



Original Article.

Safety and Effectiveness of Micafungin in Neonates: A Retrospective Analytical Study from a Tertiary Pediatric Center



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DOI: 10.21608/ANJ.2021.74624.1026

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Abstract

Background: The incidence of invasive fungal infections in neonatal intensive care units has increased dramatically over the past few decades, partly due to the increased survival rates of preterm neonates. Currently, there are limited studies concerning the usage of Micafungin in neonates. **Aim of work:** The objective of this study was to review our experience with Micafungin regarding its efficiency and side effects. **Patients and Methods:** In this retrospective analytical study, neonates who received micafungin for possible or proven invasive *Candida* infection between July 2017 and February 2020 were included. The time to achieve negative culture, the 14 days survival of the patients and the liver and renal functions as well as blood counts were recorded. **Results:** Thirty neonates with a median birth weight of 2125 grams were included. All of them were effectively treated with micafungin. Median serum aspartate aminotransferase, alanine aminotransferase, creatinine levels did not increase during and at the end of micafungin therapy. None of these patients had experienced an abnormal kidney or liver function tests due to Micafungin usage with serum aspartate aminotransferase, alanine aminotransferase, creatinine levels before an after micafungin treatment: 28 IU (13-257) vs 37 IU (18-89), $p=0.86$; 14 IU (6-180) vs 16 IU (6-50), $p=0.74$; 0.5 mg/dl (0.3-3.4) vs 0.5 mg/dl (0.4-2.1), $p=0.42$, respectively. **Conclusion:** Micafungin is a safe and effective treatment choice both in the treatment of neonatal culture proven or probable invasive *Candida* infections in both term and preterm neonates. **Key words:** Micafungin; neonates; *Candida* spp; antifungal resistance.

Introduction

Prevalence of invasive fungal infection (IFI) has increased in neonates during the last two decades due to increased survival rate even in the extremely premature [1,2]. In neonates, the immune-system is not functioning completely and is susceptible to infections. In addition, they often require invasive procedures, such as the use of central venous catheters, endotracheal intubation in addition to wide spectrum of surgeries. Also neonates are commonly exposed to broad-spectrum antibiotics, parenteral nutrition, H₂ blockers and corticosteroids. All these risk factors place neonates at high risk of IFI, particularly from *Candida* species [3, 4].

Candida spp's are the third most common etiologic agents in late-onset neonatal sepsis and were reported to be responsible for 8 to 15% of hospital-acquired infections [1-4]. *Candida* infections are responsible for an 'attributable mortality' of 18–25%,

significant morbidity and healthcare costs [3]. *Candida* infections approximately affect 10 to 20% of extremely low birth weight infants and 2 to 16% of very low birth weight neonates and are responsible for 25 to 30% of morbidity in neonatal intensive care units [3-6]. *Candida albicans* and *C. parapsilosis* are responsible for the majority of candidiasis in the neonatal intensive care unit (NICU) [6].

Early diagnosis and appropriate treatment are essential in successful management of invasive candidiasis (IC). The most recently developed class of antifungal agents is that of echinocandins consisting of caspofungin, Micafungin and anidulafungin [7-9]. They inhibit the synthesis of beta (1, 3) - D-glucan in the fungal cell wall which does not exist in the wall of mammalian cells [8, 9]. All of them have been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for

the treatment of IC in adult patients [9]. Only caspofungin and Micafungin have been approved for pediatrics by FDA and EMA [9, 10]. Micafungin usage was approved by FDA for pediatric patients aged 4 months and older while EMA approved Micafungin for children including neonates [11].

According to The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines published in 2012, Micafungin, amphotericin B deoxycholate, liposomal amphotericin B and fluconazole are recommended as first line treatment of IC in neonates [11]. Micafungin is the only echinocandin approved for neonatal use by the EMA, based on efficacy and pharmacokinetic data from neonatal populations. Although the kinetics and appropriate dosing of this agent in premature and term infants have been described in the recent years, limited information is available on the safety profile of micagungin in both preterm and term neonates. There are limited data available regarding the

efficacy and safety of Micafungin in neonates [12-17] and reported adverse effects were as follow: increased liver enzymes, cardiac failure, decreased oxygen saturation, neutropenia, intracranial hemorrhage and hypotension [12].

Our objective was to study the efficacy and safety of Micafungin received in neonates with suspected or confirmed systemic candidiasis.

Methods

All neonates, who received Micafungin between July 2017 and February 2020 in NICU of Dr. Behcet Uz Children's Hospital, were included in the study. Patients with missing liver enzymes or creatinine test results prior or during to Micafungin therapy were excluded. Maternal, perinatal and neonatal characteristics of neonates, routine laboratory assessments of biochemistry (concentrations of liver enzymes, bilirubin, creatinine, urea, albumin, electrolytes) and blood count as well as daily dose and duration of Micafungin

treatment, concomitant drugs, clinical response and adverse effects were obtained from electronic medical records. Total blood counts of the patients were studied by Sysmex XN 9100 automated hematology system.

Treatment of Micafungin was indicated at the neonates with proven invasive candidiasis (isolation in otherwise sterile body fluid like what.....blood,urine, CSF...) or suspected sepsis with candidemia.

We used a scoring system developed by Benjamin et al. [3] predict invasive fungal infections of neonates with scores ≥ 2 points. Benjamin et al developed a clinical predictive model for neonatal candidemia with high sensitivity and moderate specificity for candidemia. On the basis of the model, when a physician obtains a blood culture, the physician should consider providing antifungal therapy to neonates who are < 25 weeks' estimated gestational age and to neonates who have thrombocytopenia at the time of blood culture. In addition, if a

physician obtains a blood culture from a child who is 25 to 27 weeks' estimated gestational age and is not thrombocytopenic but has a history of third-generation cephalosporin or carbapenem exposure in the 7 days before the blood culture, then the physician should consider administration of empirical antifungal therapy. At least one blood culture obtained by peripheral vein puncture that grew *Candida* species was defined as candidemia.

Based on the study by Levy et al [18], if a single patient had a positive blood culture lasted for > 5 days starting from the first culture result indicated positive for *Candida* spp, the infection was considered persistent candidemia.

The efficacy end point was defined as achieving negative culture. Treatment failure was defined as death within 14 days after initiation of therapy or still having one positive culture with the same *Candida* species under Micafungin treatment [18,19]. For assessment of potential side effects, the biochemical

variables from the medical files including CBC, liver and renal function tests were recorded.

Ethical consideration

The study was approved by the Committee of Ethics of Dr. Behcet Uz Children's Hospital.

Statistical analysis

All statistical analyses were performed using the SPSS package program for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Values for numerical variables were provided as mean \pm standard deviation or median (minimum–maximum) depending on normality of distribution. Categorical variables were provided as absolute values or percentages, the comparisons of which were made using the chi-square test. Two-way comparisons for numerical variables were made using the Mann–Whitney U test, whereas the Kruskal–Wallis test was used for comparison involving more than two groups. A p-value of <0.05 was considered indicative of statistical significance.

Results

Thirty neonates with a median age of 36 days, with a median gestational age of 32 weeks (min-max; 24-40 weeks), with a median birth weight of 2125 gram (min-max; 440-3800 gram) were included. Twenty neonates (66.7%) were premature and 19 neonates (63.3%) were males (M/F: 1.72). The gestational age of 11 neonates (36.7%) was ≤ 28 weeks; the gestational age of 10 (36.7%) was 29-37 weeks while the gestational age of 9 neonates (30 %) was > 37 weeks (Table 1). The associated diseases and clinical features were summarized in (tables 1 & 2). Micafungin was used as a first line monotherapy in 12 (40%) patients, 18 (60%) neonates had used fluconazole treatment before switch to Micafungin treatment. The daily intravenous Micafungin dosage was 5 mg/kg/day once a day and the mean duration of Micafungin usage was 11 ± 5.12 days (ranging from 4 to 22 days). The indications for Micafungin were suspected invasive candidiasis (IC) in 22

(73.3%) patients and proven IC in 8 (26.7%) patients. According to the blood culture, the *Candida* species were as following; 2 (25%) *Candida albicans* (*C. albicans*), 1 (12.5%) *C. guilliermondii*, 2 (25%) *C. parapsilosis*, 3 (37.5%) *C. glabrata*. All of the three *C. glabrata* isolates were fluconazole resistant (Table 3).

Abdominal ultrasonography, ophthalmic examination and echocardiography were done to neonates with candidemia. Endophthalmitis, endocarditis or hepatosplenic candidiasis were not present in culture proven invasive candidiasis. Four (50%) of the eight neonates with proven IC were on fluconazole treatment at the time of candidemia (Figure 1).

Micafungin treatment was given empirically in 22 neonates suspected to have invasive candidiasis. Fourteen (63.6%) of them were receiving fluconazole treatment before switching to Micafungin treatment. Antifungal change from flucozanole to Micafungin was due to increase in liver function enzymes in

10 patients and clinical deterioration in 4 patients (Figure 2).

Blood cultures of IC patients were sterile through 2 weeks of Micafungin treatment. The median days of culture negativity was 5.5 days (ranging from 1-11 days). A neonate with a gestational age of 30 weeks with fluconazole resistant *Candida glabrata* blood stream infection and *Candida glabrata* meningitis became culture negative at the 11th day of Micafungin therapy. Another neonate with a gestational age of 40 weeks with *Candida albicans* urinary sepsis became culture negative at the 9th day of Micafungin therapy.

Adverse effects attributable to Micafungin therapy

No discontinuation of Micafungin treatment was reported due to side effects. Before the beginning of Micafungin therapy, the basal serum AST values were elevated in 8 (26.7%) patients, ALT were elevated in 4 (13.3%) patients, both AST and ALT values were elevated in 4 (13.3%) patients, serum

creatinine levels were elevated in 7 patients (mostly due to other causes like sepsis, other drugs...) and hypokalemia was present at 7 patients (Table 5).

No increase in serum AST, ALT or creatinine levels were experienced and at the end of Micafungin therapy.

Six (20%) patients died during the observation period and the causes of death were as following: respiratory failure (n=2), Klebsiella pneumonia sepsis (n=2), heart failure (n=1) and post-operative surgical complications (n=1). Culture negativity was achieved in all neonates with candidemia. None of the studied neonates died due to candidemia or treatment failure (Figure 1).

A significant increase in the the median platelets counts were observed at the end of Micafungin treatment (p=0.003). The median platelets counts taken prior to Micafungin treatment and at the end of Micafungin treatment were $210 \times 10^3/\mu\text{L}$ and $307 \times 10^3/\mu\text{L}$ respectively (Table 4).

Discussion

In this retrospective analytical study our experience with intravenous micafungin treatment in 20 preterm and 10 full-term neonates were reviewed. Intravenous Micafungin was used as a first line monotherapy in 12 patients and as salvage therapy in 18 patients treated with fluconazole prior to micafungin. Micafungin was given for suspected invasive candidiasis in 22 patients and for proven invasive candidiasis in 8 patients. Blood cultures of neonates with invasive candidemia were sterile in 2 weeks of micafungin treatment. No increases in serum AST, ALT or creatinine levels were experienced at the end of micafungin therapy.

Non-albicans Candida spp were more commonly isolated in our study, the species most frequently causing candidemia were Candida parapsilosis (57.1%), followed by C. albicans (42.9%) . In our study, 6 of 8 (75%) IC episodes were due to nonalbicans Candida spp, predominating C. glabrata. All of the three C. glabrata isolates were

fluconazole resistant and effectively treated with micafungin treatment.

In a study conducted by Leverger et al [20] in 30 neonates, 2 with proven IC, authors concluded that Micafungin treatment was effective in 28/29 patients (96.6%), with the treatment objective achieved in 22 patients (75.9%) . In a double-blind, randomized, multinational trial to compare Micafungin with liposomal amphotericin B as first-line treatment of invasive candidiasis including 19 patients who were premature at birth; indicate that Micafungin seems to be similarly effective and as safe as liposomal amphotericin B for the treatment of invasive candidiasis [21].

In our study, therapeutic objective was achieved in all neonates within 2 weeks. Blood cultures were sterile in all of the neonates up to 2 week of micafungin treatment. The median days of culture negativity of candidemia episodes were 5.5 days (1-11 days). No mortality was

reported due to treatment failure or candidemia.

All of the neonates with proven and probable IC were effectively treated with micafungin.

Antifungal therapy was changed from fluconazole to Micafungin in 18 neonates due to increase in AST levels (n=7), increase in ALT levels (n=3), and clinical deterioration in the rest of 8 patients. Serum AST and ALT levels were normalized after change to micafungin from fluconazole. Fluconazole induced liver injury has been reported in 5–10% of patients. The biochemical pattern of liver injury is predominantly cholestatic or mixed, recurring with the reinstatement of fluconazole treatment .Hepatotoxicity has been consistently reported for all of these agents and may range from mild abnormalities in liver function tests to fatal fulminant hepatic failure [22, 23]. In a study by Kyriakidis et al. [22], the elevation of liver enzymes occurred in 14% of patients receiving fluconazole, while 2 out of 103 patients in the

fluconazole arm (1.9%) had to withdraw treatment due to hepatotoxicity.

In a review conducted by Egunsola et al, [24] a total of 307 adverse effects (38.6 %) were recorded in neonates, of which 295 (96.1 %) were hepatotoxic effects. In a retrospective single-center study, 19 extremely low birth weight infants were analyzed for Micafungin efficacy and safety and no clinically relevant side effects were observed [25] and all of these data support our findings.

Similar to our findings, a study conducted by Cakır et al. [26] in 15 neonates, the authors concluded that Micafungin is a safe and effective treatment choice both in the treatment of neonatal culture proven or probable invasive candida infections that were caused by refractory Candida strains and in the case of nephrotoxicity and hepatotoxicity. These results are in agreement with our findings and literature [14, 16, 20, 26, 27].

According to a model developed by Benjamin et al [28], the physician should

consider providing antifungal therapy to neonates who are <25 weeks' estimated gestational age and to neonates who have thrombocytopenia at the time of blood culture. In our study, serum platelet levels were significantly increased at the end of micafungin therapy, correlated to blood culture sterility, attributable to treatment success.

Limitations for this study, as with any study with the sample size used in this study, the generalizability of our findings is limited. Firstly, this was a retrospective study, which has inherent limitations when compared to randomized clinical trials. Secondly, this study included all neonates with different underlying diseases, co-morbidities and risk factors which might cause potential bias for the outcome.

The area of neonatal fungal infections is an area where in recent year's new clinical scenarios, new prophylactic strategies, and new therapeutic options have determined the need for careful reconsideration of the current

management strategies. In this view, the role of micafungin therapy in neonates is promising and might become very important in the next years. As a conclusion, Micafungin may fulfil this role as its spectrum of activity includes also species not sensitive to fluconazole, and also targets biofilms where fungal colonies might have been escaping fluconazole activity. Micafungin is a safe and effective treatment choice both in the treatment of neonatal culture proven or probable invasive candida infections that were caused by refractory *Candida* strains, and in the case of nephrotoxicity and hepatotoxicity. More clinical trials studies are required to evaluate safety and efficacy of Micafungin in neonates.

Conclusions

Invasive candida infections are responsible for significant morbidity and mortality in neonates. Safety and effectiveness of micafungin is a particular concern in neonates, where data are often limited. We conclude that micafungin was effective and well

tolerated to treat neonates, including preterm infants with proven or suspected invasive candida infections.

Acknowledgements

Thanks to all our neonates and their parents and all the staff members (physicians and nurses) of NICU.

Author's contributions

The manuscript was written by Dr. Kamile Arıkan. All authors have made substantive contributions to the manuscript, and all authors endorse the data and conclusions. All the named authors have seen and agreed to the submitted version of paper.

Conflict of interest

The authors have no conflict of interests to declare.

Funding

This study received no special funding and was totally funded by the authors.

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Date received: 26th April 2021, accepted 2nd May 2021

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Table 1. Demographic variables and clinical diagnosis of studied group

Item	No.=30
Age (days) *	36 (11-231)
Gestational age (week) *	32 (24-40)
≤ 28 week **	11 (36.7)
28-37 week **	10 (33.3)
>37 week **	9 (30)
Gender **	
Male	19 (63.3)
Birth weight (gram) *	2125 (440-3800)
Prematurity **	21 (70)
Prematurity and necrotising enterocolitis **	10 (33.3)
Congenital heart disease **	7 (23.3)
Congenital anomaly **	3 (10)
Ichthyosis **	2 (6.7)
Congenital pneumonia **	1 (3.3)
Fetal hypoxia **	1 (3.3)

*Median (min-max), ** n (%)

Table 2. Risk factors for invasive candidiasis

Item	No.=30
Extended spectrum antibiotic usage	30 (100)
Orogastric drainage	30 (100)
Mechanical ventilation	29 (96.7)
Total parenteral nutrition	28 (93.3)
Presence of central venous catheter	26 (86.7)
Premature rupture of membranes	20 (66.7)
Antenatal steroid usage	17 (56.7)
Fluconazole prophylaxis	16 (53.3)
History of surgery	16 (53.3)
Neutropenia	1 (3.3)

Table 3. Antifungal resistance pattern and MIC values of Candida spp. isolated from sterile samples

Cultured Candida spp.	Fluconazole	Caspofungin	Micafungin	Amphotericin B	Anidulafungin	Prior antifungal treatment	Culture negativity (days)
Candida glabrata	resistant (12µg/ml)	intermediate resistant (0.25µg/ml)	sensitive (0.002µg/ml)	resistant (1.5µg/ml)	sensitive (0.016 µg/ml)	-	5
Candida glabrata	resistant (12µg/ml)	sensitive	sensitive (0.008µg/ml)	sensitive (1µg/ml)		fluconazole	11
Candida glabrata	resistant	sensitive	sensitive	resistant		-	8
Candida parapsilosis	sensitive	intermediate resistant	sensitive	sensitive		-	6
Candida parapsilosis	sensitive	intermediate resistant	sensitive	sensitive		fluconazole	4
Candida guilliermondii	sensitive	sensitive	sensitive	sensitive		fluconazole	3
Candida albicans	sensitive	sensitive	sensitive	sensitive		fluconazole	9
Candida albicans	sensitive	sensitive	sensitive	sensitive		-	1

MIC: Minimal inhibitory concentration

Table 4. Laboratory change before and after Micafungin treatment

Item	Before treatment	After treatment	p- value
Serum AST (IU/L)	28 (13-257)	37 (18-89)	0.86
Serum ALT (IU/L)	14 (6-180)	16 (6-50)	0.74
Serum creatinin (mg/dL)	0.5 (0.3-3.4)	0.5 (0.4-2.1)	0.42
Serum sodium (mmol/L)	136 (123-147)	136.5 (131-146)	0.56
Serum potassium (mmol/L)	4.4 (3.2-5.9)	4.37 (2.9-5.7)	0.14
Hemoglobin (gr/dL)	11.2 (6-15.1)	10.9 (7.3-14.5)	0.44
Leucocyte (x10³/μL)	9.1 (3.2-33)	10.6 (2.1-47.6)	0.58
Trombocyte (x10³/μL)	196.5 (17-613)	272 (19-937)	0.003*

*significant

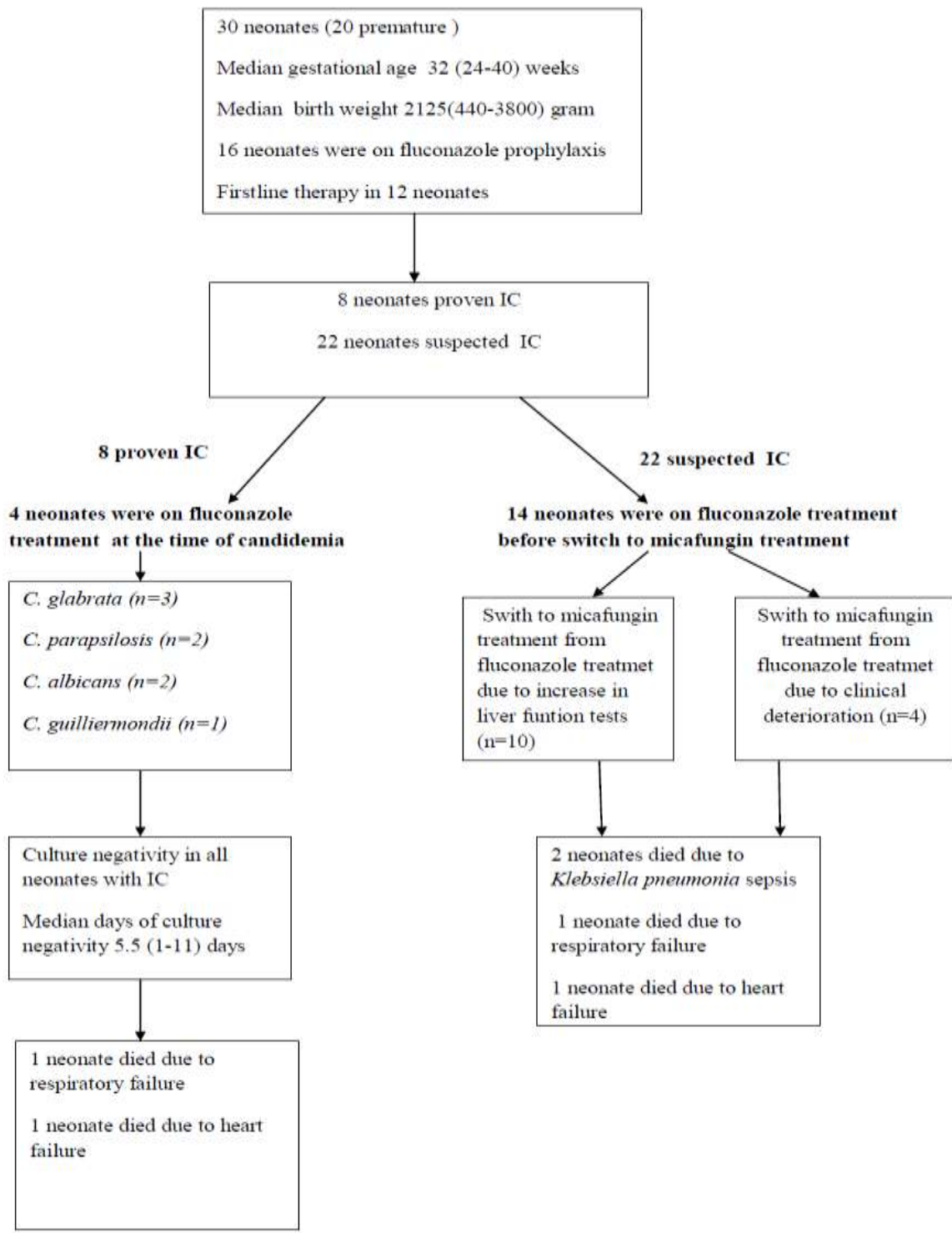


Figure1. The outcome of neonates who received micafungin

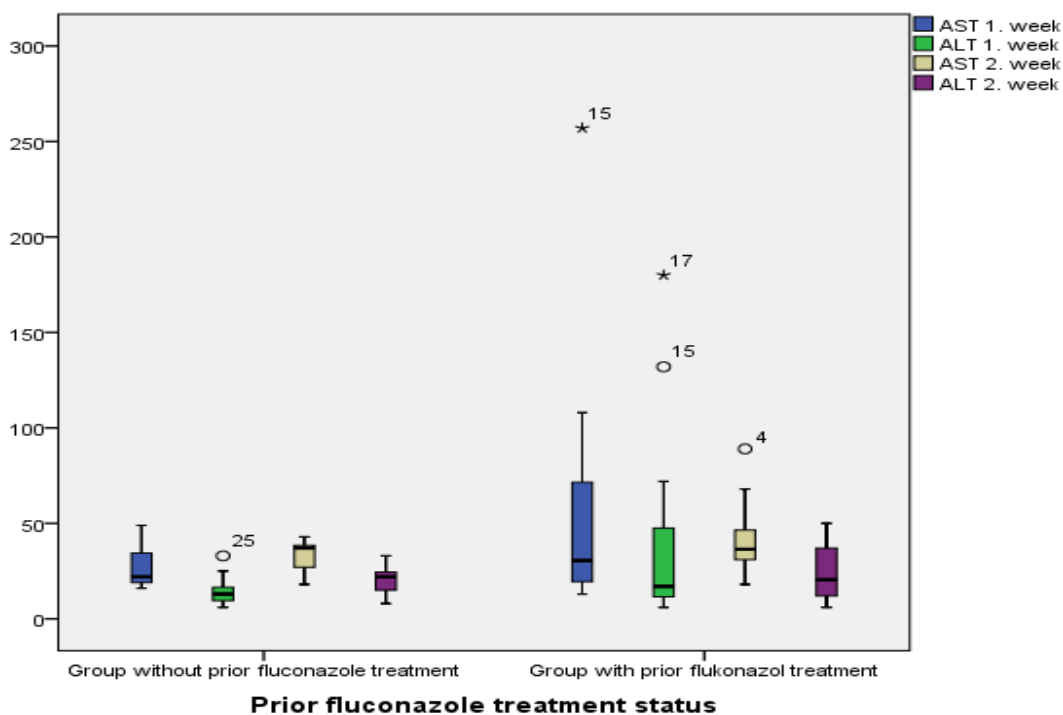


Figure 2. Changes in the serum AST and ALT in the first and second weeks in groups with and without fluconazole treatment.

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Citation: Kamile Arıkan; Oguz Han Kalkanlı; Sebnem Calkavur; Aybü ke Akaslan-Kara; Nuri Bayram; Ilker Devrim. "Safety and Effectiveness of Micafungin in Neonates: A Retrospective Analytical Study from a Tertiary Pediatric Center". *Annals of Neonatology Journal* 2021; 3(2):50-69. doi: 10.21608/anj.2021.74624.1026

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