# Antifungal prophylaxis with micafungin three times a week in children after allogeneic bone marrow transplantation

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**Abstract**

BACKGROUND The use of azoles for antifungal prophylaxis after familial allogeneic stem cell transplantation in children (SCT) is hindered by adverse events and drug interactions especially in children affected by sickle cell disease. Intermittent, higher dose of micafungin could be an alternative. METHODS A prospective, observational, longitudinal, single-center study was conducted between May 2015 and June 2018. The study included 30 patients between 2 and 18 years old who underwent allogeneic SCT and received prophylaxis with micafungin on alternating days after the bone marrow engraftment phase. FINDINGS Fifty transplants performed, 30 included prophylaxis against IFIs, with micafungin in an alternating pattern according to the previously described protocol. The indication for HSCT was hemoglobinopathies in 76.7%, acute leukemia in 20.0% and Fanconi anemia in 3.3%. The prophylaxis duration was 2.33 months (1.53 to 3.98). In our study, 40.0% (12/30) of the patients had acute GVHD, and 6.7% (2/30) had chronic GVHD, which prolonged the duration of alternating prophylaxis. No serious adverse effects of the use of micafungin were observed in any of the patients. There was also no breakthrough Invasive fungal infection (IFI) during alternating prophylaxis. CONCLUSION: In selected patients, micafungin was well tolerated without breakthrough IFI in our study.

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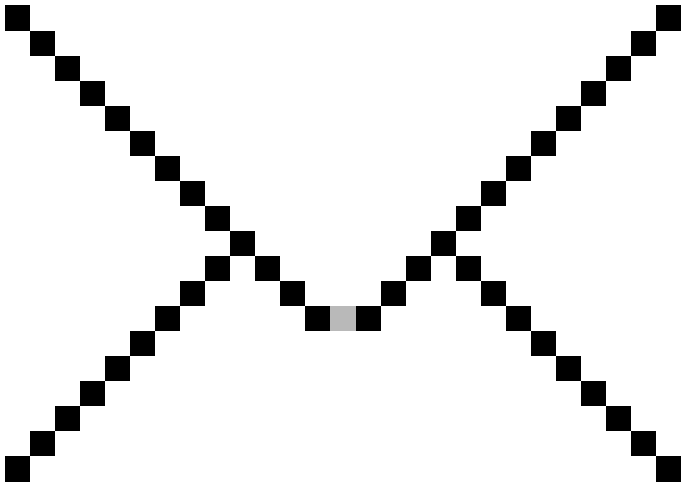

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Abbreviations

| | |
|---|---|
| CLSI | Clinical and Laboratory Standards Institute |
| ECIL-4 | Fourth European Conference on Infections in Leukaemia |
| EMA | European Medicines Agency |
| EORTC/MSG | European Organization for Research and Treatment of Cancer/Mycoses Study Group |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| GVHD | Graft-Versus-Host Disease |
| HPLC | High-Performance Liquid Chromatography |
| HSCT | Hematopoietic Stem Cell Transplantation |
| IFI | Invasive Fungal Infection |
| MIC | Minimum Inhibitory Concentration |
| PD | PharmacoDynamics |
| PK | PharmacoKinetics |
| SCD | Sickle Cell Disease |
| SCT | Stem Cell Transplantation |

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in children with cancer or diseases that require hematopoietic stem cell transplantation (HSCT) for their cure.
- The use of azoles for antifungal prophylaxis after familial allogeneic stem cell transplantation in children (SCT) is hindered by adverse events and drug–drug interactions especially in children affected by sickle cell disease (SCD).
- Some studies suggest the use of micafungin every 48 h as a safe alternative in pediatric patients to facilitate its administration; however, those series are small.

## WHAT THIS STUDY ADDS

In our patients, determinations of serum levels of micafungin were performed and 100% of the levels exceeded the threshold of 0.25 mg/L, regardless of age, weight, administered dose, albumin levels, creatinine and the presence or absence of graft-versus-host disease (GVHD).

The poor interaction of micafungin with other drugs, its safety profile and the administration on alternating days suggest a decrease in toxicity and days of hospitalization, especially for patients with SCD, without an increase in breakthrough on alternating days in pediatric patients.

## ABSTRACT

**BACKGROUND**

The use of azoles for antifungal prophylaxis after familial allogeneic stem cell transplantation in children (SCT) is hindered by adverse events and drug interactions especially in children affected by sickle cell disease. Intermittent, higher dose of micafungin could be an alternative.

**METHODS**

A prospective, observational, longitudinal, single-center study was conducted between May 2015 and June 2018. The study included 30 patients between 2 and 18 years old who underwent allogeneic SCT and received prophylaxis with micafungin on alternating days after the bone marrow engraftment phase.

**FINDINGS**

Fifty transplants performed, 30 included prophylaxis against IFIs, with micafungin in an alternating pattern according to the previously described protocol.

The indication for HSCT was hemoglobinopathies in 76.7%, acute leukemia in 20.0% and Fanconi anemia in 3.3%.

The prophylaxis duration was 2.33 months (1.53 to 3.98). In our study, 40.0% (12/30) of the patients had acute GVHD, and 6.7% (2/30) had chronic GVHD, which prolonged the duration of alternating prophylaxis. No serious adverse effects of the use of micafungin were observed in any of the patients. There was also no breakthrough Invasive fungal infection (IFI) during alternating prophylaxis.

**CONCLUSION:** In selected patients, micafungin was well tolerated without breakthrough IFI in our study.

**INTRODUCTION**

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in children with cancer or diseases that require hematopoietic stem cell transplantation (HSCT) for their cure (1). IFIs in children and adolescents differ in multiple ways from those in adults in terms of epidemiology, diagnostic methods, drug doses, pharmacokinetics (PK), pharmacodynamics (PD) and the absence of clinical trials (2). The highest degree of evidence on IFIs in pediatrics is included in the guidelines of the Fourth European Conference on Infections in Leukemia (ECIL-4) (3).

The incidence of IFI one year after bone marrow transplantation reported in several retrospective series varies between 13 and 20%, with 50-83% mortality. *Candida spp* . and *Aspergillus spp* . are the most common agents causing IFI after HSCT. *Candida spp* . present increased risk during the neutropenia phase posttransplant, while*Aspergillus spp* . present a bimodal distribution, with a first peak at approximately 16 days and a second peak at 96 days after transplantation (4, 5). Recent studies in pediatric patients focus on myeloid and lymphoid leukemia, allogeneic HSCT and/or immunodeficiencies (1).

Our center, a national referral hospital for erythropathology, performs a significant percentage of HSCT in sickle cell disease (SCD) (6). Patients with SCD have vasculopathy, poor tolerance of immunosuppressants and high renal, arterial and neurological toxicity (6-8).

The incidence of IFIs in transplant patients with SCD is currently unknown. Isolated cases have been published in the literature (8-11). Mortality after HSCT is approximately 7%, and infections are the main cause (12). At present, transplantation guidelines recommend the use of antifungal prophylaxis in this population.

A retrospective review of IFI cases in the last 10 years in our center found a cumulative incidence of 15% in pediatric bone marrow transplant patients with different pathologies (13); IFI in other patients at risk was not included.

Voriconazole has been shown to be an effective and safe prophylaxis in the pediatric population and has the advantage of oral administration (3). However, voriconazole interacts with several immunosuppressants.

Molina et al. (14) published a pediatric series in which 17.8% of patients experienced adverse effects associated with its use, leading to longer hospital stays and higher costs of care. Posaconazole has the advantage of oral administration and is the treatment of choice for graft-versus-host disease (GVHD). Its main limitations are its use in patients >13 years and the lack of pharmacokinetic data for pediatric patients, especially in children under 2 years of age (15, 16).

In our clinical experience, the transition to oral azoles after the administration of micafungin in the early phase of HSCT involves a high rate of side effects and the prolongation of hospital stays.

Among echinocandins, micafungin is known for its safety profile; it is a very well-tolerated drug with few side effects (17, 18). Its use for prophylaxis during the hospital phase of transplantation, at a dose of 1 mg/kg/day, has been shown to be at least as effective as fluconazole during the engraftment phase in large prospective studies. However, post- engraftment evidence is still limited, and daily intravenous use negatively affects the quality of life of patients at discharge.

Micafungin as a prophylaxis in HSCT has been shown to be effective in adults and children (5, 17, 19). Current data suggest differences in PK between adults and children. Safety and PK studies in infants, children and adolescents reinforce the use of micafungin for prophylaxis in HSCT in this population (20, 21).

The PK parameters of micafungin have been well-studied in children and depend on age and weight: in younger children, micafungin showed greater clearance, greater volume of distribution and a shorter half-life than in older children.

Some studies suggest the use of micafungin every 48 h as a safe alternative in pediatric patients to facilitate its administration (22-25); however, those series are small. Some PK studies show greater clearance of the drug and volume of distribution according to patient weight. The dose of 3 mg/kg/48 h seems to be the safest and most commonly used in pediatric patients with lower weight and younger age (23).

In adults, Neofytos et al. (26) studied the efficacy of intermittent doses (300 mg of micafungin 2-3 times weekly) in patients with acute leukemia and HSCT. This regimen was well tolerated, with a low incidence (6%) of breakthrough fungal infection.

OBJECTIVE:

To analyze whether the implementation of an antifungal prophylaxis protocol with alternate-day micafungin administration three times weekly (Monday, Wednesday and Friday) after bone marrow engraftment in pediatric transplant patients is a safe practice in terms of toxicity and breakthrough infections in our patients and setting.

## MATERIALS AND METHODS

### Study design

A prospective, observational, longitudinal, single-center study was conducted between May 2015 and June 2018 in the Department of Pediatric Hematology of Gregorio Marañón Hospital, located in Madrid, Spain. The study included 30 patients between 2 and 18 years old who underwent allogeneic bone marrow transplantation and received prophylaxis with micafungin on alternating days after the bone marrow engraftment phase.

### Study population

Inclusion criteria

Pediatric patients requiring antifungal prophylaxis after allogeneic HSCT and bone marrow engraftment.

Patients with toxicity to azoles or amphotericin B requiring a change of therapy.

Age between 2 months and 18 years.

Informed consent from parents or guardians for all patients and informed assent for mature minors (over 12 years) following current regulations (Declaration of Helsinki, Law 14/2007 of July 3 on Biomedical Research).

Exclusion criteria

Severe allergic reaction to micafungin.

Grade 4 toxicity attributable to previous use of micafungin.

Breakthrough IFI during previous use of micafungin.

No informed consent from the patient and/or legal guardian.

**Protocol** (Figure 1)

1. Micafungin was administered at a dose of 1 mg/kg/day as an antifungal prophylaxis starting at the onset of the transplant conditioning regimen and continuing as long as prolonged neutropenia is anticipated.

2. The alternating prophylaxis protocol was initiated after bone marrow engraftment, that is, when patients present sustained neutrophil counts [?]500 according to the following guidelines: - In patients weighing <33 kg: 3 mg/kg/dose on Mondays, Wednesdays and Fridays, with a maximum dose of 100 mg.

-In patients weighing between 33 and 60 kg: 50 mg/dose on Mondays, Wednesdays and Fridays. -In patients weighing >60 kg: 100 mg/dose on Mondays, Wednesdays and Fridays.

The doses were agreed upon with the hospital pharmacy based on existing data in the literature and the available presentation of the drug. In children weighing [?]33 kg, agreement was based on existing publications in pediatrics that suggest maintaining a dose of 3 mg/kg/48 h to minimize the risks of greater clearance and greater volume of distribution described in patients with lower weight (22-24). In patients with a higher weight and older age, the doses were adjusted to those used in the Adult Hematology Unit of the center and reported in studies, that is, an alternating dose of 300 mg/weekly in adults (26).

Administration is performed on Mondays, Wednesdays and Fridays on an outpatient basis.

Drug administration schedule

Micafungin (diluted in 0.9% saline solution to a 1 mg/mL standardized concentration in a horizontal laminar flow booth of the pharmacy department to garantee its adequate sterility (27)) was administered as an intravenous infusion for 1 hour, preferably using an infusion pump. The medication was administered through a Port-a-Cath central line by expert nurses in the department. The solution should be adequately protected from light to prevent its degradation.

Alternating prophylaxis was maintained at least until 75 days after transplantation and was suspended if the patient did not require immunosuppressants and the CD4 count was >400.

In children with GVHD and/or CD4 [?]400, prophylaxis was maintained until the resolution of GVHD, the withdrawal of immunosuppression and/or an increase in the CD4 count.

Serum micafungin levels

Determinations of the valley levels of micafungin were performed in an alternating schedule. Blood was collected into a 5-mL vacutainer tube with heparin as an anticoagulant and was protected from light. The samples were transported under refrigeration to the microbiology laboratory. The plasma was frozen at -80oC until analysis. The concentration of micafungin in human plasma samples was determined by a high-performance liquid chromatography (HPLC) technique with a linearity coefficient >0.99 for the entire concentration range studied, an accuracy of 85-115% and a precision (coefficient of variation) <20% for the intraday and interday variability, respectively, and a limit of quantification of 0.5 mg/L (28).

**Study variables**

The clinical and analytical variables were underlying disease, weight, height, age, sex, dose of micafungin administered and presence of toxicity during the prophylaxis phase.

Adverse events were analyzed according to the NCI Common Terminology Criteria for Adverse Events. Grade I/II allergic reactions consisted of skin reactions, whereas symptomatic bronchospasm requiring parenteral medication and anaphylaxis were graded as grade III and IV adverse events, respectively. Creatinine levels up to 1.5 and >1.5 (3 times the upper limit of normal (ULN)) were categorized as grade I and II adverse events, respectively, whereas levels >3–6 * ULN and >6 * ULN were categorized as grade III and IV adverse events (29).

Breakthrough fungal infection

Additionally, in children with clinical suspicion of breakthrough IFI, blood cultures and/or sterile liquid cultures were performed, as were imaging and galactomannan testing and fungal cultures of bronchoalveolar lavage samples. Galactomannan tests were not used for IFI detection because of their limited usefulness (30). Proven or probable IFIs according to the definitions of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) were considered prophylaxis failure (breakthrough IFI) (31).

**Statistical analysis**

The data were input into IBM SPSS Statistics version 21 and analyzed. Quantitative variables are described as the mean, median, range and interquartile range. Categorical variables are expressed as proportions and percentages. The probability was estimated with a 95% confidence interval. In all tests, a p-value [?]0.05 was considered statistically significant.

**Ethical approval**

This study was approved by the Ethics Committee of Gregorio Maranon Hospital (CEIC-A1; study number GAR-2016-01).

**RESULTS**

Between 2015 and 2018, of a total of 50 transplants performed, 30 included prophylaxis against IFIs with micafungin in an alternating pattern according to the previously described protocol. The underlying disease and patient characteristics are shown in Table 1. Fifty percent (15/30) of the patients were male, and the remaining were female. The median age at the start of prophylaxis was 5.82 (3.14-9.80) years, and 70.0% (21/30) of patients were under 8 years old. Regarding weight, 87.1% weighed <33 kg. The indication for HSCT was hemoglobinopathies in 76.7% (23/30), acute leukemia in 20.0% (6/30) and Fanconi anemia in 3.3% (1/30). The donor was a family member in all cases an HLA-identical sibling in 93.3% (28/30) and an HLA-haploidentical sibling in 6.7% (2/30) of cases. The source of the transplant was bone marrow in 90.0% and apheresis in 10.0%.

In 80.0% of the patients, the alternating Monday-Wednesday-Friday schedule was followed, with doses adjusted according to weight after bone marrow engraftment. In the remaining 20.0%, treatment with azoles (voriconazole or posaconazole) was initiated at discharge due to GVHD, with a switch to alternating micafungin due to azole toxicity, presenting as severe renal insufficiency and cutaneous symptoms. The immunosuppressant treatments were primarily cyclosporine, mycophenolate mofetil, tacrolimus and/or sirolimus.

The prophylaxis duration was 2.33 months (1.53 to 3.98). In our study, 40.0% (12/30) of the patients had acute GVHD, and 6.7% (2/30) had chronic GVHD, which prolonged the duration of alternating prophylaxis. No serious adverse effects of the use of micafungin were observed in any of the patients. There was also no breakthrough IFI during alternating prophylaxis.

Determinations of serum levels of micafungin were performed in 14 patients. In these patients, 100% of the levels exceeded the threshold of 0.25 mg/L, regardless of age, weight, administered dose, albumin levels, creatinine and the presence or absence of GVHD.

Compliance was adequate in all patients.

The statistical comparison tests did not show significant differences in micafungin levels according to patient weight (considering different cut-off points for weight (20, 25, 33 kg) (p = 0.819, p = 0.533, p = 0.825). There were also no significant differences in micafungin levels found between patients who developed GVHD and those who did not (p = 0.28).

There was no significant correlation between age (cut-off point 8 years) and serum micafungin levels (Z = -1.292, p = 0.196).

Likewise, when investigating whether albumin levels may explain differences in the levels of micafungin determined over time, the association was not significant (p = 0.841, p = 0.726, p = 0.870 p = 0.873, respectively). The same was true for creatinine levels, although high levels of micafungin were found to coincide with renal failure (Table 2). A 19-year-old patient had a micafungin level of 18.21, creatinine of 3.23 mg/dL and a glomerular filtration rate (GFR) estimated by cystatin of 32 mL/min/1.73 $m^2$. A 7-year-old girl had a micafungin level of 12.50, a creatinine level of 1.03 mg/dL and GFR estimated by cystatin of 51 mL/min/1.73 $m^2$. A 1-year-old girl had a micafungin level of 9.30, a creatinine level of 0.54 mg/dL and a GFR estimated by cystatin of 53 mL/min/1.73 $m^2$.

## DISCUSSION

In children, primary antifungal prophylaxis is indicated in HSCT (4, 5, 18, 21). Echinocandins are among the drugs available for this indication. Micafungin has been the only echinocandin authorized for pediatric use since 2008 by the European Medicines Agency (EMA). Its main disadvantage is its exclusively intravenous use. Micafungin exhibits linear PK, and the steady state is typically reached in 4 or 5 days.

The usual practice at the center for patients undergoing allogenic HSCT consisted of initial prophylaxis with micafungin at a dose of 1 mg/kg/day during the conditioning phase and until bone marrow engraftment, followed by oral azoles at discharge. In recent years, after an increase in the number of transplants in patients with SCD (approximately 10-15 transplants/year), we observed an increase in drug toxicity derived from the interactions of azoles with immunosuppressants, which are poorly tolerated in this population, with prolongation of hospital stay, viral reactivations and undesirable GVHD in SCD. This has led many clinicians to seek alternatives and explore the use of prophylaxis on alternating days.

There are studies in adults and children on the PK and PD of micafungin that reinforce the safety of these regimens. Muilwijk et al. (32) published a randomized multicenter study of 20 adult patients in which they found, from the PK/PD standpoint, that administering micafungin 300 mg twice weekly is equivalent to the administration of micafungin 100 mg once a day. Neofytos et al. published a series of 75 adult patients undergoing allogeneic bone marrow transplantation or with leukemia who received 300 mg micafungin three times weekly without adverse effects at the hepatic or renal levels, with an incidence of breakthrough IFI of 6% (26).

The administration of micafungin 3-4 mg/kg/day every other day has been shown to be safe in some pediatric series (17). Although Metha et al. (25) found that the micafungin levels reached at 48 h were greater than 0.2 mcg/mL, they concluded that after adjustment for high protein binding, the free micafungin concentrations were only suitable for highly susceptible fungal species. Recent studies suggest that a regimen of 5 mg/kg every 72 h is adequate (33).

To our knowledge, this is the largest series on alternating prophylaxis in pediatric patients. It also shows the safety of the drug when administered at different doses according to weight and pharmaceutical presentation. Most of the patients were children weighing <33 kg, and 87.1% received doses of 3 mg/kg. To date, no serious adverse effects or hepatic toxicity has been observed. There have not been any breakthrough IFIs. In this sense, our work raises the question of whether the population with SCD, which comprised the majority of the series, presents the same risk of IFI during and after HSCT as pediatric patients with malignant hematological disease. Although the use of double immunosuppression to avoid graft failure suggests that the risk is similar, the data that currently exist do not resolve this issue, and randomized studies are needed. The incidence of

IFI in this population is unknown, although there are some case reports on HSCT. Publications with large series of transplant patients with SCD do not make reference to this complication or did not have cases of IFI (8, 10).

The incidence of breakthrough IFI in pediatric patients was described recently in a retrospective study that identified 8 pediatric patients (2.4%) out of 319 cases treated with micafungin who had breakthrough IFI by *Candida.* In 7 of the cases, the species was *C. parapsilosis.* The minimum inhibitory concentration (MIC) was susceptible ([?] 0,01 mg/L) in all cases (34). Chan et al. (35) described a study that examined adult patients on prophylaxis with echinocandins with an incidence of breakthrough IFI by *Candida spp.* of 1.5%. Pfeifer et al. (36) reported an IFI incidence of 1.8% in 649 adult patients treated with micafungin 100 mg/day for different indications. The main pathogens were wild-type *C. glabrata* and *C. parapsilosis.* The prospective multicenter OLYMPE study (NCT02127788) found an IFI incidence of 13.1% in patients of all ages after HSCT (37).

Micafungin has been shown to be a suitable drug against the most common species of *Candida,* including *Candida albicans* ,*Candida glabrata* and *Candida tropicalis* , all of which have a MIC [?] 0.06 mg/L. Higher values have been observed for *Candida parapsilosis* (0.25-2 mg/L) and *Candida guilliermondii* (0.5-2 mg/L), although the clinical impact of this observation is doubtful.

The MIC of micafungin in the 150 cases of pediatric IFI by*Candida* species in our hospital during the study period reveals a $MIC_{50}$ of 0.015 mg/L and a $MIC_{90}$ of 2 mg/L for micafungin, the most prevalent species being *C. albicans*and *C. parapsilosis* . No resistance was observed. In the case of *Aspergillus* , the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) report a lack of evidence to determine MIC cut-offs (37,38), but there are publications that set cut-offs at 0.0125 mg/L for the most common species (39).

In 14 of the 30 analyzed cases in which micafungin levels were determined, we found no difference in children when the levels were correlated with weight, age and albumin values. Despite the different doses administered and the heterogeneity of the analyzed group, in 100% of the cases in which serum levels could be determined, they were above 0.25 mg/L, and in 10/14 (73%), serum levels exceeded the 2 mg/L cutoff for *C. parapsilosis* suggested in the reference methods (EUCAST) (38).

At present, serum levels of micafungin are not monitored for clinical purposes of dose adjustment since there is no evidence of the relationship between micafungin levels and clinical response and/or toxicity, for which PK/PD studies would be necessary. Our study is not intended to be a PK study (41).

The poor interaction of micafungin with other drugs, its safety profile and the administration on alternating days suggest a decrease in toxicity and days of hospitalization, especially for patients with SCD, without an increase in breakthrough on alternating days in pediatric patients.

## AUTHORSHIP CONTRIBUTIONS & CONFLICT OF INTEREST

All authors approved the manuscript and this submission. The authors have nothing to disclose.

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**TABLES**

| | |
|---|---|
| Age in years - Median (range) | 5.82 (3.14-9.80) |
| Sex | Female 15/30 (50.0%) |
| Weight (kg) Median(range) | 23 (14.4-29.7) |
| Underlying disease: N (%) | Hemoglobinopathies: 23 (76.7) |
| | Fanconi Anemia 1 (3.3) |
| | Acute lymphoblastic leukemia 4 (13.3) |
| | Acute myeloblastic leukemia 2 (6.6) |
| Conditioning regimen N (%) | Myeloablative: 28 (93.3) |
| | Non myeloablative: 2 (6.7) |
| HSCT recipient N (%) | HLA identical: 28 (93.3) |
| | Haploidentical: 2 (6.7) |
| Acute graff vs host disease Grade 2 o higher N (%) | Acute: 12 (40.0) |
| | Chronic: 2 (6.7) |
| Previous prophylaxis N (%) | Micafungina 1mg/kg/24h: 26 (86.6) |
| | Azoles: 4 (10.0) |
| Reason change N (%) | Infection: 0 (0.0) |
| | Azols toxicity: 4 (13.3) |

TABLE 1. Characteristics of patients

| Age (years) | Gender | Weight (kg) | Underlying Condition | HSCT recipient | GVHD | Cr (mg/dl) | L1 (mg/l) | L2 (mg/l) | L3 (mg/l) |
|---|---|---|---|---|---|---|---|---|---|
| 5 | M | 14 | Fanconi anemia | AMR | No | 0,31 | 0,89 | 1,39 | 0,74 |
| 6 | F | 18,6 | Sickle cell disease | AMR | No | 0,37 | 1,64 | 0,81 | 2,27 |
| 1.4 | M | 11 | AML | AMR | Yes | 0,54 | 3,16 | 9,5 | 4,73 |
| 9 | F | 26 | Sickle cell disease | AMR | No | 0,34 | 2,9 | 3,48 | 5,8 |
| 2.6 | M | 14,3 | Sickle cell disease SS | AMR | No | 0,3 | 0,59 | 2,2 | 2,73 |
| 4 | M | 18 | Sickle cell disease | AMR | No | 0,25 | 2,46 | X | X |
| 3 | F | 20,7 | Sickle cell disease | AMR | No | 0,67 | 0,69 | 3,75 | 4,04 |
| 19 | M | 70 | ALL | Haploidentical | Yes | 3,2 | 18,21 | X | X |
| 10 | F | 29 | Sickle cell disease SS | AMR | No | 0,66 | 1,94 | 0,62 | 3,8 |
| 7 | F | 26 | Sickle cell disease | AMR | No | 1,03 | 0,92 | 2,59 | 7,74 |
| 12 | F | 38 | Sickle cell disease | AMR | No | 0,6 | 1,32 | 2,04 | 4,13 |
| 9 | F | 30 | Sickle cell disease | AMR | No | 1,02 | 0,92 | X | X |
| 6 | M | 30 | ALL | AMR | No | 0,46 | 2,32 | 1,7 | X |
| 11 | M | 26,8 | Sickle cell disease | AMR | No | 0,41 | 4,2 | 0,72 | X |

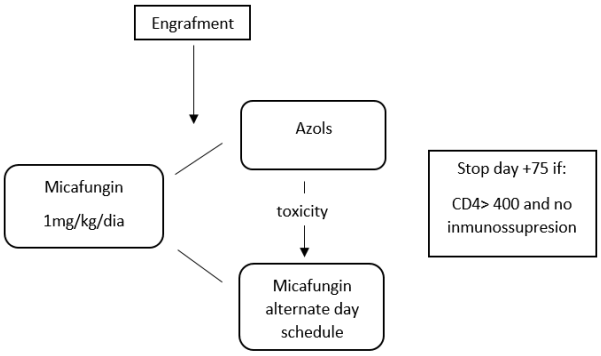
TABLE 2. Characteristics of children with micafungin levels

AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; AMR: Allogenic matched related; Cr: creatinine; L1: level of micafungin week 1; L2: level of micafungina week 2; L3: level of micafungin week 3; L4: level of micafungin week 4; X: not available

## FIGURE LEGENDS

Figure 1. Treatment Scheme Chart

FIGURE 1 Treatment scheme chart.

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