



A Prospective Study Of Blood Stream Infections With Candida Species At A Tertiary Care Hospital: Changing Pattern Of Occurrence And Antifungal Susceptibility With An Insight Into Prevention And Treatment Protocols- A Four Year Study

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Abstract

Objective: Candidemia is the presence of blood stream infection with Candida species. There is an increasing incidence of Candidemia with a high mortality rate. Contrary to the findings from Western literature, Indian studies have shown a high incidence of Candida non albicans species. Hence we have taken up the study, to look at the profile of Candidemia, their current epidemiological trend, clinical management, resistance trends and outcome in terms of mortality at our setting.

Materials and Methods: We have conducted a four year prospective observational study among all adult in-patients, admitted to a tertiary care hospital from January 1st 2017 to January 1st 2021, who have positive isolates of Candida species in bloodstream. Incidence rate of Candidemia was calculated and distribution of Candidemia with respect to characteristics like age, gender, comorbid illness, mechanical ventilation, prior antibiotic therapy, prolonged ICU stay, indwelling devices were assessed. Outcome was assessed in terms of mortality.

Results and discussion: Out of 1600 blood stream infection isolates, Candidemia was fourth most common blood stream isolate infection with an incidence rate of 7.5%. Candida tropicalis was the predominant species (30.8%). Mortality rate due to Candidemia was found to be high (61%). Urethral catheterization, Central venous access, Mechanically ventilation, neutropenia at presentation, prior antibiotic therapy, renal failure, patients on TPN, Dialysis patients, prolonged ICU stay were some of the risk factors which were found to be statistically significant in assessing the mortality of patients in our study.

Conclusion: All patients with Candidemia should be treated with an antifungal agent at the earliest, as delay causes an increase in mortality. All vascular catheters should be removed to help clear Candida from blood more quickly. Improved survival was found with the use of an Echinocandin. Our study and mortality prediction risk factors can help triage and manage high-risk Candidemia patients better.

Keywords: Antifungal therapy, Candidemia, Fungal infection, Intensive care unit, Resistance

INTRODUCTION

Candidemia describes the presence of Candida variety of diseases including Candidemia, species in the blood. Invasive Candidiasis embodies a disseminated Candidiasis, meningitis, and

endophthalmitis. Most common form of invasive Candidiasis is Candidemia. Candidemia is a life threatening affliction in most of the patients. The incidence of practically all forms of Candida infections has risen abruptly. Candidiasis is a significant cause of morbidity and mortality for certain groups of patients. Invasive candidiasis has been of a concern as there is increased length and cost of hospitalizations as well as mortalities of patients. Currently Candidemia is the fourth most common etiological agent for nosocomial bloodstream infections.

Candida species reside normally in the gastrointestinal and genitourinary tracts and on the skin. As colonizers, Candida species do not cause infection, unless there is a defect in host defense mechanism. The common risk factors in Candidemia are prolonged hospitalization, ICU stay, use of broad-spectrum antibiotics, prolonged central venous catheters, acute and chronic renal failure, solid neoplasms, transplantation (bone marrow or solid organ), recent chemotherapy/radiation therapy, use of immunosuppressive drugs, parenteral alimentation, use of internal prosthetic devices, organ transplant, hemodialysis, mechanical, surgical procedures. Certain ICU populations, especially HIV and burn victims, are at even higher risk for Candida infection than is the typical ICU patient. Hence, Candida in a blood culture should never be viewed as a contaminant and should always prompt a search for the source of the bloodstream infection.

In the last 2 decades a change in the epidemiology of Candidemia has been noticed across the world. Recently there is a change noted and although *C. albicans* remains as the most frequently isolated species worldwide, its incidence is decreasing and there is a shift to non-*albicans* species. Therefore, the knowledge of the local epidemiology of Candidal infections is important to offer the sound management of invasive Candidiasis. With the change in the spectrum of Candida species causing Candidemia incidence of antifungal resistance of those yeasts are also on rise. With a high mortality rate of 35–75 % early antifungal treatment is essential for survival. Untreated candidemia has a mortality rate of over 60 percent. With treatment, the overall mortality of Candidemia is approximately 30 to 40 percent. The hands of healthcare workers are

frequently the source of exogenous infections affecting the patients' skin or CVCs.

As there is a change in spectrum of Candida species causing Candidemia, with high mortality rate, multiple risk factors involved, antifungal resistance development, there is an immediate need of the hour to establish the current trend pattern at our centre to comprehensively elucidate the disease burden, epidemiology, microbial circulation, resistance pattern, management and challenges of adult acquired Candidemia in a tertiary care hospital of Hyderabad.

We aim to utilize this information for better management and survival of these patients

OBJECTIVES:

The primary objective of our study is to determine the incidence of bloodstream infections with Candida species among the total number of positive bloodstream infections in a tertiary care hospital in Hyderabad over a period of four years. Secondary objective is to study the distribution of Candidemia with respect to characteristics like age, gender, comorbid illness, mechanical ventilation, prior antibiotic therapy, prolonged ICU stay, indwelling devices, current pattern of antifungal susceptibility and to determine the outcome, in terms of ICU admission and mortality.

MATERIALS AND METHODS:

Ethics Statement - This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethical Committee, DCGI registered, NABH accredited. All participants have given a formal written informed consent for being included in the study.

Research design – All adult in-patients admitted to a Tertiary care hospital in Hyderabad, above 18 years of age, who have positive isolates of Candida in bloodstream infections among the positive blood culture samples received to the Microbiology department from January 1st 2017 to January 1st 2021, have been included in this study after getting written informed consent. A total of 1600 patients were included in this study. Patients referred from another healthcare facility, having positive blood isolates of Candida and have been reconfirmed with Candidemia isolate on repeat blood sample test in our

Hospital were included in the study population. Patients in Medical ward as well as Medical ICU were included in the study. Patients with non-Candidemia yeast in blood isolate are excluded from the study.

Sample size: Based on the incidence rate of Blood stream infections with *Candida* among Adults, reported in an earlier publication(Reference name of Article: PMID 24029196, serial number 5 among reference list) and with 95% of confidence and 20% allowable error, minimum sample size comes to 1600 samples of any infection among adults.

Statistical Analysis: Percentage incidence rate of incidence of bloodstream infections with *Candida* among the total number of positive bloodstream infections was computed. To test the statistical significance of the association of various distributive factors of blood stream infections, chi square test was applied. To obtain the association between outcome and selected variables, chi-square test and continuity correction method were applied. A P value of < 0.05 was considered significant.

RESULTS AND DISCUSSION:

We found an overall incidence of 120 cases of Candidemia among 1600 positive blood cultures over four years with an incidence of 7.5%. Candidemia was fourth most common blood stream isolate infection in our study after *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*. In an another prospective nationwide multicentre observational study, conducted at 27 Indian ICUs from April 2011 to September 2012 in India, 1400 Candidemia cases were isolated. A study done in SGPGI Lucknow in 2002 found to have 1.61% incidence of blood stream infections due to Candidemia and it was 8th most common blood stream infection. In Gangaram medical college, the incidence was 1.74%, while in Rohatk medical college it was 8.1%, 6% in AIIMS, and 6.9% in MAMC New Delhi.

Most of the people with Candidemia in our study were >60 years old (39.2%), which was in concordance with other studies where most of the Candidemia isolates belonged to patients with mean age group between 59.0–66.2 years 1,2. Majority of the patients with Candidemia in our study were males (60.8%). Patients with *Candida non albicans* (93)

were more compared to *Candida albicans* (27) in our study. *Candida tropicalis* (30.8%) was the predominant species in our study. Species wise distribution of *Candida* in our study has been described in Table 1. This is in contrast to the developed world, where *C. tropicalis* is uniformly less common (5.6–12.0 %) 3-7, and *C. albicans* (45.0–74.0 %) and *C. glabrata* (16.7–22.6 %) are more prevalent 4, 7-10 where as we have encountered *C. glabrata* Candidemia in only 0.83 % of patients.

In an earlier study, 82 % of health care providers were found to carry yeast on their hands and 80% were *C. tropicalis* 11. Therefore, horizontal transmission and compromise of infection control systems are distinct possibilities for the high rate of *C. tropicalis* candidemia in India. The high rate of *C. tropicalis* candidemia was observed in other Asian countries as well 12. Proper hygienic measures are required to curb the incidence of horizontal spread of Candidemia.

Most of the Cases of Candidemia were admitted under General Medicine department (30%). Comorbidities of our patients are similar to a certain extent to earlier reports. In the current study frequency of Candidemia was higher in Diabetic population (63.3%). Earlier studies have showed that they have also reported sizable proportions of diabetes (10.7–28.0 %) in their Candidemia population. 1-3, 6, 9, 10, 13, 14.

In our study 5% of patients with Candidemia had an underlying hematological malignancy, which was less compared to other studies where the incidence was 24.6–36.1 % 2, 14. Patients with Candidemia who had HIV infection in our study were only 1.7%, which was almost in concordance with other studies, where the frequency was 4.0–6.0 %. 4, 6, 9, 10. In our study 9.2% of the patients with Candidemia were neutropenic at presentation, which was almost similar to other studies where the frequency was 6.6–19.7 % 4, 6, 9, 10. Only 1.7% of the patients in our study with Candidemia had a prior abdominal surgery, which was less compared to 44.7–66.1 % seen in other series of studies 1, 2. Among types of surgery, abdominal surgery is considered a leading risk factor for Candidemia 15. Central venous catheterization was present in 66.7% of the patients with Candidemia in our study which was almost in concordance with other studies where the incidence was found to be

88.5–100 %. 1,14 Invasive mechanical ventilation was present in 49.2% of the patients with Candidemia in our study as compared to 72.1–97.4 % in other studies 1,14. Urethral catheterization was present in 73.3% of the patients with Candidemia in our study compared to 86.7–97.4 % in other studies 1,10, which was almost in concordance with our study.

Frequency of Candidemia in patients who were on Hemodialysis was 19.22% compared to 17.5–32.5 % 3,9 in other studies, which was in concordance with our study. Frequency of Candidemia in patients who were on TPN was 15% which was less compared to 43.7–71.1 % in other studies 1,3. Candidemia was present in 36.7% of patients in our study who received prior antibiotic therapy, 31.7% of patients who had prior renal failure, 6.7% of patients who received prior corticosteroid therapy, 1.7% of patients who received solid organ transplant therapy.

73 people among 120 people in our study (60.8%) with Candidemia succumbed to their illness which is higher compared to the EPIC II international series where they found a mortality of 42.6% 14. Mortality rate of patients in our study has been described in Figure 1. Highest mortality rate in our study was noticed among patients with *Candida hemolunii* (76%) infection. Mortality rate according to type of *Candida* species has been described in Figure 2. Mortality rates vary across the globe, they vary between 35–75 % 1. Candidemia-attributable mortality also varies widely (5.0–49.0 %) between centers 1,2,5,16

Urethral catheterization, Central venous access, Mechanically ventilation, Neutropenia at presentation, prior antibiotic therapy, renal failure, Dialysis patients, on TPN, prolonged ICU(Intensive care unit) stay were some of the risk factors which were found to be statistically significant in our study while assessing the mortality of patients in our study with a p value of <0.001. Most of the patients with *Candida hemolunii* infections (71.4%) in our study had maximum ICU stay (more than 7 days). Survival rate was less in patients who had ICU stay for more than 7 days. Survival in relation to ICU stay has been described in Table 2

In our study 3 variables were found to be significant while assessing the outcome in terms of mortality, they are urethral catheterization, mechanical

ventilator and ICU stay. The multivariate analysis for above variables has been depicted in Table 3. If patients were urethrally catheterized, there was 22 times more chance of succumbing to their illness due to Candidemia than if they were not urethrally catheterized. If patients were on mechanical ventilator, there were 4 times more chance of succumbing to their illness due to Candidemia than if they were not mechanically ventilated. If patients had prolonged ICU stay, then there were 15 times more chance of succumbing to their illness due to Candidemia than if they did not have any ICU stay.

Most of the patients with Candidemia in our study were sensitive to Amphotericin (77.5%) and Fluconazole (76.7%). Mortality rate in our study according to the antifungals used has been described in Table 4

Certain measures are to be taken to prevent further spread of infection and to effectively control the infection in such patients and prevent further morbidity and mortality. Decolonisation, screening the high risk patients, infection prevention and control measures with prophylaxis, environmental control, with appropriate timely treatment might help in improving the outcome in patients with Candidemia.

Screening- Screening is highly recommended in units that have ongoing cases or colonisations. All hospitals are encouraged to develop a screening policy after local risk assessments are undertaken. Screening is also advised for patients coming from other affected hospitals. Based on the predilection of *Candida* species to colonise the skin and mucosal surfaces, the suggested screening sites are mouth, respiratory and genitourinary tract with swabs taken from nose, throat, groin, urine/urethral swab, perineal/low vaginal swab, sputum, endotracheal secretions, cannula entry sites. All screen positive patients should be isolated or cohorted. As for other healthcare associated infections, a series of three negative screens taken 24 hours apart are needed to de-isolate the patient. As there is clinical experience of recurrence of colonization, the need for ongoing vigilance in the form of weekly screens in certain clinical environments should be considered by performing local risk assessments.

Decolonization- Decolonization is a recommended control strategy for preventing and treating colonization. Some of the decolonization strategies which are highly effective are strict adherence to central and peripheral catheter care bundles, urinary catheter care bundle, care of the tracheostomy site, with skin decontamination and mouth gargles with chlorhexidine washes and use of topical Nystatin or Terbinafine for venous cannula entry sites.

Infection, prevention and control(IPC)- The precise mode of transmission within the healthcare environment is not known. However, experience during these outbreaks suggests that *Candida* might substantially contaminate the environment of rooms of colonized or infected patients. Transmission directly from fomites (such as blood pressure cuffs, stethoscopes and other equipment in contact with the patient) is a particular risk, however this does not preclude transmission via hands of healthcare workers and hand hygiene needs to be strictly adhered to.

The possible equipment used for the infected/colonized patient should not be shared with other patients on the ward unless between-patient cleaning can be assured. It is essential that all healthcare providers work in a multi-disciplinary team with their Clinical Microbiologists and under the direction of their specialist IPC team.

Control measures should include isolation of all patients infected with the organism in a single room with ensuite facilities wherever possible. There should be strict adherence to standard precautions including hand hygiene using soap and water followed by alcohol hand rub. Personal protective equipment in the form of gloves and aprons (or gowns if there is a high risk of soiling with blood or body fluids) should be strictly adhered to. Visitors of infected or colonised patients need to be briefed about the infection prevention and control precautions should be reinforced; including the need for robust hand hygiene and use of protective aprons. Daily bathing of ICU patients with chlorhexidine can also be considered, as this measure decreased the incidence of bloodstream infections, including Candidemia 17.

The Environment and fomites-Individual Hospitals should adopt a local cleaning policy and regimen

depending on the level of contamination and case load. Domestic staff will require training and supervision until declared competent. A chlorine releasing agent is currently recommended for cleaning of the environment at 1000 ppm of available chlorine. Once the patient has left the environment a terminal clean should be undertaken preferably using hydrogen peroxide vapour, all equipment should be cleaned in accordance with manufacturer's instructions and where relevant returned to the company for cleaning.

Waste and Linen disposal-Hospitals should pay attention to appropriate bagging and isolation of soiled linen and waste so that the environment is not contaminated.

Treatment-It is important to start antifungal medication as early as possible to successfully treat invasive *Candida* infection. Any small delay (approximately 12-24 hr) in starting treatment may result in a significantly excessive mortality rate. Hence any blood cultures or any other sterile site with *Candida* species as a contaminant should be promptly treated. It is also important to remove/change intravenous or any indwelling catheter. For Candidemia, among non-neutropenic adult patients the drug of choice is fluconazole; 800 mg as loading dose then 400 mg/day for at least 2 wk after clinical improvement or negative blood culture. Amphotericin B is equally efficacious. For Candidemia, among neutropenic adult patients the drug of choice is Echinocandin is (Caspofungin 70 mg IV loading dose then 50 mg/day IV or Micafungin 100 mg/day IV for at least 2 wk after clear blood culture and after clinical improvement. For disseminated Candidiasis, fluconazole is the drug of choice. Surgical care includes drainage, removal of any foreign bodies and surgical debridement.

CONCLUSION:

In our study we found Candidemia to be the fourth most common blood stream infection among all blood stream isolates. *C. tropicalis* was the leading pathogen among our patients (30.8%). Most of the patients with Candidemia in our study were sensitive to Amphotericin (77.5%) and Fluconazole (76.7%). Most of the patients with *Candida hemolunii* infections (71.4%) in our study had maximum ICU stay (more than 7 days). Survival rate was less in

patients who had ICU stay for more than 7 days. 61% of our population in study with Candidemia succumbed to their illness showing a high mortality rate. Highest mortality rate was noticed among patients with *Candida hemolunii* (76%) infection.

Urethral catheterization, Central venous access, Mechanically ventilation, Neutropenia at presentation, prior antibiotic therapy, renal failure, Dialysis patients, on TPN, prolonged ICU stay were some of the risk factors which were found to be significant in assessing the mortality of patients in our study. In our study 3 variables were found to be significant while assessing the outcome in terms of mortality in multivariate analysis, they were Urethral catheterization, Mechanical ventilator and ICU stay. Our study and mortality prediction risk factors can help triage and manage high-risk Candidemia patients better.

Hence we conclude with an inference that all patients with Candidemia should be treated with an antifungal agent at the earliest, including patients who have only one blood culture that yields *Candida* and those with a vascular catheter tip that yields *Candida*. Any delay in initiation of treatment, showed an increase in mortality rates. All vascular catheters should be removed because removal has been shown to help clear *Candida* from blood more quickly. Repeated blood cultures should be obtained to ascertain that the fungemia has resolved, and treatment should continue for 2 weeks after the date of the first negative blood culture. Improved survival and clinical success was found with the use of an echinocandin and the removal of central venous catheters.

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Figure 1: Survival rate among patients with Candidemia

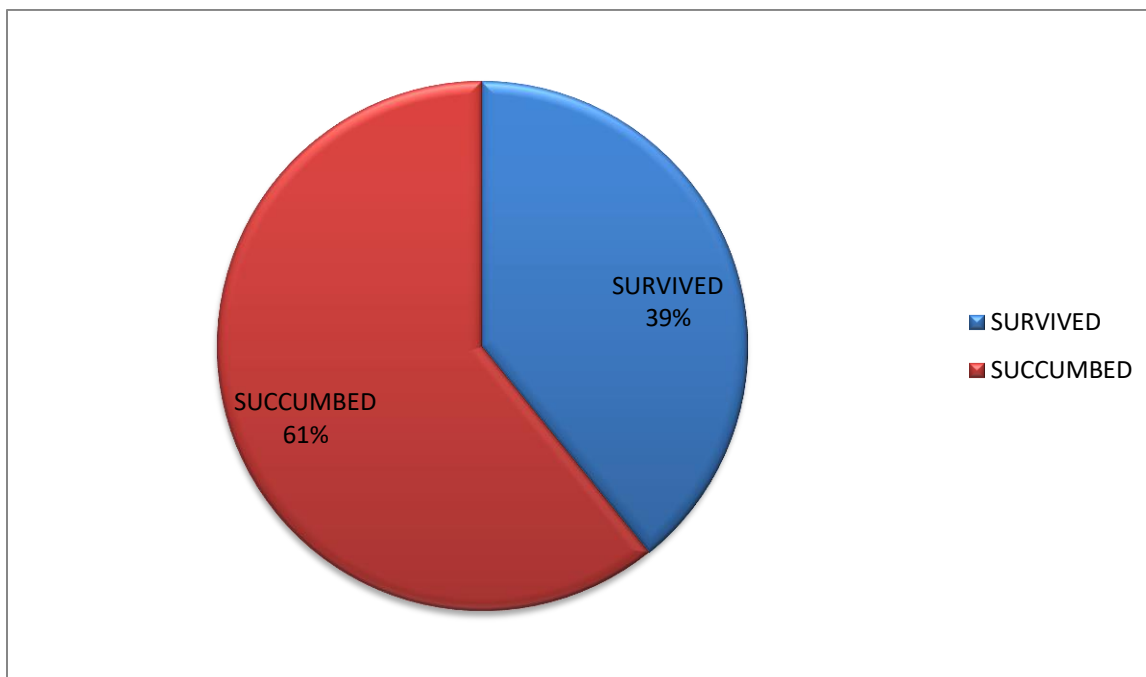
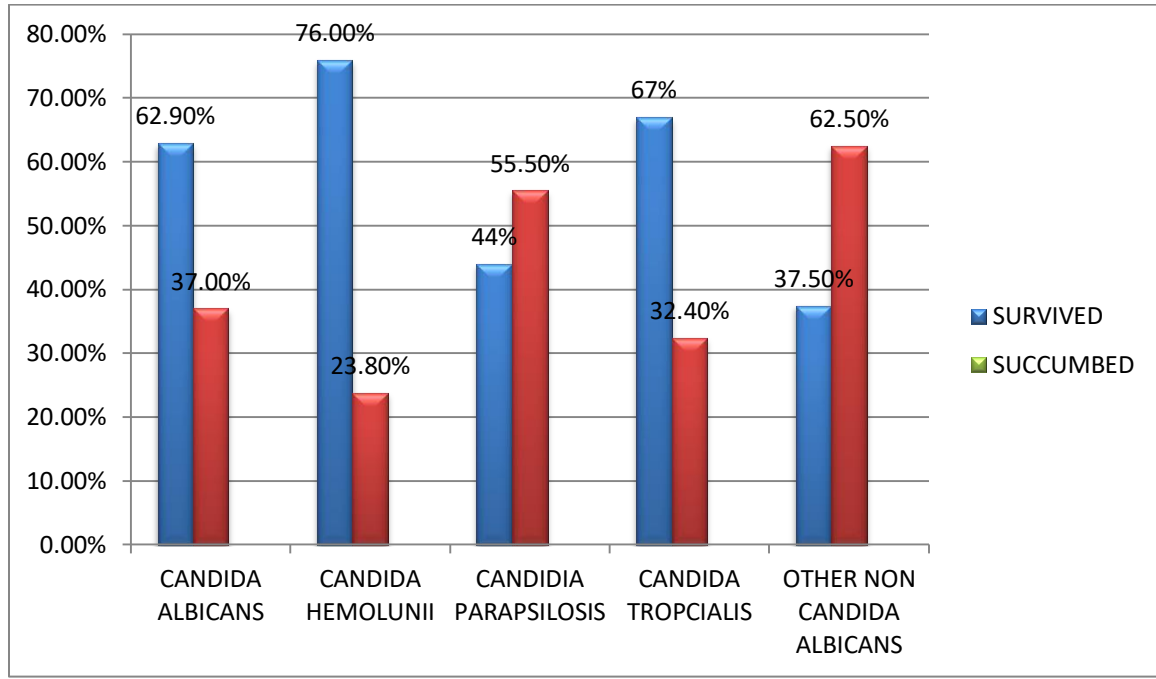


Figure2: Mortality rate due to Candidemia according to species-wise distribution



Other Non CandidaAlbicans include: C.famata, C.glabrata, C.guilliermondii, C.rugosa and C.krusei.

Table 1: Frequency Of Candida Species (n=120)

Species	FREQUENCY	PERCENTAGE
Candida albicans	27	22.5%
Candida haemolunii	21	17.5%
Candida parapsilosis	27	22.5%
Candida tropicalis	37	30.8%
Other non candidaalbicans	8	6.7%
Total	120	100%

Other Non CandidaAlbicans include: C.famata, C.glabrata, C.guilliermondii, C.rugosa and C.krusei

Table 2: Survival rate among Candidemia patients with relation to ICU stay (n=73)

	DURATION OF ICU STAY	SUCCUMBED	SURVIVED	TOTAL	P VALUE
ICU STAY	≤ 7days	22(39.3%)	34(60.7%)	56(100%)	<0.001
	> 7 days	51(79.7%)	13(20.3%)	64(100%)	
	Total	73(60.8%)	47(39.2%)	120(100%)	

ICU=Intensive Care Unit

Table 3: Multivariate analysis for different variables in assessing the outcome of patients

DURATION OF ICU STAY	SIGNIFICANCE	ODDS RATIO	95% C.I FOR O.R	
			LOWER	UPPER
Urethral catheterization	0.001	22.078	3.804	128.125
Mechanical ventilator	0.042	4.305	1.056	17.544
ICU stay	0.000	15.509	3.817	63.006

ICU=Intensive Care Unit

Table 4: Mortality rate due to Candidemia in patients who were treated with different antifungals (n=120)

TREATMENT GIVEN	OUTCOME				p VALUE
	Death		Alive		
	N	%	n	%	
Amphotericin(14)	5	35.7%	9	64.3%	0.115
Caspofungin(11)	9	81.8%	2	18.2%	
Fluconazole(77)	48	62.3%	29	37.7%	
Micafungin(7)	3	42.9%	4	57.1%	
Voriconazole(11)	8	72.7%	3	27.3%	