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The use of micafungin in neonates and children: A systematic review

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Abstract

About 10% of newborns under 1000 g have problems related to candidiasis. The mortality rate is still very high today, and new types of drugs are used for the treatment. To this end, the researcher conducts a systematic review concerning the clinical use of the micafungin drug in children and its impact regarding cost-effectiveness. The research used the PRISMA statements methodology to include all clinical and economic findings concerning the treatment of candidiasis through micafungin in infants and children. The research considers 13 clinical sources related to the use of micafungin belonging to the echinocandin family and a source of an economic nature. As highlighted by the research, micafungin is used in neonates for candida treatment [illegible] in children, [illegible] ment period between 5 and 45 days. The use and efficacy of micafungin are features validated by several international clinical trials, success rates and conclusions confirm its validity. The analysis present in the literature on costs highlights how this disease is associated with higher costs due to the high number of days of hospitalization and for the administration of the drug.

Key words: micafungin, neonates, children, cost-effectiveness

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1. Introduction

Candidiasis management can occur using different pharmaceutical therapies. According to the paper by Santolaya et al. (Santolaya et al., 2013; Santolaya Maria E. et al., 2013), the choice is based on the clinical background of the individual patient, the level of disease spread and the existence of other risk factors. Several drugs can be used in the treatment of candida. The first type refers to medications belonging to the antimycotic class of triazole, which includes fluconazole which is administered orally (Greenberg & Benjamin, 2014). The further possibility is given by antifungal therapies (caspofungin, anidulafungin, and micafungin).

In particular, micafungin is a semi-synthetic lipopeptide antifungal, it belongs to the class of echinocandins (Sucher et al., 2009) and it is produced by modifying the fermentation of "*Coleophoma empetri*" (Buck M., 2014). Its use is implemented in newborns and pediatric children with candidiasis by intravenous infusion throughout 60 minutes. The single daily dose of the drug allows to have a low rate of adverse events in patients (Smith et al., 2009). The drug has been shown to have a broad spectrum of efficacy against candida (Manzoni et al., 2014).

Patients with candida generally present a clinical picture aggravated by low immunocompetent defences. For this reason, often the medical staff is forced to invasive procedures such as the using of external oxygen, central venous catheters, endotracheal tubes, broad-spectrum antibiotics, high doses of corticosteroids (Manzoni et al., 2014).

In newborns, the most severe risk cause for candidiasis is age (Santolaya et al., 2013). The incidence of the disease for newborns weighing less than 1000 g is around 10% (Benjamin et al., 2010); the mortality rate in the case of age <28 weeks and <1000 g is between 40-50% of cases (Benjamin et al., 2004, 2006; Makhoul et al., 2002).

For children older than 28 weeks and up to 18 years, the main risk factor for candidiasis infection is cancer (Blyth et al., 2009). In addition to this, the disease occurs in the case of prolonged treatments that cause severe mucositis neutropenia, patients undergoing induction of acute myeloid leukemia, non-Hodgkin's lymphoma, patients in post-transplantation of bone marrow with a myeloablative regimen (Santolaya Maria E. et al., 2013). An increased risk can also be brought about by inherited immune disorders (Hill, 1998). For this evidence, candidiasis is one of the significant causes of morbidity and mortality, particularly in the case of invasive candidiasis (Steinbach, 2016).

For this evidence, candidiasis is one of the significant causes of morbidity and mortality, particularly in the case of invasive candidiasis (Steinbach, 2016).

One of the features of candidiasis in pediatric age is that it has higher rates of aggression towards subjects already in critical condition, this leads to a mortality rate of 10% (T. Zaoutis, 2010).

This situation has a particular impact on the economic management aspects of healthcare companies. In many cases, the days of hospitalization are prolonged for an

average period of 21.1 days, which creates an average increase in hospital costs of $ 39.331 (T. E. Zaoutis et al., 2005).

The systematic review intends to give a clinical and economic vision to the use of micafungin in newborns and children under the age of 19.

2. Materials and methods

The systematic research was set up according to the criteria of the Preferred Reporting methodology items for Systematic reviews and Meta-Analyses (PRISMA) statements (Liberati et al., 2009).

The search for results took place in October and November 2018 by questioning the PubMed and Scopus platforms.

For the selection of results, the team independently used the following keywords: Micafungin AND Infants, Micafungin AND cost-effectiveness AND Infants, Micafungin AND costs AND Infants, Micafungin AND cost-effectiveness.

The collection of references used the following criteria:

-papers are written in Italian, English or Spanish;
-publication date from 2005;
-papers on patients of child and/or pediatric age, both clinical and economic;
-reading of the title and the abstract.

Inversely, the following exclusion criteria were used:

-articles that consider the risk of infection exclusively and not the clinical and/or economic aspect;

- articles with analysis exclusively for adults.

The choice that has been made, due to the lack of cost-effectiveness analysis of the treatments, has been to include in the same article both clinical and economic elements.

For the selection of clinical cases, the research team reported in Table 1 the information present in the sample of selected articles. The Table shows the number of clinical cases analysed, the country, the population target divided among newborns or infants, the progress of the disease, the dose of the administered drug, additional information regarding the type of patient and weight (when available), the duration of the treatment, the success rate/conclusion of the study in question.

The selection of causes related to the cost-effectiveness of micafungin treatment, in Table 2, included information regarding the country, the age of patients, the number of patients, the minimum and the maximum number of days of hospitalization and the minimum and maximum increase of costs incurred by hospitals.

3. Results

Systematic research has obtained 599 results.

After selecting the articles according to the inclusion criteria above, 22 sources were selected for full reading (Figure 1). Of these 8 were double; 14 articles were valid for inclusion in the systematic review (Arrieta et al., 2011; Bochennek et al., 2015; Buck M., 2014; Hope et al., 2010; Kawaguchi et al., 2009; Kobayashi et al., 2015; Kovanda et al., 2018; Maximova et al., 2017; Queiroz-Telles et al., 2008; Santolaya et al., 2013; Santolaya Maria E. et al., 2013; Smith et al., 2009; Styczynski et al., 2016).

The selection of the keywords did not allow to find a sufficient study sample concerning the cost-effectiveness of the administration of micafungin in the case of infants and children. In one case, explicit reference is made to the issue of economic evaluation; the result will be presented in table 2.

Figure 1. Flow of literature review

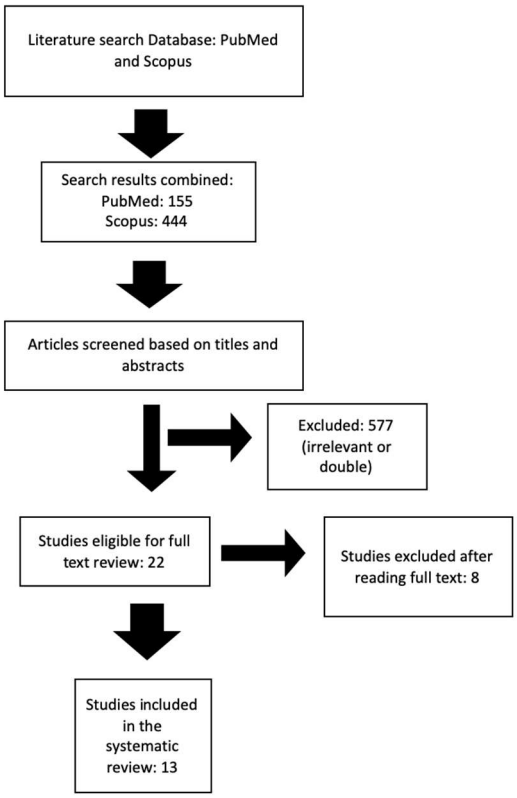

Figure 1. Flow chart of the included and excluded studies. Information flow chart of the different steps of the systematic review.

For a more proactive analysis, we believe it is useful to start with the target of the population as the reference benchmark (except for the case presented by Buck M. (Buck M., 2014), in which we will first refer to the subdivision of patients' weight). From this element it will then be possible to activate further verification elements that include the number of clinical cases, the degree of spread of the disease, the dose of the administration, the additional information (weight or presence of particularities in the

administration), duration of treatment, the rate successful with relative conclusion of the clinical trial. Finally, the year of publication of the results will be highlighted.

First of all, the articles retrieved consider as "infants" the subjects between 3 days and 28 weeks after birth. In this population, the presence of candidiasis provides a treatment between 0.4 and 10 mg/ kg/day. The treatment period is between 1 and 34 days with a more used treatment period of 15 days. The clinical trial establishes the good tolerability of the drug. It must be considered the heterogeneity of the studies. For example, the research of Arrieta et al. (Arrieta et al., 2011) includes 40 % of patients with neutropenia, while in other studies the range of weight of subjects examined was very different. In the analysis of Kawaguchi et al. (Kawaguchi et al., 2009) the range of weight was 579.3 g (± 80.5 g) with a while in the analysis of Kovanda et al. (Kovanda et al., 2018) it is between 0.5 and 4.8 kg.

If the disease has a more advanced and systemic stage of development there is a remodeling of the treatments; in particular, the treatment involves a higher dosage between 8-15 mg/kg /day. Again, it must be taken into account the heterogeneity of studies retrieved.

The research of Hope et al. (Hope et al., 2010) considering newborns with a weight between 640 g and 4615 g, the doses of micafungin administered are divided between loading dose equal to 15 mg/kg/day and 10 as loading dose equal to 10 mg/kg/day, the period of administration is between 5 and 45 days. The therapy did not present any adverse events.

In the case of Maximova et al. (Maximova et al., 2017), the average weight is 3240 g with a treatment administered in patients three days after allogeneic stem cell transplantation the micafungin was administered for doses between 8 and 15 mg/kg/day, the success rate of the therapy was equal to 78.20%. Santolaya et al. (Santolaya et al., 2013), instead, considered patients are weighing more than 1000 g, and the treatment in these subjects was given at a dose of 15 mg/day for seven days (Queiroz-Telles et al., 2008), the success rate of therapy was 57,10%.

In case of suspected systemic infection, the dose is 15 mg/ kg/day, the weight of the newborns is 775 g with a treatment of 5 days (Smith et al., 2009).

The sample of clinical trials concerning pediatric patients covers a period of birth from 2 months to 18 years. In the case of candidiasis, the conventional treatment is between 0.8 and 7.7 mg/ kg/day with a duration between 15 and 19.7 days. The success rate for Arrieta et al. (Arrieta et al., 2011) it is not shown but as the authors say, micafungin was well tolerated by children of all ages, for Kobayashi et al. (Kobayashi et al., 2015) is 88,20%, in the case of Queiroz-Terres et al. (Queiroz-Telles et al., 2008) is 72,90%.

In evidence of increased invasiveness of candidiasis, research in the literature suggests a dose of micafungin ranging from 2 to 6 mg/ kg/day. Invasive candidiasis is usually associated with hospitalized patients who have undergone surgery and who have been given broad-spectrum antibiotics. Indeed, in the research of Santolaya Maria E. et al. (Santolaya Maria E. et al., 2013) the minimum dose that is administered is 2 mg/kg/day, but in case of non-response to treatment, it is possible to increase it with 4 mg/kg/day

others. This applies to patients weighing less than 40 kg, plus in this case, the successful treatment occurs 14 days after the first negative hemoculture. The duration of the treatment is between 14 and 313 days.

Then there are clinical cases involving patients with pediatric hemato-oncology (PHO) and hematopoietic stem cell transplantation (HSCT).

The research of Steinbach (Steinbach, 2016) considered patients with PHO. The administration of micafungin was made for doses ranging from 1 to 2 mg/kg/day for 11 days; in 63 patients already treated for 4.2 months with acute leukemia therapy. The doses of micafungin administered in these patients ranged from 1 to 2 mg/kg/day for 11 days, and the success rate was around 85%. Even, the research of Steinbach (Steinbach, 2016) included pediatric patients in HSCT, the therapy based on micafungin is between 1 and 2 mg/kg/day for a period of administration of 15 days. In that study, the 30 patients came from 2.3 months of treatment for HSCT, and the success rate of micafungin treatment was 60%. Also, the research by Bochennek et al. (Bochennek et al., 2015) refers to children treated for Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), and acute high-risk relapse, as well as children undergoing allogeneic hematopoietic stem cell transplantation. In this case, the administration does not take place through daily intravenous infusions, but biweekly, this element represents the exception compared to other studies. The dose, in this case, is 3-4 mg/kg/day.

The evidence of Buck M. (Buck M., 2014) refers to a trial of the University of Virginia School of Medicine, in particular, is made to the classification of patient weight and pharmacokinetic data, in particular, the study concerning the use of micafungin takes into account children (from 4 months to 16 years) with a weight of less than 30 kg. In the first case the dose of the drug was daily and equal to 1, 2, 3 mg/kg/ day; children weighing more than 30 kg received a daily dose of 1, 2, 2.5 mg/kg/ day. Our systematic review also includes the elements of evaluation concerning the cost-effectiveness of the treatment (table 2). This information makes it possible to verify the number of resources invested in the treatment of candidiasis. The economic information allows evaluating the concept of efficiency understood as the maximum value obtainable and the result achieved for each unit of expenditure (Zilberger M. D. & Shorr A. F., 2010). The search criteria used allowed to obtain only one result referred to the cost-effectiveness in the use of micafungin. According to the analysis by Santolaya Maria E. et all. (Santolaya Maria E. et al., 2013) which considers 1118 hospital admissions for candidiasis, children suffering from this disease have a time of hospitalization equal to 44.8 days against an average period of 23.7 days in case of absence. The value of direct and indirect costs for a patient with candidiasis is $ 183,645 compared to a cost of $ 91,379 for patients hospitalized but without candidemia (T. E. Zaoutis et al., 2005). This creates an increase in hospitalization days averaging 21.1 and costs of $ 92.266. In the end, the research team provides a timeline of the analyses included in the systematic review. In the case of newborns, 50% of the results are before 2013, and only 3 elements are more recent. Studies concerning the use of micafungin in pediatric age, on the other hand, confirm greater attention in recent years, in particular, 75% of the results were published after 2013, only 25% before this year.

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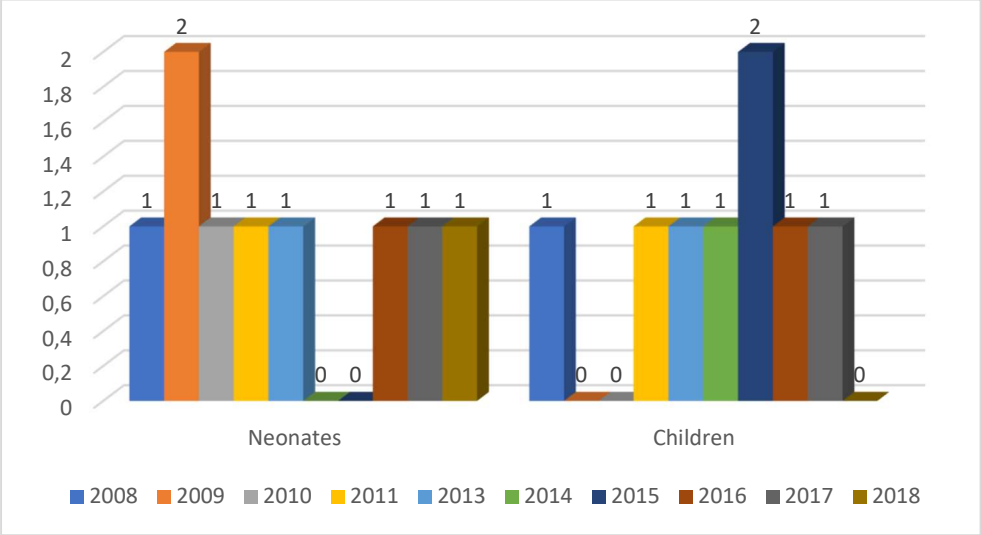

Figure 2.— Search results per year

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Table 1. Studies characteristics for micafungin in neonates and children. The table summarizes the main characteristics of the different studies regarding the number of clinical studies, country, target population, stage of disease, micafungin dose, additional information, duration of treatment, successful rate/conclusion and year.

Source	Number of clinical studies	Country	Target population	Stage of disease	Micafungin dose	Additional information	Duration of treatment	Successful rate - Conclusion	Year
(Arrieta et al., 2011)	296	Europe, USA and Asia	Neonates: < 4 weeks and Children (0 - 16) years	Candidiasis	0.4 - 8.6 mg/kg/day and 0.8 - 7.7 mg/kg/day	40% of patients are neutropenic	15 days	Micafungin was well tolerated by children at all ages including those with life-threatening underlying conditions.	2011
(Bochennek et al., 2015)	21	UK	Children (0.2 - 16) years	Invasive fungal disease	3 - 4 mg/kg/twice weekly	Na	20 - 313 days	Approved dosages	2015
(Buck M., 2014)	229	USA	Children (4 months - 16 years)	Candidadias (Acute, Esophageal, Infections in HSCT Recipients)	1 - 2 - 3 mg/kg/day and 1 - 2 - 2.5 mg/kg/day	Weight < 30 kg and Weight > 30 kg	Na	Na	2014
(Hope et al., 2010)	47+18	UK	Neonates 26.8 weeks and Infants	Systemic candidiasis Suspected or proven disseminated candidiasis	Loading dose 15 mg/kg/day - maintenance dose 10 mg/kg/day (neonates) 0,75 - 15 mg/kg/day (infants)	Weight: 640.0–4615.0 g (Neonates) Weight: 0.54 - 4.5 kg (Infants)	5 days - max 45 days (validated by the doctor and based on maintenance dose) for Infants	No adverse event associated (neonates) - 82,6% (infants)	2010

Table 1. Continued.

Source	Number of clinical studies	Country	Target population	Stage of disease	Micafungin dose	Additional information	Duration of treatment	Successful rate - Conclusion	Year
(Kawaguchi et al., 2009)	4	USA	Premature Neonates mean 27weeks 0.9 - 24,1 weeks	Premature infants diagnosed with Candida infections	0,5 - 1.0 mg/kg/day	Weight: 579,3 g (± 80.5 g)	3.1 - 9.8 days	Effective and tolerable	2009
(Kobayashi et al., 2015)	201	Japan	Children (0 - 16) years	Candidiasis	1 mg/kg/day up to 6 mg/kg/day	Na	19.7 days	88,20%	2015
(Kovanda et al., 2018)	12+27	Europe	Neonates (3 - 119) days	45% of invasive candidiasis	2 - 10 mg/kg/day	Weight: 0.5 - 4,8 kg	1 to 34 days (14 days)	73% - 83%	2018
(Maximova et al., 2017)	47+18	Italy	Children (0 - 17) years - Neonates mean 2.33 months	Hematopoietic stem cell transplantation (HSCT) patients - Systemic candidiasis	mean 105.9 +- 28.9 mg/m2/day - 8 - 15 mg/kg/day	Treatment with micafungine began 3 days after transplantation - Weight: 3,24 kg	13.1 - 30.1 days	87,2% (children) - 78,20% (infants)	2017
(Queiroz-Telles et al., 2008)	48	USA	Neonates and children (0 - 16) years	Na	2 mg/kg/day	Na	15 days	72,90%	2008

Table 1. Continued.

Source	Number of clinical studies	Country	Target population	Stage of disease	Micafungin dose	Additional information	Duration of treatment	Successful rate - Conclusion	Year
(Santolaya Maria E. et al., 2013)	88	Latin America	Children (0,2 - 18 years)	Invasive; after 4 days of antibacterial therapy that continued with fever and neutropenia	2 mg/kg/day if the body weight is <=40 kg	The study recommends that the dose can be increased up to 4 mg / kg / day if the response to the drug is not appropriate for patients weighing <= 40 kg.	14 days after the first negative blood culture and after the clinical resolution of the infection.	Na	2013
(Santolaya et al., 2013)	213	Latin America	Neonates <= 28 days	Invasive	0,75-3.0 mg/kg with a body weight >1000 g (Heresi et al., 2006)	15 mg/kg/day once daily, success treatment in 7 days (Queiroz-Telles et al., 2008)	14 days after the first negative blood culture and after the clinical resolution of the infection.	57,10%	2013
(Styczynski et al., 2016)	12	USA	Neonates mean 27weeks	Suspected systemic infections	15 mg/kg/day	Weight: 775 g	5 days	Na	2009
(Styczynski et al., 2016)	63+30	Poland	Children (0,1 - 19) years and Children (0,2 - 17,8) years	Pediatric hemato-oncology (PHO) and Hematopoietic stem cell transplantation (HSCT) patients	1 - 2 mg/kg/day	The 63 patients come from 4.2 months of acute leukemia therapy, while the other 30 comes from 2.3 months of cure for HSCT.	11 days (PHO) and 15 days (HSCT)	85% (PHO) - 60% (HSCT)	2016

Table 2. Economic evaluations referred to micafungin treatment for pediatric patients.

			Increase days of hospitalization		*Increase in total per-patient hospital charges*			
Source	**Country**	**Age**	**Hospital admission**	**Number of days minimum**	**Number of days maximum**	**Minimum value**	**Maximum value**	**Year**
(T. Zaoutis, 2010)	USA	1 to 18 years old	1118 patients	14.4	27.8	65,058$	119,474$	2005

4. Discussion

The 13 medical articles characterize the scientific evidence and focus exclusively on the clinical features related to the diagnosis and pharmacokinetics of micafungin. The intrinsic nature and the applicability of the drug have allowed creating different interpretations to study the effects of children both in neonatal and pediatric age.

The analysis reported studies that selected patients not only under conditions of stable candidiasis but also invasive or exposed to organ transplants or neutropenic patients.

The articles that analyse in their studies the effects of the drug in newborns consider a period of birth between a few days and 24 weeks (Arrieta et al., 2011; Hope et al., 2010; Kawaguchi et al., 2009; Kovanda et al., 2018; Maximova et al., 2017; Queiroz-Telles et al., 2008; Santolaya et al., 2013; Smith et al., 2009; Steinbach, 2016) and reflect a level of administration up to 10 mg/kg/day.

Only two results deal with the analysis and efficacy of micafungin in infants younger than one month of life (Kovanda et al., 2018; Santolaya et al., 2013), in these cases the initial dose is fixed in 2 mg/kg/day with a possible increase up to 15 mg/ kg/day in order to mitigate the risks from overexposure to candidiasis (Queiroz-Telles et al., 2008). The frequency of drug administration in these results is always daily.

The remaining sample deals with effects in children aged one to 19 years (Arrieta et al., 2011; Bochennek et al., 2015; Buck M., 2014; Kobayashi et al., 2015; Queiroz-Telles et al., 2008; Santolaya Maria E. et al., 2013; Styczynski et al., 2016). These cases have lower amounts of drug intake compared to newborns; inversely there is an increase in the duration of treatment. The reported cases present a frequency of administration mostly daily with a single bi-weekly administration element.

In addition, the two articles of Santolaya Maria E. et al and Santolaya et al. (Santolaya et al., 2013; Santolaya Maria E. et al., 2013) discuss the direct issue of the treatment of candidiasis in infants and children respectively in the case of standard prophylaxis, and in case of invasive treatments for advanced diseases. The approach that is shown, in a first phase, in fact, consists in a real action of detecting risks and subsequently mitigating them; key elements to reducing the incidence of the disease and associated costs (T. E. Zaoutis et al., 2005).

The main limitation of the study consisted of the low number of cost-effectiveness analyses not yet present for the target object of study. The economic analysis in these cases allows to evaluate better and make decisions essential for the correct application of care; even in the healthcare world, economic analysis can support choices, especially in a context of scarcity of resources (Zilberger M. D. & Shorr A. F., 2010).

5. Conclusions

The condition of candidiasis still shows a very high percentage of incidence, the most worrying values concern the newborns who have mortality rates between 40% and 50%.

The use of echinocandins including micafungin allows clinicians to manage the disease and obtain response rates that increase in the case of initial and newly diagnosed candidiasis and decrease for the most severe cases.

What emerges from the literature included in the systematic analysis is a high and multidimensional clinical knowledge regarding neonatal and pediatric age that also includes invasive levels of elevated candidiasis. A different case is the analysis of cost-effectiveness, limited in this case to a single result which, however, shows how the incidence of the disease leads to an increase in hospital management costs of 49.76% compared to non-patients. affected by this pathology; this, therefore, involves very high costs due both to the increase in the days of hospitalization of patients and to the administration of micafungin (T. E. Zaoutis et al., 2005).

The aim of the research was to highlight how the drug is used in infants and children and what hospital costs are associated with candida treatment.

In conclusion, the review highlights that:

- micafungin is used in newborns to treat candida with a dose between 0.4 and 10 mg/kg/day on average for 15 days;
- micafungin is used in newborns with invasive candida with a higher dose of between 8 and 15 mg/kg/day with a treatment period varying between 5 and 45 days;
- micafungin is used in children with candida with a dose between 0.8 and 7.7 mg/kg/day with a duration between 15 and 19.7 days. This also happens in the case of invasive candida but with a treatment period between 14 and 313 days;
- the cost-effectiveness analysis shows that the incidence of costs for candidiasis cases is about 50% higher compared to neonatal and pediatric patients not affected by candidiasis (T. E. Zaoutis et al., 2005);
- the high rates of mortality and high costs require the adoption of effective measures to prevent and treat the disease.

What is hoped for is to provide a more comprehensive picture of the use of the drug from a clinical point of view; the aim is to act promptly to eradicate the disease by increasing patients' survival and decreasing the associated costs.

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