Efficacy of Prophylactic Fluconazole in Reducing Candidemia in High Risk NICU and PICU Patients

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Abstract: Background: Candida infection is a common cause of morbidity and mortality in neonatal intensive care unit (NICU) and pediatric intensive care unit(PICU) patients ,especially those with risk factors. **Objectives:** To determine the prevalence of Candida species in risky NICU and PICU patients and evaluate the efficacy of prophylactic Fluconazole in reducing Candida colonization and subsequent invasive candidemia in those patients. **Design:** Prospective, randomized, double blind placebo controlled clinical study. **Setting:** Tertiary level intensive care units at pediatric department. **Subjects:** 80 intensive care unit high risk group patient of neonatal and pediatric age. **Intervention:** children were randomly grouped during first three days to receive either Fluconazole or placebo till 28 days or less, if discharged or died earlier. Weekly surveillance cultures from oropharyngeal swabs, urine , stool and sputum (when available), samples were collected from all patients and cultured on sabaroud dextrose agar media . Blood culture on Bact/ALERT®3D culture system for Candida detection was done when candidemia was suspected. For positive cultures, isolates were identified by API 20c biochemical identification strips. Liver enzymes were monitored. **Results:** Baseline risk factors for Candida infection in Fluconazole and Placebo groups were similar. Candida colonization was reported in 35 patients (87.5%) in the placebo group which was significantly higher (P =0.0001) than that detected among patients in the Fluconazole treated group [10 patients (25%)] . Fluconazole treated group showed significantly lower colonization with Candida albicans (C. albicans) and higher colonization with non Candida albicans (non-C. albicans)versus placebo group. Invasive Candida infection was significantly higher (P =0.03) among placebo group than Fluconazole treated one .Invasive non-C. albicans infection was reported in 9/13 patients [6 patients (66.6%) in Placebo group and 3 patients (33.3%) in Fluconazole treated group]. No significant hepatotoxicity was noticed during Fluconazole therapy. **Conclusion:** Prophylactic Fluconazole in risky neonatal and pediatric patients in ICU is effective in reducing Candida colonization especially C. albicans but not invasive candidemia.

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Key words: Candida colonization; candidemia; antifungal prophylaxis; Fluconazole; risk factors for candidemia; ICU infection and nosocomial infection.

1. Introduction:

Bloodstream infections due to Candida have took considerable attention in several medical fields over the past few years due to their increasing incidence (57-61%) and attributed mortality rates(10-49%) [1,2], also the appearance of non-albicans species which displaying a different resistant susceptibility profile[3-5].

Candida species are responsible for around 80% of nosocomial fungal infections, and around 10-20% of all nosocomial bloodstream infections in intensive care units (ICUs)[6-8] especially patients with abdominal surgery, hematologic malignancies, and solid organ or bone marrow transplantation[9-11]. It is the third most common pathogens as cause of nosocomial bloodstream infections in premature infants[12] and the fourth commonest cause of blood stream infections in pediatric ICU patients[13].

The development of such infections is associated with increased overall morbidity, which lengthens the duration of ICU stay and increases the cost of hospitalization[14,15].

Many risk factors contributing to the development of fungal infections in ICU were identified. The main risk factors for candidemia include the prematurity[16,17], wide use of broad spectrum antibiotics therapy for a long time, long hospital stay especially with immunosuppressive drugs as in oncological diseases, immune-compromised patients, multiple organ failure (MOF), abdominal surgery, parenteral nutrition, hemodialysis, and the use of any invasive procedure like central venous catheter, and mechanical ventilation[18-20].

Prophylaxis with antifungal regimens has been proposed as an effective (and probably cost-effective) approach to prevent such infections in high-risk patients[21-23] but it remains controversial in most populations including surgical intensive care unit patients[24].In low candidemia rate populations the benefit of instituting preventative or prophylactic

strategies is weighed against the potential risks (eg, antifungal drug resistance or toxicity)[25]. So in order to reduce the morbidity and mortality contributed to this widespread type of fungal infection. Azoles and polyenes were used in a number of randomized controlled studies to assess their effectiveness as prophylactic regimens[26-28]. Azoles are associated with fewer adverse effects compared with polyenes and can be administered orally[29-31].

Our objectives were to determine the prevalence of Candida species in risky NICU and PICU patients at Zagazig University hospital which is a tertiary referral hospital, serving a large governorate in Egypt and to estimate the efficacy of using fluconazole as prophylactic therapy in those high risk patients.

2. Study Period, Patients, and Entry Criteria.

This study was a prospective, randomized, controlled double-blind study. Eighty consecutive risky patients from October 2009 to July 2011 were enrolled in this study. These patients were between neonatal age and 12 years of age and were admitted to the intensive care units of pediatric hospital, Zagazig University hospitals.

These patients included if they were admitted to NICU or PICU with risk factors for fungal infection including: prematurity, central line insertion, catheterization, mechanical ventilation, immune-compromised patient ,patients on immunosuppressive drugs neutropenia, patients with abdominal surgery, dialysis, or patients under total parenteral nutrition(T.P.N.).

They were randomized as soon as a preliminary report of sterile cultures and swabs were received, usually within 48–72 hrs.

Exclusion criteria: patients who were already on antifungal therapy, had positive Candida cultures, had known hypersensitivity to azole group of drugs, or those who had severe impairment of liver function at admission.

Informed written consent was obtained from the patient's parents. We recorded details of primary diagnosis, symptoms at the time of detection of candidemia, physical examination findings, and known risk factors for candidemia at the time of entry into the study. Randomization was done at the time of enrolment to receive either solution A or solution B (one of them being Fluconazole and other being placebo) by the shuffled sealed envelope method. So they were divided into two groups; group (I) include patients who received prophylactic fluconazole and group (II) include patients who received placebo one.

Baseline data on the demographic and clinical characteristics of the patients were collected and relevant clinical data was prospectively collected throughout the course of the study on a pre-designed Performa. Presence of one or more clinical signs consistent with fungal infection (e.g., temperature instability, increase in frequency of apnea, increase in oxygen requirement, etc.) was noted. Solution A or solution B was administered intravenously at dose of 3mL/kg/day as a single dose every 72 hours till day 14 and subsequently every 48 hours till day 28 of life in the neonatal period, while in patients older than 3 months the dose was doubled and given as a daily dose. Fluconazole preparation used for the study was colorless, in the strength of 1 mL = 2 mg. The placebo group received an equal volume of normal saline as it physically matched the Fluconazole solution. Candida surveillance cultures were collected on the day of randomization (day 1 to 3) and days 7, 14, 21, 28 and also as indicated by the treating physician. Candida workup for Candida colonization pattern obtained including weekly surveillance cultures from oropharyngeal swabs, urine, stool and sputum (when available), samples were collected in all patients and cultured on sabaroud dextrose agar media (Oxoid, Ltd.USA). Candida colonization defined as at least one positive surveillance culture[10]. The obtaining of surveillance cultures were discontinued before the determined four-week treatment period if systemic fungal infection documented, if the infant was discharged, died or transferred to another unit, or if significant hepatotoxicity was diagnosed based on biochemical monitoring. Decision of exclusion of any patient from the study and review of Candida culture pattern was done weekly.

If a baby developed invasive Candida infection determined clinically and by Candida growth in blood culture, solution A / B was stopped and Candida sepsis was treated with intravenous Amphotericin B.

Blood culture for candidemia on Bact/ALERT®3D culture system (biomerieux, Inc) cup to 4 ml blood was drawn under standard recommended antisepsis procedures and inoculated in pediatric blood culture bottles (Bact/Alert PFbottle) ,bottles were monitored for the presence of bacterial growth every 10 min. by the Bact/ALERT®3D culture system (automated continuously monitoring blood culture instrument). If the Bact/ALERT system recorded any positive bottle, direct gram stain and subculture on sabaroud,s dextrose agar media were done. Negative cultures were incubated till completion of the remainder period. All colonies appeared on the media were examined macroscopically, gram stain, C. albicans by germ tube test and finally by API 20c biochemical identification strips (biomerieux,Inc).

Complete blood counts, renal function test, and liver function tests were obtained at the start of therapy and repeated weekly for the duration of therapy.

Patients who did not have a follow-up blood culture were considered to have recovered as they were asymptomatic at discharge time from hospital and first follow-up visit. Further deterioration (not attributable to other cause) or positive blood culture (invasive candidemia) or urine culture for Candida after therapy was defined as prophylactic failure.

Statistical analysis:

Chi square χ^2 test ,fisher exact probability test were used when appropriate. P <0.05 was considered significant. Results were analyzed using SPSS software version 10.0.

3. Results

Data were collected, summarized, analyzed and presented in the following tables:

There was no difference in the demographic pattern, clinical characters or the risk factors for Candida colonization and candidemia between both fluconazole treated and the placebo groups (Tables 1 and 2).

Candida colonization occurred significantly more commonly in the placebo group as compared to the Fluconazole treated group (87.5% vs 25%, P = 0.0001) . The colonization rate by C. albicans was 60% with significant increase in placebo group (71.4%) in comparison to fluconazole treated group (20%) while "non C. albicans" colonization rate was 40% with significant increase among fluconazole treated group (80%) versus (28.6%) among placebo group (Tables 3,4).

The incidence of candidemia in the overall patients was (21.3%) among it (52.9%) were non C. albicans with profound increase (75%) among fluconazole treated group while increase of C. albicans (53.8%) among placebo group was detected (Table 5).

Regarding the clinical picture of candidemia among patients there was significant difference in the severity of the associated symptoms with candidemia between the two groups as regard lethargy and poor reflexes, mucocutaneous affection and hepato-splenomegaly (Table 6). Five patients died in the fluconazole treated group and seven in placebo group. Out of 12 patients who died, 6 patients had developed invasive fungal infection prior to death (2 in fluconazole treated group and 4 in placebo group). All those patients were started on Amphotericin B. Fluconazole was not found to be hepatotoxic with the dosage and the Duration used.

Table (1): Demographic and clinical characteristics of the patients in the studied groups

Characteristic		Group(I)		Group(II)		**P**
		N:40	(%)	N:40	(%)	
Sex (male/female)		27/13	(67.5/23.5)	22/18	(55/45)	0.25
Age	Preterm	8	(20)	10	(25)	0.59
	neonates	10	(25)	6	(15)	0.26
	Infancy	10	(25)	11	(27.5)	0.8
	preschool	8	(20)	7	(17.5)	0.77
	school age	4	(10)	6	(15)	0.5
Location	NICU	18	(45)	16	(40)	0.65
	PICU	22	(55)	24	(60)	0.65
Cause of admission						
-Prematurity		8	(20)	10	(25)	0.59
-Neurological disease		3	(7.5)	1	(2.5)	0.61
-Sepsis		5	(12.5)	5	(12.5)	1.00
-Post operative		7	(17.5)	3	(7.5)	0.17
-Oncolgical		4	(10)	1	(2.5)	0.35
-Hematological malignancies		2	(5)	3	(7.5)	1.0
-Pulmonary disease		4	(10)	6	(15)	0.49
-Dialysis		6	(15)	6	(15)	1.00
-Cardiac disease		1	(2.5)	5	(12.5)	0.09

Table (2): Risk Factors of Candida colonization and candidemia in the studied groups .

Risk Factor	Group(I) n:40		Group(II) n:40		P
	N	(%)	N	(%)	
-No. of antibiotics					
1-2	2	(5)	6	(15)	0.26
3-4	3	(7.5)	2	(5)	1.0
>4	4	(10)	1	(2.5)	0.35
-Mechanical ventilation	7	(17.5)	5	(12.5)	0.39
-C.V.catheter	6	(15)	5	(12.5)	1.0
-T.P.N.	6	(15)	7	(17.5)	0.76
-Surgery	5	(12.5)	6	(15)	1.0
-Corticosteroid therapy	6	(15)	5	(12.5)	0.1
-Neutropenia	3	(7.5)	5	(12.5)	0.7
-dialysis	4	(10)	3	(7.5)	1.0

Table (3): Surveillance cultures results and rate of colonization among both studied groups

Colonization rate	Group (I) n:40		Group (II) n:40		**Total** n:80	
	No	(%)	No	(%)	No	(%)
●No colonization	30	(75)	5	(12.5)	35	(43.7)
●Colonization rate	10	(25)	35	(87.5)	45	(56.3)
●Positive surveillance cultures:						
-One anatomic site of colonization	3	1+ve Oroph.* 1+ve Stool 1+ve urine	10	5+ve Oroph.* 1+ve Sputum 2+ve Stool 2+ve urine		
- Two anatomic sites of colonization	5	1+ve Oroph.*&sputum 1+ve Oroph.*&stool 2+ve Oroph.*&urine 1+ve Stool & urine	19	4+ve Oroph.*& sputum 6+ve Oroph.*& stool 2+ve Oroph.*& urine 7+ve Stool & urine		
- More than two anatomic sites of colonization	2	1+ve Oroph.*,stool & urine 1+ve Oroph*,stool & sputum	6	4+veOroph.*,stool & urine 2+veOroph.*,stool & sputum		

* Oroph.=oropharyngeal

Table (4): Different Candida species colonization among both groups

Species	Total n:80	Group(I) n:40		Group(II) n:40		P
	N (%)	N	(%)	N	(%)	
Total colonization rate .	45 (56.3)	10	(25)	35	(87.5)	0.0001*
●**C. albicans** species	27 (60)	2/10	(20)	25/35	(71.4)	0.008*
●**Non C. albicans** species	18 (40)	8/10	(80)	10/35	(28.6)	0.008*
-C.tropicalis		4	(40)	7	(20)	
-C.glabrata		2	(20)	2	(5.7)	
-C. krusi		1	(10)	0	-	
-C.parapsilosis		1	(10)	1	(2.9)	

*Comparison between group I and group II.

Table (5): Candida species candidemia among both groups

Species	Total n:80	Group(I) n:40		Group(II) n:40		P
	N (%)	N	(%)	N	(%)	
Total invasion rate	17 (21.3)	4	(10)	13	(32.5)	0.03*
●**C. albicans** species	8 (47.1)	1/4	(25)	7/13	(53.8)	0.6
●**Non C. albicans** species	9 (52.9)	3/4	(75)	6/13	(46.2)	0.6
-C.tropicalis		2	(66.7)	3	(42.9)	
-C.glabrata		1	(33.3)	2	(28.6)	
-C.parapsilosis		0	-	1	(14.3)	

*comparison between group I and group II

Table (6): Clinical picture of candidemia in both groups

Clinical picture	Group(I) N:4	Group(II) N:13	P
-Lethargy & poor reflexes	1	11	0.05*
-Hypothermia	2	5	1.0
-Fever	2	3	0.54
-Mucocutenous lesions	1	12	0.02*
-H.Smegaly	0	9	0.03*
-Food intolerance	3	8	1.0
-Death	2	4	0.58

4. Discussion

Candida species have become important and common causes of bloodstream infections in children, especially those hospitalized in PICUs, with an increasing incidence [32]. Although C. albicans remains the most frequently isolated species, there is a shift to non- C. albicans species, including C. parapsilosis, C. tropicalis, and C. glabrata, with an associated increase in mortality and antifungal resistance[33,34]. Morbidity and mortality remain high, underlining the importance of primary prevention of candidemia in PICU patients[32].

Patients with different risk factors for Candida colonization and candidemia were included in this study as patients with immunosuppressive therapy, immune-deficiencies, using broad-spectrum antibiotics, administrating of parenteral alimentation, dialysis, surgery were also included. These risk factors and more were mentioned in different reports[12,13,34-36].

In the present study, The total colonization rate was 45/80 (56.3%) with significantly (p=0.0001) less number of fungal colonization reported in Fluconazole treated group (25%) in comparison to the placebo group (87.5%) during the 28 days surveillance period . **Singhi and Deep [33] found** colonization by Candida in 69% patients by the end of two weeks stay in PICU. **Kicklighter et al [37] & Kaufman et al [38]** reported colonization rate 23% and 46%, respectively and after fluconazole treatment reduction to 4.9% and 15.1%, respectively was detected that was consistent with this study results as colonization in fluconazole treated group was significantly less than the placebo group .

The colonization rate by "non C. albicans" in the present study was (40%) with significant increase among fluconazole treated group (80%) versus (28.6%) among placebo group which is respectable to studies by **Baley et al [39]** and **Kicklighter et al [37]** in whom the colonization rate by "non C. albicans" was 39% and 47%, respectively .

Rodriguez-Nunez[40] mention that antifungal treatment seems to play an important role in the Candida species isolated, with C. parapsilosis and C. krusei being seen most commonly after fluconazole therapy, and C. glabrata after both amphotericin B and fluconazole.

The incidence of candidemia in the overall population is increasing (Candida is one of the leading causes of bloodstream infections in developed countries), and the rate of increase is greater in pediatric patients than in adults[34,41].

In the current study, The incidence of candidemia was (21.3%) among it (52.9%) were non C. albicans with profound increase (75%) among fluconazole treated group while increase of C. albicans (53.8%) among placebo group was detected.

Study by **Narang et al [11]** in the year 1998, from North India showed 22.8% incidence of invasive fungal infection in preterm neonates. Another study from the same institution showed that among the different Candida species, there is a shift from C. albicans to non C. albicans species as 56.5% fungal isolates from patients with fungal sepsis were non C. albicans (C. tropicalis in 21.7%, C. guillermondii in 13%, C. parapsillosis in 13% and C. krusei in 8.7%)[42]. In study by **Kaufman et al [38]** the incidence of invasive fungal infection was 20% in the placebo group and out of 10 fungal isolates 50% were non C. albicans. Interestingly C. krusei and C. glabrata are species with intrinsic resistance to Fluconazole[3,5,43] while C.tropicalis and C. parapsilosis tend to be less susceptible to Fluconazole than C. albicans[4,33].

Fluconazole is used in our ICUs since last four years, which could be the reason for high incidence of non- C. albicans species, which are less susceptible to Fluconazole. Similar timing of presentation of invasive fungal infection caused by those non- C. albicans species in the Fluconazole and placebo group highlights the fact that Fluconazole was not effective in preventing invasive fungal infection in the present study. Long-term repeated exposure of Candida species to a specific antifungal class may result in the gradual eradication of susceptible species like C. albicans and promote the proliferation of resistant species. There may be other significant factors apart from superficial colonization that contribute to fungal sepsis; as in **Kicklighter et al [37]** study, a reduction of fungal colonization by

prophylactic fluconazole did not bring down rate of invasive fungal infection.

The role of prior colonization seems to be very important for candidemia, and appears to be a necessary step before infection[44]. This was observed in this study as with increase colonization in placebo group (87.5%) versus Fluconazole treated group (25%), the candidemia increased as it became (32.5%) in placebo group versus (10%) in Fluconazole treated group. **Verduyn et al** [45] reported that colonization with Candida has been shown to precede candidemia and is regarded as an independent risk factor for systemic fungal infection. Also, in one group of pediatric patients with burns, the incidence of candidemia was remarkably increased from 0% when the fungus colonized one site, to 22.2% with two sites and 34.4% with three or more colonized sites[44].

Candida species are known to adhere to epithelial layers, endothelial cells, blood clots, plastic and acrylic producing a number of adhesive molecules that enhances their ability to persist, invade and disseminate. So, monitoring for colonization may help in predicting subsequent infection with identical strains in critically ill children being treated in PICU[33].

In the present study , mortality rate were (35.3%).which was on line with results obtained by **Filioti et al** [35] who mention that the mortality rate among infants can be as high as 43% to 54%. Several studies reported range (10% to 49%) mortality rate in children which is interestingly lower than the rate in adults, (31% to 78%) probably because of the difference in Candida species distribution between the two populations[1,2,33,34].

The question which is often raised is whether the morbidity and mortality in patients with invasive candidiasis is directly attributable to candidemia or should it be attributed to the critical nature of the underlying disease. **Wey et al** [46] found excess mortality attributable to candidemia apart from the underlying disease was 38%.

In conclusion, in view of the serious nature of candidemia with its attributable mortality, the early prophylaxis with fluconazole may be effective in limiting the Candida colonization and subsequent invasion (candidemia) which is a very strong reason for morbidity and mortality in NICU and PICU. Further studies should focus on validation of the risk factors that may contribute in candidemia in order to identify the population that could benefit most from antifungal prophylaxis and other preventive measures.

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