk factors for increased mortality in patients receiving antifungal treatment are delayed Candida antifungal treatment or inadequate dosing.[22] Multivariate analysis of 157 patients with Candida BSI, APACHE II score, prior antibiotic treatment and delay in antifungal treatment were independent risk factors for mortality with odds ratio of 1.24, 4.05 and 2.09, respectively.[23]Delayed treatment is also associated with increased fluconazole resistance as compared to early treatment and preventive treatment.[24] Inadequate antifungal medication dose and retention of central venous catheters were also associated with increased mortality in a study of 245 Candida BSI, with adjusted odds ratios of 9.22 and 6.21, respectively.[25,26]

Candida albicans accounts for 38.8-79.4 % of the cases of Candida BSI. C. Glabrata is responsible for 20-25% of cases of candidaemia and C. tropicalis is responsible for less than 10% of cases of candidaemia in the US.[9,20] ICU patients are frequently colonised with different Candida species. Candida colonisation can be from either endogenous or exogenous sources. Candida colonisation rates vary with the site- tracheal secretion (36%), throat swabs (27%), urine (25%) and stool (11%).[27] Candida colonisation increases with the duration of the stay, use of urinary catheters and use of antibiotics.[28,29,30]

The role of Candida colonisation in Candida BSI is frequently debated. Some studies have suggested that Candida colonisation of one or more anatomical sites are associated with increased risk of candidaemia.[31,32,33,34] Typically, 84-94% of the patients developed candidaemia within a mean time of 5- 8 days after colonisation according to two studies.[35,36] In another study, only 25.5% of colonised patients developed candidaemia.[37] Similarity between strain identified in blood culture and that identified at various colonising sites was observed in one study.[38] Candida colonisation by exogenously acquired species has also been implicated as a cause of candidaemia.[39] In one study, 18-40% of cases of candidaemia were associated with clustering defined as "isolation of 2 or more strain with genotype that had more than 90% genetic relatedness in the same hospital within 90 days." [40] Similar correlations for clusters are also noted for C. tropicalis candiduria[41] and for C. Parapsilopsis.[42] In a prospective study of 29 surgical ICU patients colonised with Candida, the APACHE II score, length of previous antibiotic therapy and intensity of Candida colonisation was associated with a significant risk of candidaemia. The Candida colonisation index calculated by non-blood body sites colonised by Candida over the total number of distinct sites tested for patients, was associated with a 100% positive and negative predictive value of candidaemia.[29] Other studies do not support Candida colonisation as a risk factor for candidaemia. In a case-control study of trauma patients, only total parenteral nutrition was associated with an increased risk of candidaemia. Candida colonisation, steroid use, use of central venous catheters, APACHE II score, mechanical ventilation for more than 3 days, number and duration of antibiotics, haemodialysis, gastrointestinal perforation and number of units of blood transfused in first 24 hours of surgery. were not significant risk factors for candidaemia.[43] NEMIS study found that in a surgical ICU, prior surgery, acute renal failure, total parenteral nutrition and triple lumen catheters were associated with increased risk of candidaemia; the relative risk for each risk factor being 7.3, 4.2, 3.6 and 5.4, respectively. Candida colonisation in urine, stool or both were not associated with increased risk of candidaemia.[15]

The effect of Candida colonisation of the respiratory tract on candidaemia and on mortality and morbidity is unclear. In a retrospective study of 639 patients, Candida respiratory tract colonisation was associated with increased hospital mortality (relative risk of 1.63) and increased length of stay (median increase of 21 days).[30] In a study of 803 patients by Azoulay et al., respiratory tract colonisation was associated with prolonged ICU and hospital stays. These colonised patients were at increased risk of ventilator-associated Pseudomonas pneumonia, with an odds ratio of 2.22.[44] However, in a postmortem study of 25 non-neutropaenic mechanically ventilated patients, 40% of the patients were colonised with Candida, but only 8% had Candida pneumonia.[45,46] Jordi et al. found that out of 37 patients, definite or possible colonisation was found in 89% of patients and only 5% of cases were defined as Candida BSI.[47].The effect of candiduria is also ill defined. Candida colonisation in urine has been implicated as a risk factor in certain studies. In a study done by Bross J et al., central lines, bladder catheters, 2 or more antibiotics, azotaemia, transfer from another hospital, diarrhoea and candiduria were significant risk factors for candidaemia. Candiduria had an odds ratio of 27 for development of candidaemia.[48] Similar findings about candiduria were noted by Alvarez-Lerma et al.[49]

IDSA recommends starting empirical antifungal treatment for high risk neutropaenic patients who fail to improve on antibiotics after 4 days. Recommendation to start empirical antifungal therapy in low-risk neutropaenic patients and non-neutropaenic patients are not made by IDSA because of low risk of candidaemia.[8] However, early detection of Candida BSI is vital because of increased mortality associated with delayed antifungal treatment and failure to remove central venous lines. Early detection of Candida BSI in a colonised patient can be facilitated by using a score based on the risk factors.[50,51]Similarly, b-D glucan assays can be used in patient

colonised with Candida, to determine Candida BSI and need for antifungal treatment.[52] Combined used of such risk factor identification systems and b-D glucan assays will help to detect candidaemia in earlier stages and will decrease mortality. Our study suggests that total parenteral nutrition, previous or current antibiotic use, central lines, candiduria and respiratory tract colonisation are risk factors for Candida BSI. With the help of our candidaemia risk score system, a score of more than 2 is associated with a higher risk of Candida BSI. This risk factor scoring system along with b-D glucan assays can be used to detect Candida BSI in earlier stages.

Conclusion:

Our study suggests that urine or respiratory tract colonisation is associated with an increased risk of Candida BSI, along with total parenteral nutrition, central venous lines and previous or current antibiotic use. We identified a scoring system which can be used along with a b-D glucan assay to detect candidaemia earlier.

Acknowledgements
None
Competing Interests
None
Author Details
SETU K PATOLIA, MD, ENEH KENNEDY, MD, MEHJABIN ZAHIR, MD, SWATI S. PATOLIA, MD, NEERJA GULATI, MD, DHARANI K. NARENDRA, MD, RAKESH VADDE, MD, SAURAV POKHAREL, MD, FRANCES M. SCHMIDT, MD, FACP, DANILO ENRIQUEZ, MD, JOSEPH B QUIST, MD,
Interfaith Medical Center, Brooklyn, NY, USA.
CORRESSPONDENCE: SETU K PATOLIA, MD, Interfaith Medical Center, Brooklyn, NY, USA.
Email: patoliasetu@gmail.com

REFERENCES

1. Edmond MB, Wallace SE, McClish DK et al. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis. August 1999;29(2):239-244.
2. Kao AS., Brandt ME, Pruitt WR et al. The Epidemiology of Candidaemia in Two United States Cities: Results of a Population-Based Active Surveillance. Clin Infect Dis. November 1999;29(5):1164-1170.
3. Ásmundsdóttir LR, Erlendsdóttir H and Gottfredsson M. Increasing Incidence of Candidaemia: Results from a 20-Year Nationwide Study in Iceland. J. Clin. Microbiol. September 2002;40(9):3489-3492
4. Bouza E, Muñoz P. Epidemiology of candidaemia in intensive care units Int J Antimicrob Agents. November 2008;32(2):87-91.
5. Falagas ME, Apostolou KE and Pappas VD. Attributable mortality of candidaemia: a systematic review of matched cohort and case-control studies. Eur J Clin Microbiol Infect Dis. July 2006;25(7):419-425.
6. Morgan J, Meltzer M, Brian D et al. Excess Mortality, Hosptial Stay and Cost Due to Candidaemia: A Case-Control Study Using Data From Population Based Candidaemia Surveillance. Infect Control Hosp Epidemiol. June 2005;26(6)540-547.
7. Viudes A, Pemán J, Cantón E et al. Candidaemia at a Tertiary-Care Hospital: Epidemiology, Treatment, Clinical Outcome and Risk Factors for Death Eur J Clin Microbiol Infect Dis. November 2002;21(11):767-774.
8. Pappas PG, Kauffman CA, Andes D et al. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America, Clin Infect Dis. March 2009;48(5):503-535.
9. Sandven P. Epidemiology of candidaemia Rev Iberoam Micol September 2000;17(3):73-81.
10. Wisplinghoff H, Bischoff T, Tallent SM et al. Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study Clin Infect Dis. August 2004;39(3):309-317.
11. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on Candida species Clin Infect Dis. June 1995;20(6):1526-1530.
12. Horn DL, Neofytos D, Anaissie EJ et al. Epidemiology and Outcomes of Candidaemia in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry. Clin Infect Dis. June 2009;48(12):1695-1703.
13. Wey SB, Mori M, Pfaller MA et al. Risk factors for hospital-acquired candidaemia. A matched case-control study. Arch Intern Med. October 1989;149(10):2349-2353.
14. Wey SB, Mori M, Pfaller MA et al. Hospital-Acquired Candidaemia The Attributable Mortality and Excess Length of Stay. Arch Intern Med. December 1988; 148(12):2642-2645.
15. Rangel-Frausto MS, Wiblin T, Blumberg HM et al. National Epidemiology of Mycoses Survey (NEMIS): Variations in Rates of Bloodstream Infections Due to Candida Species in Seven Surgical Intensive Care Units and Six Neonatal Intensive Care Units M. Clin Infect Dis. August 1999;29(2):253-8.
16. Zaoutis TE, Argon J, Chu J et al. The Epidemiology and Attributable Outcomes of Candidaemia in Adults and Children Hospitalized in the United States: A Propensity Analysis. Clin Infect Dis. November 2005;41(9):1232-1239.
17. Olaechea PM, Palomar M, León-Gil C et al. Economic Impact of Candida Colonization and Candida Infection in the Critically Ill Patient. Eur J Clin Microbiol Infect Dis. April 2004;23(4):323-330.
18. Cheng MF, Yang YL, Yao TJ et al. Risk factors for fatal candidaemia caused by Candida albicans and non-albicans Candida species. BMC Infect Dis. April 2005;5:22.
19. Komshian SV, Uwaydah AK, Sobel JD et al. Fungemia caused by Candida species and Torulopsis glabrata in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis. May-June 1989;11(3):379-390.
20. Gudlaugsson O, Gillespie S, Lee K et al. Attributable Mortality of nosocomial Candidaemia, Revisited. Clin Infect Dis. November 2003;37(9):1172-1177.
21. Oude Lashof AM, Donnelly JP, Meis JF et al. Duration of antifungal treatment and development of delayed complications in patients with candidaemia. Eur J Clin Microbiol Infect Dis. January 2003;22(1):43-48.
22. MacCallum DM, Odds FC. Need for Early Antifungal Treatment Confirmed in Experimental Disseminated Candida albicans Infection. Antimicrob. Agents Chemother. December 2004;48(12):4911-4914.
23. Morrell M, Fraser VJ, Kollef MH. Delaying the Empiric Treatment of Candida Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality. Antimicrob. Agents Chemother. September 2005; 49(9):3640-3645.
24. Walsh TJ, Aoki S, Mechinaud F et al. Effects of Preventive, Early, and Late Antifungal Chemotherapy with Fluconazole in Different Granulocytopenic Models of Experimental Disseminated Candidiasis. J Infect Dis. April 1990;161(4):755-760.
25. Labelle AJ, Micek ST, Roubinian N et al. Treatment-related risk factors for hospital mortality in Candida bloodstream infections. Crit Care Med. November 2008;36(11):2967-2972.
26. Eppes SC, Troutman JL, Gutman Lt. Outcome of treatment of candidaemia in children whose central catheters were removed or retained. Pediatr Infect Dis J. February 1989;8(2):99-104.

27. Petri MG, König J, Moecke HP et al. Epidemiology of invasive mycosis in ICU patients: a prospective multicenter study in 435 non-neutropenic patients. Intensive Care Med March 1997;23(3):317-325.
28. Charles PE, Dalle F, Aube H et al. Candida spp. colonization significance in critically ill medical patients: a prospective study. Intensive Care Med. March 2005;31(3):393-400.
29. Pittet D, Monod M, Suter PM et al. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg. December 1994;220(6):751-758.
30. Delisle MS, Williamson DR, Perreault MM et al. The clinical significance of Candida colonization of respiratory tract secretions in critically ill patients. J Crit Care. March 2008;23(1):11-17.
31. Wiley JM, Smith N, Leventhal BG et al. Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. J Clin Oncol. 1990 Feb;8(2):280-286.
32. Martino P, Girmenia C, Venditti M et al. Candida colonization and systemic infection in neutropenic patients. A retrospective study. Cancer. November 1989;64(10):2030-2034.
33. Magill SS, Swoboda SM, Johnson EA et al. The association between anatomic site of Candida colonizaton, invasive candidiasis, and mortality in critically ill surgical patients. Diagnostic Microbiology and Infectious Disease. August 2006;55(4):293-301.
34. Schwartz RS, Mackintosh FR, Schrier SL et al. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. Cancer. February 1984;53(3):411-419.
35. Reagan DR, Pfaller MA, Hollis RJ et al. Characterization of the sequence of colonization and nosocomial candidaemia using DNA ?ngerprinting and a DNA probe. J Clin Microbiol. December 1990;28(12):2733–2738.
36. Voss A, Hollis RJ, Pfaller MA et al. Investigation of the sequence of colonization and candidaemia in nonneutropenic patients. J Clin Microbiol. April 1994;32(4):975-980.
37. Chen YC, Chang SC, Tai HM et al. Molecular epidemiology of Candida colonizing critically ill patients in intensive care units J Formos Med Assoc. December 2001;100(12):791-797.
38. Pfaller MA. The use of molecular techniques for epidemiologic typing of Candida species. Curr Top Med Mycol. 1992;4:43-63.
39. Shin JH, Og YG, Cho D et al. Molecular epidemiological analysis of bloodstream isolates of Candida albicans from a university hospital over a five-year period. J Microbiol. December 2005;43(6):546-54.
40. Asmundsdóttir LR, Erlendsdóttir H, Haraldsson G et al. Molecular epidemiology of candidaemia: evidence of clusters of smoldering nosocomial infections. Clin Infect Dis. July 2008;47(2):17-24.
41. Rho J, Shin JH, Song JW et al. Molecular investigation of two consecutive nosocomial clusters of Candida tropicalis candiduria using pulsed-field gel electrophoresis. J Microbiol. June 2004;42(2):80-6.
42. Ahmad S, Khan Z, Mustafa AS et al. Epidemiology of Candida colonization in an intensive care unit of a teaching hospital in Kuwait. Med Mycol. December 2003;41(6):487-93.
43. Borzotta AP, Beardsley K. Candida Infections in Critically Ill Trauma Patients A Retrospective Case-Control Study. Arch Surg. June 1999;134(6):657-665.
44. Azoulay E, Timsit JF, Tafflet M et al. Candida Colonization of the Respiratory Tract and Subsequent Pseudomonas Ventilator-Associated Pneumonia. CHEST January 2006; 129(1):110–117.
45. El-Ebiary M, Torres A, Fàbregas N et al. Significance of the Isolation of Candida Species from Respiratory Samples in Critically Ill, Non-neutropenic Patients An Immediate Postmortem Histologic Study. Am. J. Respir. Crit. Care Med., August 1997;156(2):583-590.
46. Meersseman W, Lagrou K, Spriet I et al. Significance of the isolation of Candida species from airway samples in critically ill patients: a prospective, autopsy study. Intensive Care Med. September 2009;35(9):1526-1531.
47. Rello J, Esandi ME, Díaz E et al. The Role of Candida sp Isolated From Bronchoscopic Samples in Nonneutropenic Patients. CHEST. July 1998; 114(1):146-149.
48. Bross J, Talbot GH, Maislin G et al. Risk factors for nosocomial candidaemia: a case-control study in adults without leukemia. Am J Med. December 1989; 87(6):614-620.
49. Alvarez-Lerma F, Nolla-Salas J, León C et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med. July 2003;29(7):1069-1076.
50. León C, Ruiz-Santana S, Saavedra P et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. March 2006;34(3):730-737.
51. León C, Ruiz-Santana S, Saavedra P et al. Usefulness of the "Candida score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study. Crit Care Med. May 2009;37(5):1624-1633.
52. Takesue Y, Kakehashi M, Ohge H et al. Combined Assessment of ß-d-Glucan and Degree of Candida Colonization before Starting Empiric Therapy for Candidiasis in Surgical Patients. World J Surg. June 2004;28(6):625-630.