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ORIGINAL ARTICLE

Candidaemia in Neonatal Intensive Care Units (NICU) at Beni-Suef Governorate

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ABSTRACT

Background: *Neonatal sepsis is a cause of mortality among neonates. Fungal infections are important hospital-acquired pathogens in neonates and infants admitted to the neonatal intensive care unit (NICU). Most neonatal fungal infections are due to Candida species, particularly Candida albicans. The sources of candidiasis in NICU are often endogenous following colonization with fungi. About 10% of these babies get colonized in the first week of life and up to 64% babies get colonized by 4 weeks of hospital stay.* ***Objectives:*** *To assess the frequency of fungal infections in neonates attending (NICU) in Beni-Suef Governorate. Also, to correlate their presence with different risk factors.* ***Methodology:*** *A total of 52 neonates admitted to NICU in Beni suef Governorate. Blood culture both aerobically and anaerobically were done. Subcultures on blood agar, chocolate agar, MacConkey's agar, Sabouraud dextrose agar and bile esculin azide agar daily for 7 days before reporting blood cultures as negative. Candida spp. on SDA was identified by standard laboratory methods such microscopic and Gram stain identification, chla-mydospore formation on cornmeal agar, and Germ tube test to differentiate Candida albicans from other Candida species.* ***Results:*** *fungal infections were significantly assosciated with maternal candidiasis (P=0.003), higher level of CRP (P=0.023) and with respiratory distressand jaundiced cases (P = 0.001, 0,001) respectively. There were insignificant differences regarding type of antibiotics given to neonates and fluconazole use as a prophylaxis in NICUs. There was a higher resistance to fluconazole and high susceptibility to amphotericin B.* ***Conclusion:*** *Mechanical ventilation has been associated with an increased risk, so continuous good hygiene measures and possibly antifungal prophylaxis in selected high-risk neonates is needed. Candida spp. may be resistant to azoles.*

INTRODUCTION

Neonatal sepsis refers to an infection involving the bloodstream in newborn infants less than 28 days old. It remains a leading cause of morbidity and mortality among neonates, especially in middle and lower-income countries.[1]

Neonatal sepsis is divided into two groups based on the time of presentation after birth: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis in neonates at or before 72 hours of life (some experts use seven days), and LOS is defined as sepsis occurring at or after 72 hours of life [2].

Invasive fungal diseases (IFD) are an important cause of morbidity and mortality in premature neonates.[3]

Candida species are particularly important hospital-acquired pathogens in infants admitted to the neonatal intensive care unit (NICU). Reported rates of invasive Candida infections in the NICU setting range from 0.5 to 2 percent depending on the average gestational age and birth weight. [4]

METHODOLOGY

In this study, a total of 52 neonates admitted to NICU in Beni suef Governorate (Twenty two cases were collected from Beni- Suef University Hospital, 25 cases were collected from Beni -Suef General Hospital and 5 cases were collected from Al-Zahraa Hospital).

Blood samples were taken under complete sterile conditions. Blood culture bottles were incubated aerobically and anaerobically at 37°C for 7 days. The bottles were examined daily for evidence of bacterial growth. Subcultures were done on blood agar, chocolate agar, MacConkey's agar, Sabouraud dextrose agar and bile esculin azide agar and observed for growth daily for 7 days before reporting blood cultures as negative.

Chocolate agar and blood agar plates were incubated in a CO2 incubator with 5% to 10%CO2 for up to 48 hours while other culture plates were incubated aerobically overnight at 37ºC. [5]

Isolates from subcultured plates were taken for identification. Identification of blood cultures isolates and catheters cultures were based on colony morphology, Gram staining, biochemical tests such as catalase, coagulase, oxidase, urease and sensitivity to optochin and bacitracin. CoNS or other commensal skin flora were considered pathogenic if they were isolated from two blood cultures. BSI was considered to be catheter-related if both blood and catheter tip cultures were positive for the same organism [6].

Candida spp. grown on SDA was identified by standard laboratory methods such microscopic and Gram stain identification, chlamydospore formation on cornmeal agar, and Germ tube test to differentiate *Candida albicans* from other Candida species [7].

Disc diffusion test was done according to modified Kirby-Bauer susceptibility testing technique on Mueller–Hinton agar plates according to interpretative criteria recommended by Clinical and Laboratory Standards **(CLSI 2020)**[8] were done to fungal isolates using the following discs

Amphotericin B (AMPhO) 10 ug, Ketoconazole (KETOC) 15 ug, Itraconazole (ITRAC) 10 ug, Fluconazole (FLUCZ) 25 ug, Voriconazole (VOR.1)1 ug, Fluorocytosine (FLU.1)1 &10 ug, Posaconazole (POSAC) 5 ug, Caspofungin (CASP5) 5 ug, Terbinafine (TERBI) 30 ug, Nystatin (NYSTA) 100 IU and Griseofulvin (GRISE) 25 ug.

RESULTS

The present study the gestational age of the studied group ranged from 28-42 weeks, male gender was more presented than female (61.5 % versus 38.5 %), most cases were from urban areas (55.8 % versus 44.2 %), their birth weight ranged from 950-4200 gms and their presenting weight ranged from 900-4000 gms. Concerning clinical data, the mean of heart rate was 148.3 ± 8.9 beat/min, respiratory rate 45.6 ± 12.8 cycle/min and duration of admission 8.4 ± 6.01.

Concerning maternal factors showed the mean of their mother age was 25.4 ± 5.7 years, most of their mothers were multigravida (71.2 % versus 28.8%), most of the studied neonates were delivered at hospitals (61.5 %) at clinics (26.9 %) and the rest (11.5 %) at homes. Concerning maternal problems, only 13.5 % had history of PROM , 32.7 % had abortions , 46.2 % had suggestive history of maternal candidiasis , 5.8 % had pre-eclampsia, 3.8 % had polyhydramnios and only 1.9% had D.M.

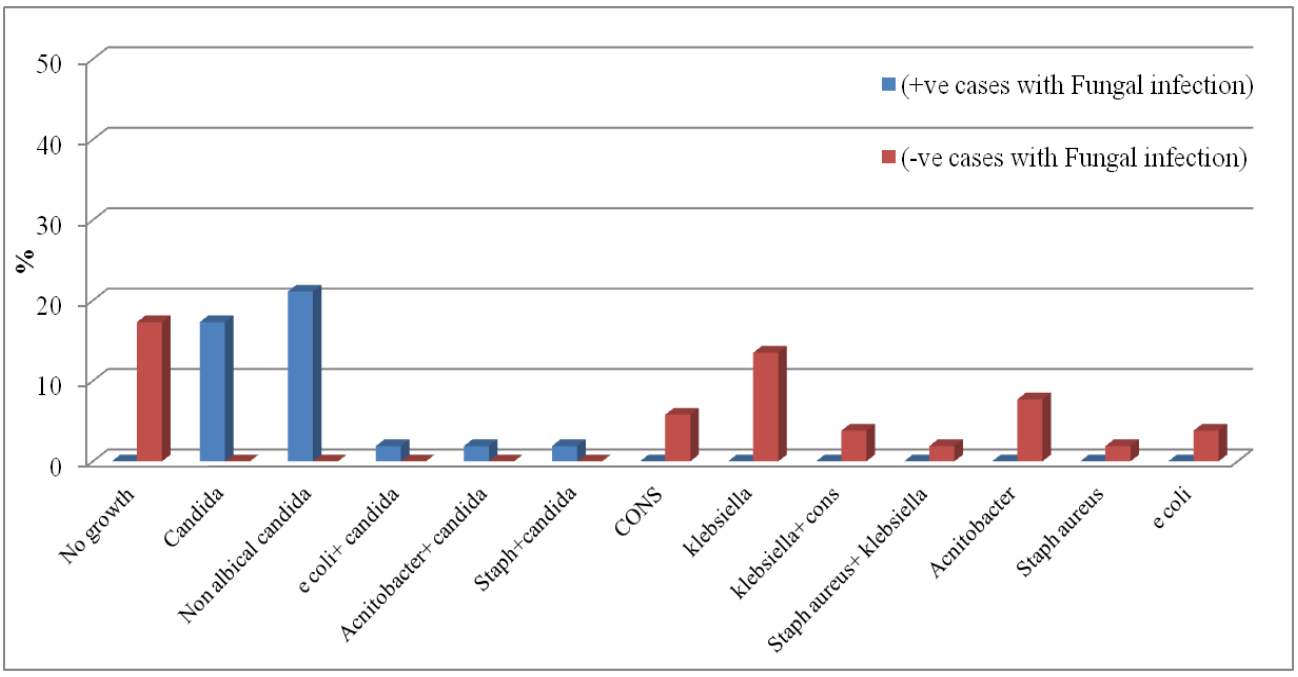

Fig. 1: Description of blood culture results

As shown in table (1) positive fungal infected neonates were significantly older than those without fungal infection (P = 0.001). On the other hand, there were insignificant differences between them as regarding other parameters e.g gender, residence and birth weight (P > 0.05).

Also, neonates with fungal infection were significantly had suggestive history of maternal candidiasis than those without fungal infection (P=0.003).

Positive fungal infected cases had only significantly higher level of CRP than negative fungal infected cases (P=0.023). Also, were significantly presented with respiratory distress and jaundice than negative fungal infected cases (P = 0.001, 0,001) respectively.

Positive fungal infected cases had significant mechanical ventilation than those without fungal infection (P = 0.005). On the other hand, there was insignificant difference between them as regarding other mentioned invasive procedures (P > 0.05).

There were insignificant differences between positive and negative fungal infected cases as regarding type of antibiotics given to neonates and their duration (P > 0.05) or as regarding fluconazole use and duration in NICUs (P > 0.05) .

We demonstrated that there were insignificant differences between positive and negative fungal infected cases as regarding different clinical signs of sepsis (P > 0.05) or a**s** regarding coloured aspirates or congenital anomalies (P > 0.05).

Table 1: Comparison between *Candida albicans* and *non candida albican* infected cases as regarding some clinical data

Clinical data	*Candida albicans* No.=12		*Non candida albican* No.= 11		P value	Sig.
	Mean	SD	Mean	SD		
Gestational age (weak)	35.9	4.0	35.6	3.9	0.867	NS
Postnatal age (Day)	17.3	9.6	17.2	6.4	0.965	NS
Birth weight (gm)	2275	534.5	2000	515.7	0.224	NS
Weight (gm)	2250.0	618.6	2009.1	622.0	0.363	NS
APGAR score (min)	6.8	1.5	6.8	1.1	0.979	NS
Duration of admission(day)	9.0	5.5	11.7	7.8	0.337	NS
Duration of antibiotics use (day)	13.3	9.7	14.2	9.3	0.817	NS
Respiratory rate (cycle/min)	44.2	12.9	47.1	9.3	0.544	NS
Heart rate (beats/min)	144.2	11.2	151.4	8.7	0.102	NS

Concerning infection with *candida albican* there were insignificant differences between *Candida albicans* and *non candida albican* infected cases regarding some clinical data (P > 0.05) .

While **as shown in table (2)** *candida albicans* infected cases had lower white blood cell count than *non candida albican* infected cases where (P = 0.012) . On the other hand there were insignificant differences between them as regarding Hb level, platelet count or CRP level (P > 0.05).

Table 2: Comparison between *candida albicans* and *non candida albican* infected cases as regarding some laboratory parameters

Laboratory parameter	*Candida albicans* infected cases No.= 12		Non *Candida albicans* infected cases No.= 11		P value	Sig.
	Mean	SD	Mean	SD		
Hb level (g/dl)	12.1	3.6	11.8	3.1	0.853	NS
Platelets(cell/mm³)	137500	89633.1	168181.8	83644.3	0.407	NS
White blood cells(cell/mm^3)	4883.3	3721.1	10763.6	6327.4	**0.012**	**S***
CRP (mg/dl)	46.1	29.1	36.4	35.2	0.477	NS

S*, Significant (P value < 0.005); Hb, Haemoglobin

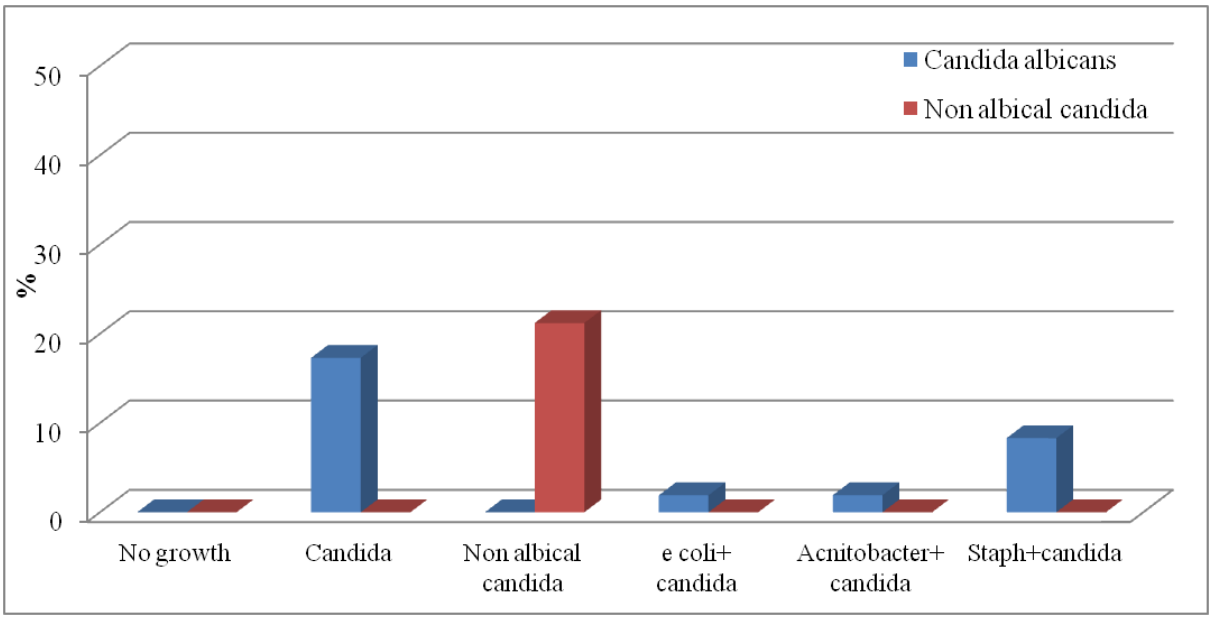

Fig. 2: Percentages of *candida albicans* and *non candida albicans* in pure and mixed infections.

Table 3: Comparison between the results of blood culture and the results of oral colonization:-

Results of oral swabs	Results of blood culture							
	Fungal growth				Bacterial growth No. = 20		No growth No. = 9	
	Cadida albicans No. = 12		*Non Cadida albicans* No. = 11					
	No.	%	No.	%	No.	%	No.	%
Oral colonization with *candida albicans*	12 / 12	100	7 / 11	63.6	6 / 20	30	0 / 9	0
Oral colonization with *non Cadida albicans*	0 / 12	0	3 / 11	27.3	0 / 20	0	0 / 9	0
No growth in oral swab	0 / 12	0	1 / 11	9.1	14 / 20	70	9 / 9	100

Concerning results of oral swabs, **table (3)** demonstrated that colonization by yeasts was detected in 28 of 52 studied neonates, yielding an overall colonization rate 53.8 %. The most frequent isolates were *C. albicans* from 25 neonates (89.3 % of colonized neonates) and *non candida albicans* colonized 3 neonates (10.7 % of colonized neonates) . All *candida albicans* infected cases (12 cases; 100%) were previously orally colonized by infecting species and *non candida albicans* infected cases (11 cases) divided into (3 cases; 27.3 %) were previously orally colonized by the infecting species and (7 cases; 63.6 %) were previously orally colonized by *candida albicans* and (1 case; 9.1 %) was not orally colonized. Regarding bacterial infected cases (20 cases), they divided into (6 cases; 30 %) were colonized by *candida albicans* and (14 cases; 70 %) were not orally colonizad. Finally, cases with no growth in blood culture (9 cases; 100 %) showed no oral colonization.

Table 4: Comparison between *candida albicans* and *non candida albicans* strains as regarding sensitivity to antifungal drugs:-

Antifungal drugs	Degree of susceptibility	*Candida albicans* strains No. (%)	*non candida albicans* strains No. (%)	P value	Sig.
Amphotericin B	**S**	12(100)	9(81.8)	0.303	NS
	I	0(0)	1(9.1)		
	R	0(0)	1(9.1)		
Ketoconazole	**S**	5(41.7)	5(45.5)	0.524	NS
	I	0(0)	1(9.1)		
	R	7(58.3)	5(45.5)		
Fluconazole	**S**	3(25)	0(0)	0.053	NS
	I	2(16.7)	0(0)		
	R	7(58.3)	11(100)		
Itraconazole	**S**	3(25)	1(9.1)	0.592	NS
	I	4(33.3)	4(36.4)		
	R	5(41.7)	6(54.5)		
Econazole	**S**	10(83.3)	6(54.5)	0.206	NS
	I	0(0.0)	2(18.2)		
	R	2(16.7)	3(27.3)		
Nystatin	**S**	5(41.7)	2(18.2)	0.321	NS
	I	2(16.7)	1(9.1)		
	R	5(41.7)	8(72.7)		
Capsofungin	**S**	6(50)	6(54.5)	0.297	NS
	I	4(33.3)	1(9.1)		
	R	2(16.7)	4(36.4)		
5-flucytosine	**S**	6(50)	2(18.2)	0.217	NS
	I	1(8.3)	3(27.3)		
	R	5(41.7)	6(54.5)		
Vorioconazole	**S**	5(41.7)	6(54.5)	0.699	NS
	I	3(25)	3(27.3)		
	R	4(33.3)	2(18.2)		
Miconazole	**S**	5(41.7)	1(9.1)	0.157	NS
	I	1(8.3)	3(27.3)		
	R	6(50)	7(63.6)		

S, Sensitive; I, Intermediate susceptibility; R, Resistant or dose dependant

As shown in **table (4),** Isolates obtained from blood and mouth of neonates during the study period were evaluated for drug susceptibility and showed that all *C. albicans* strains 12 (100%) were found to be completely susceptible to amphotericin B and some non albicans strains 9 (81.8%) exhibited high susceptibility to it. On the other hand, all non-albicans strains 11 (100%) were fully resistant to fluconazole and some *C. albicans* strains 7 (58.3%) exhibited some resistance to it. For econazole, 10 (83.3%) isolates of *C. albicans* and 6 (54.5%) isolates of non albicans species exhibited high susceptiblity to it. In contrast, 2 (16.7) isolates of *C. albicans* and 3 (27.3) isolates of non albicans species were found to be resistant to econazole.

Table 5: Outcome of the studied group as regard survival rate:-

	+ve fungal infected cases No = 23		-ve fungal infected cases No = 29		P value	Sig.
	No.	%	No.	%		
Survival	13	**56.5**	22	**75.9**	**0.233**	**NS**
Death	10	**43.5**	7	**24.1**		

Table (5) shows that there was insignificant differences between positive and negative fungal infected cases as regarding survival of neonates.

DISCUSSION

Candida is a major cause of neonatal infection in preterm infants, especially in extremely low and very low birth weight infants. Successful management of neonatal candidiasis requires effective treatment of *Candida* infection, with appropriate antifungal therapy and supportive care, as well as preventive measures to reduce the risk of systemic *Candida* infections [9]

Egypt is a developing country where the problem of infection is more evident due to lack of health services and hygiene practices [10].

Beni-Suef is the capital of a Governorate in Upper Egypt with high unemployment and poor living conditions, which make the problem of infection more complicated. So, the aim of our study was to assess occurrence of fungal infections in neonates attending (NICU) in Beni-Suef Governorate. Also, to correlate their presence with different risk factors in order to demonstrate more effective prevention strategies.

For positivity of fungal infection, the current study reported that 44.2% of our studied neonates had positive fungal infection. This result was higher than the incidence of 5–15% which was reported in other studies[11].

On the other hand our result was in agreement with a similar higher incidence in another study recorded in Neonatal Intensive Care Unit, Cairo University Specialized Pediatric Hospital (CUSPH) in 2013 Where 98 (91.6%) out of 107 studied cases were culture positive for fungus.

This variation in incidence of fungal infection between our result and the other results could be explained by different incidence between developed and developing countries. Also, by interunit differences in care practices, particulary infection control, enteral feeding and antibiotic prescribing policies which were potentially modifiable risk factors.

Moreover, we found that *candida albicans* was the leading causative agent of fungal infection in positive cases, it was isolated in 23.1% of the studied neonates. This result was in agreement with who found that the most common pathogen of fungal infections in neonatal infants was candida, with candida albicans the most common species[11].

Non candida albican species were isolated from 21.1% of studied neonates group, this was in agreement with [12] who found that candida species other than *C. albicans*, such as *candida paraspilosis*, is increasing.

Our study showed that positive fungal infections were significant in old neonates than young one. This observation is consistent with the status of candida species as one of the primary pathogens isolated in late-onset sepsis, which occurs at 4-90 days of life. On the other hand, There were insignificant differences between positive and negative fungal infected cases as regarding other parameters where (P > 0.05). Pana et al [13] found no gender difference while Scheller [14] found that the frequency of neonatal sepsis was significantly higher in males. This difference in both results may be related to racial or genetic difference.

Neonates with fungal infection were significantly had suggestive history of maternal candidiasis than those without fungal infection.

Neonates with positive fungal infection in our studied group had significantly higher CRP than those without fungal infection. This result was in agreement with Krause et al [15] who demonstrated that C-reactive protein is the most accessible and widely used as a marker for detecting infection. On the other hand, there were insignificant differences between them as regarding platelet count, Hb level or WBC count (P > 0,05).

Concerning neonatal problems, our results demonstrated that the incidence of fungal infections in jaundice and respiratory distress cases was significantly higher. The most likely explanation was that jaundice accounted for a large proportion of clinical manifestations in infants with sepsis. On the other hand, there were insignificant differences between them as regarding other neonatal causes of admission.

Regarding duration of admission, we found that there was insignificant difference between positive and negative fungal infected cases. In contrast to our results Akin et al., [16] found that length of stay > 7 days in hospital was a significant risk factor for candidemia .

Concerning type of feeding, our results showed that there were insignificant differences between positive and negative fungal infected cases as regarding different types of feeding as shown in. In contrast to our study, Wang et al., [17] demonstrated that parenteral nutrition was a risk factor for candidemia.

In our work there was a significant difference between positive and negative fungal infected cases in mechanically ventilated neonates where (P=0.005). This result was in agreement with Decker et al,[18] who demonstrated that ventilatory support was risk factor for candidemia and with those findings reported in earlier studies by a Wunsch et al.,[19].

Moreover, this result was in agreement with the results obtained by Harrington [20] who identified assisted ventilation as a major factor that correlate to candida infection. On the other hand, there was insignificant value of fungal infection between neonates under other mentioned invasive procedures like CPAP, head box or nasal prong

Regarding exposure to antibiotic therapy, our study demonstrated that there were insignificant differences between positive and negative fungal infected cases as regard the type of antibiotics given to neonates or their duration where (P > 0.05)**.** In contrary to our study, Mantadakis et al., [21] reported that infants with acquired fungal sepsis were more likely to have been treated with broad spectrum antibacterial agents than control infants. Also, Chan et al.,[22] identified previous antibiotic therapy as a major risk factor that lead to *candida* infection. The most likely explanation was that the exposure to antibiotics was high in both groups in our study.

Moreover, we reported there were insignificant differences between positive and negative fungal infected cases a**s** in fluconazole use in NICUs. In contrast to our results, results from several single-center studies and one multicenter trial by Tsalik[23], suggested that fluconazole prophylaxis for high-risk preterm infants significantly lowers the incidence of invasive *Candida* infections.

Furthermore, our results demonstrated that there were insignificant differences between positive and negative fungal infected cases as with different clinical signs of sepsis.

In comparison between positive and negative fungal infected cases with gastric coloured aspirates or congenital anomalies, we reported that there were insignificant differences between positive and negative fungal infected cases.

Concerning results of oral swabs, colonization rate by yeast was high. studies by Covington et al., [24] and Similarly, Schuetz et al.,[25] reported that the intestinal colonization was strongly associated with subsequent development of fungemia in neonates hospitalized in the NICU. This could be explained by the ease with which Candida spp. can invade mucocutaneous barriers when such barriers lose their intactness through disease or invasive procedures.

For the evaluation of neonatal isolates for drug susceptibility, our results demonstrated that all *non-albicans* strains 100% were fully resistant to fluconazole and some *C. albicans* strains exhibited some resistance to it. This was in aggreement with De Pascale et al.,[26] who found a similar percentage of neonatal *non Candida albican* isolates that were not susceptible to fluconazole. Although the clinical relevance and importance of this phenomenon of decreased susceptibility to azoles in neonatal isolates is still under investigation, dissemination of azole-resistant clones of such strains had been described by[27]**.**

There was an agreement in mortality rate of positive fungal infected cases in our results with other[28] results.

CONCLUSION

Since there is an intense need for researches in the field of drug resistance for implementing strict antibiotic control policies in hospitals, health care centers, laboratories etc.,

N.B: On behalf of all authors, there is no conflict of interest in the article.
In addition, a written consent was obtained from the patients included in our study.

The above-mentioned manuscript has not been published, accepted for publication or under editorial review for publication elsewhere. All authors have seen and approved the content of the manuscript and have contributed significantly in the work.
The study was approved for ethical point of view.

Approval No: FMBSUREC/06112022/Tohamy

Thank you for your consideration.

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