

REVIEW

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## Invasive Fungal Infections in Infants—Focus on Anidulafungin

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### Abstract

**Introduction:** Invasive fungal infection in pediatric intensive care units (PICU) is a rising challenge. *Candida* species are the most common microorganisms in these infections. Due to growing resistance against fluconazole, echinocandins are being used for the appropriate therapy. However, the recent IDSA guidelines recommend them only in cases where fluconazole or Amphotericin B cause treatment failure or are contraindicated. In a literature review, the importance of invasive fungal infections in PICU settings and the role of anidulafungin shall be examined.

**Materials and Methods:** Articles were retrieved from PubMed covering the years 2000–2012. Various search terms were used. Then the articles were clustered in different types like ‘review,’ ‘pharmacokinetics,’ ‘case reports’ and others.

**Results:** From 67 search results, 14 articles were selected. Of these, 7 were related to anidulafungin, while 7 were related to echinocandins or fungal infections in the PICU. Anidulafungin was examined in 4 PK/PD studies where a good safety profile was found. No serious adverse events occurred. The articles reporting risk factors show that central venous catheters, receipt of antibiotics, receipt of parenteral nutrition, and neutropenia are the most important independent risk factors for invasive fungal infections in PICU. Three reviews of antifungal agents show that echinocandins may be useful due to their safety profile; micafungin is the best examined one and further trials are needed.

**Discussion:** The published literature on invasive fungal infections in PICU settings has grown over the years. There are only a few articles, however, which are directly related to the use of anidulafungin in this setting. A most recent publication showed good PK/PD dynamics and a good safety profile for anidulafungin. So far, no RCT in the area of invasive candidiasis in infants and neonates has been published. A review of currently registered trials at ClinicalTrials.gov has shown one more trial related to PK/PD and two trials that investigate the use of anidulafungin or anidulafungin in combination with Voriconazole in pediatrics.

**Conclusion:** The small body of existing literature on anidulafungin in infants shows success in treatment, no drug-related adverse events, and good pharmacodynamics. A dosing of 0.75 mg/kg/day or 1.5 mg/kg/day is as effective as 50 mg/day or 100 mg/day in adults. More trials on the use in clinical reality of PICU or NICU should follow.

**Keywords:** antifungal therapy, infants, echinocandins, anidulafungin, review, pediatric intensive care unit, PICU, neonatal intensive care unit, NICU

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## Introduction

Invasive fungal infections in infants and neonates, especially in pediatric ICU settings (PICU), are a problem in clinical treatment as they are accompanied with a high mortality.<sup>1,2</sup> Although the overall incidence of candidemia is decreasing from 0.92 to 0.2 infections per 1,000 central IV line days, treatment is still a challenge.<sup>3</sup>

Risk factors have been well investigated. Most important are central venous catheters, use of vancomycin > 3 days in 2 weeks prior to admission on PICU, and administration of antimicrobial agents against gram-negative bacteria. Mortality is 44% in case patients compared to 14% in control patients.<sup>4</sup>

*Candida* is the most common source of fungal infections in PICU. While *Candida albicans* is still the most common pathogen, responsible for approximately 50% of the infections, the number of non-*albicans* strains is rising.<sup>1,3</sup>

According to the 2009 IDSA guidelines, the first line treatment for candidiasis in neonates and infants is Amphotericin B or fluconazole (FCZ).<sup>5</sup> However, Echinocandins are playing an ever important role in therapy of invasive fungal infections as the resistance of *Candida* spp. against FCZ is an issue of rising concern. Between 2.8% to 17% of *Candida* strains are found to be resistant. Moreover, treatment failure of FCZ is observed even if in vitro susceptibility is shown.<sup>6</sup>

Anidulafungin is the most recently introduced echinocandin. Its activity is exhibited by inhibiting the 1,3- $\beta$ -d-glucan synthase leading to lysis of the fungal cell wall. It has fungicidal activity against most *Candida* spp. and fungistatic activity against *Aspergillus* spp. It seems to have a good side effect profile. Most side effects are due to dosage and infusion rate. Fever, rash, headache, hypotension, dyspnea, flushing, dizziness, nausea, diarrhea, hypokalemia, minor elevations in hepatic parameters, neutropenia, and leukopenia are previously reported side effects.<sup>7</sup>

In this article we try to give an overview on published data as well as the current situation on ongoing trials. Questions of dosing and clinical results using anidulafungin in the PICU setting were in our focus.

## Materials and Methods

We performed a search of the literature to detect relevant articles for this review. Initially a systematic review according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations was intended.<sup>8</sup> As the number of results was very low and the articles turned out to be quite heterogenous, we decided to report all findings directly related to anidulafungin and children/infants in the result section.

As a first step, search terms were formulated. The following search terms were used: 'Anidulafungin and infants,' 'Anidulafungin and pediatric,' 'Anidulafungin and neonates,' 'Anidulafungin and PICU,' 'Anidulafungin and neonatal intensive care,' 'Anidulafungin and pediatric intensive care.'

The search results were examined and possibly relevant articles were selected for further examination. From every article, the abstract was pulled and examined by one reviewer.

The directly or generally related articles were classified in categories including general review, PK/PD study, pharmacology related, articles describing epidemiology, or risk factors for fungal infections and case report.

All retrieved articles were reviewed and results have been extracted for comparison.

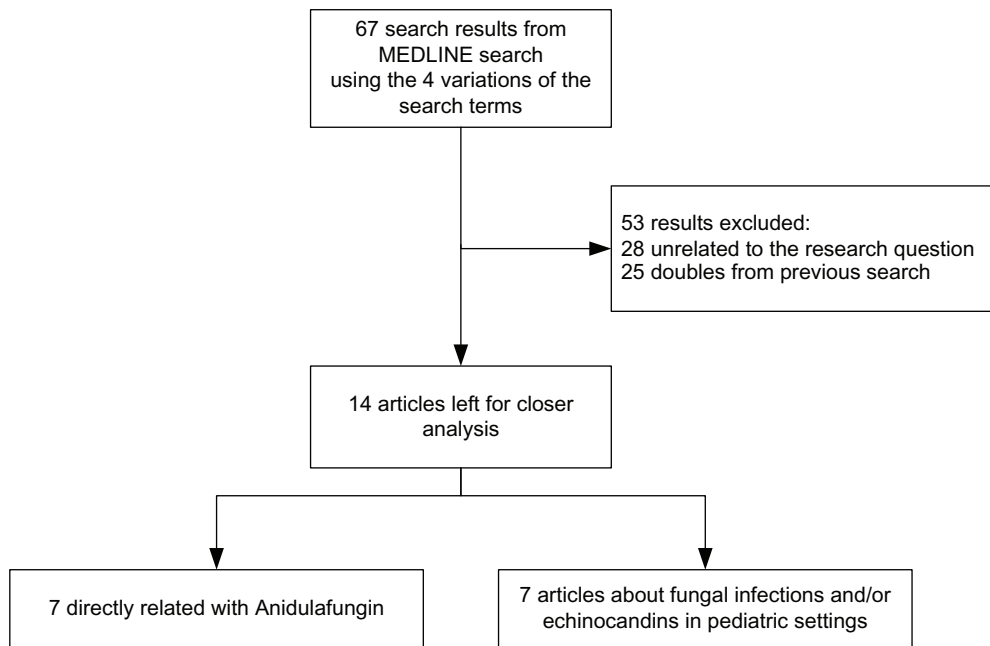
## Results

We had a total of 67 search results when using the search terms in a PubMed search from April 29, 2012. Of these, 53 results were excluded as 28 were unrelated to our primary research focus (eg, in-vitro testings, early phase-II reports or other topics), and 25 were duplicates already found with at least one other of our 4 search terms.

The flowchart in Figure 1 provides an overview on the selection process. The articles by author, year, main topic and Classification are shown in Table 1.

From the 7 studies directly related to anidulafungin, two turned out to be general articles and not directly related to children or infants.<sup>9,10</sup> The five remaining articles can be divided in three PK/PD studies, one review article and one case report.

Benjamin et al (2006) collected blood samples of children at high risk of invasive fungal infection



**Figure 1.** Overview of article selection process.

due to neutropenia. Patients were divided in two age groups (2–21 years and 12–27 years) and received ascending dosing of anidulafungin sequentially, first 0.75 mg/kg daily then 1.5 mg/kg daily. Plasma concentrations were assayed. No serious adverse events

were observed. The authors concluded that the described dosing is safe and provides concentration profiles similar to adults receiving 50 mg or 100 mg/day.<sup>11</sup>

Cohen-Wolkowicz et al (2011) administered 1.5 mg/kg body weight to infants and neonates with

**Table 1.** Overview of selected articles.

No.	Author	Year	Topic	Classification
1	Varisco	2009	Anidulafungin in neonatal peritoneal candidiasis	Case report
2	VandenBussche	2010	Echinocandins in pediatric patients	General
3	Caudle	2012	Echinocandins use in neonatal intensive care	General
4	Cohen-Wolkowicz	2006	Anidulafungin	Pharmacology
5	Almirante	2007	Antifungals in neonates	Pharmacology
6	Estes	2009	Pharmacology of anidulafungin	Pharmacology
7	Manzoni	2010	Echinocandins in neonates	Pharmacology
8	Benjamin	2006	Anidulafungin in children with neutropenia	PK/PD study
9	Cohen-Wolkowicz	2011	Safety and pharmacokinetics of anidulafungin in infants	PK/PD study
10	Warn	2012	Anidulafungin for neonatal <i>Candida</i> meningoencephalitis	PK/PD study
11	Tapisiz	2011	Review: is anidulafungin a treatment option in pediatric invasive fungal infections	Review
12	Benjamin	2010	Neonatal candidiasis, epidemiology, risk factors, clinical	Risk factors
13	Zaoutis	2010	Risk factor and predictors for candidemia in PICU	Risk factors
14	Brissaud	2012	Invasive fungal diseases in PICU: epidemiology and risk factors	Risk factors



a high risk of invasive candidiasis. No drug-related serious adverse events were observed. The study results indicate that neonates and infants receiving 1.5 mg/kg/day have anidulafungin exposure levels similar to those in children receiving similar weight-based dosing and in adult patients receiving 100 mg/day.<sup>12</sup>

Warn et al (2012) tested the efficacy of anidulafungin in neonatal hematogenous meningococcal meningitis (HCME). Therefore they used a well established and proven rabbit model and applied a mathematical model to translate the results in effects in humans. They conclude that the current dosing regimen of 1.5 mg/kg daily with a loading dose of 3 mg/kg is not sufficient to treat HCME.<sup>13</sup>

The fourth article is a review from Tapisiz, where the basic mechanism of action, the fungal species and pharmacokinetics, as well as pharmacodynamics are described.<sup>7</sup> Moreover the results of the above mentioned PK/PD studies are reported. The author concludes that the results from adult studies cannot be extrapolated on pediatric populations. Owing the lack of results from large prospective randomized studies in this area the answers of the ‘best choice’ in pediatric fungal infections is still pending.

The fifth article was a case report, where the treatment of neonatal peritonitis in an 11 day old newborn with Hirschsprung enterocolitis and a perforation was described.<sup>14</sup> The patient had an intra-abdominal compartment syndrome and positive *Candida* culture results. After initial treatment with liposomal Amphotericin B 5 mg/kg/day, anidulafungin 1.5 mg/kg/day was added. After 4 days of treatment, *Candida* cultures were negative. The patient slowly recovered and was discharged after 68 days. The authors conclude that Anidulafungin is a good therapy alternative in the described setting. The safety profile and its good antifungal activity seem to recommend anidulafungin especially when a high rate of fluconazole resistance is known.

The publications concerning the general evaluation of echinocandins in infants and neonates or referring to incidence of and risk factors for fungal infections in this patient population reveal the following findings.

Important risk factors for fungal infections and related odds ratios from various publications<sup>1,2,4</sup> are shown in Table 2.

## Discussion

The literature on the use of echinocandins in infants is rare. Anidulafungin was examined in two published PK/PD studies and only one case report exists to date. Two publications look into the use of echinocandins in infants,<sup>15,16</sup> while one older article is a general review of antifungal agents in this setting.<sup>17</sup>

Two recent reviews from 2010 and 2012 did yet not take the results of Cohen-Wolkowicz’s PK/PD study into account.<sup>12</sup> However these reviews find that echinocandins can be useful in the PICU setting due to their safety and efficacy profiles. Micafungin appears to be the agent best examined in this setting.<sup>16,18</sup> Assuming that anidulafungin has a particularly good safety profile,<sup>14</sup> it may be very useful. On top of reviewing the literature, a search in clinicaltrials.gov was performed. One study was listed that investigated antimicrobial PK in infants with suspected or confirmed infections (NCT00491426). The study is completed due to the information on clinicaltrials.gov yet no publication is available at the date of completion of this review.<sup>19</sup> A review on antifungal therapy for newborn infants with invasive fungal infections published in the Cochrane library states that there is ‘insufficient data to inform practice.’<sup>19,20</sup> Therefore randomized control trials investigating the clinical efficacy of echinocandins in invasive fungal infections in the PICU, NICU setting are recommended.

**Table 2.** Risk factor for an invasive fungal infection in the PICU—setting.

Risk factor	Unadjusted odds ratio	95% confidence interval
Presence of a central venous catheter	13.4	4.8–37.42
Receipt of antibiotics within 15 days	5.44	1.87–15.77
Neutropenia within 15 days	5.58	1.12–27.79
Receipt of total parenteral nutrition	5.3	2.8–10.05



## Conclusion

There is only a small body of literature and little evidence on the use of echinocandins in the PICU in general and for anidulafungin in particular. Micafungin seems to be the best examined agent and is recommended by several authors to be the echinocandin of choice in this setting.

Anidulafungin in infants maybe a useful alternative/extension treatment, especially when risk factors are present that make an invasive fungal infection probable and the local resistance of *Candida* strains against fluconazole is high, or when fluconazole treatment fails. A dosage of 0.75 mg/kg/day or 1.5 mg/kg/day results in appropriate concentrations in infants, in comparison to a dosage 50 mg/day or 100 mg/day in adults.

Further evidence from comparative trials is most desirable.

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