**INTRODUCTION**

Disseminated candidiasis results in significant morbidity and mortality in premature infants ([1-3](#_ENREF_1)). The mortality associated with invasive candidiasis (IC) is three-times higher than that of uninfected infants of similar gestational age and birth weight ([4](#_ENREF_4)). The involvement of the central nervous system (CNS) is especially detrimental for subsequent neurodevelopmental outcomes and mandates meticulous attention to the selection of safe and effective antifungal regimens ([5-7](#_ENREF_5)).

There is a large safety and efficacy database that supports the role of micafungin for the treatment of IC in both adults and children ([8-11](#_ENREF_8)). Micafungin has broad-spectrum anti-*Candida* coverage and a favorable safety profile ([12](#_ENREF_12), [13](#_ENREF_13)). Micafungin demonstrates linear pharmacokinetics (PK); dose adjustment is not required in the setting of renal and/or hepatic impairment, and therapeutic drug monitoring is not required in any patient populations ([14](#_ENREF_14)).

The pharmacodynamics (PD) of micafungin for the treatment of hematogenous *Candida* meningoencephalitis (HCME) has been explored in a well-characterized experimental model ([15](#_ENREF_15)). PK-PD bridging studies suggest that a neonatal regimen of 10 mg/kg is required for effective treatment of *Candida* infections ([15](#_ENREF_15), [16](#_ENREF_16)). These studies were used to justify the choice of this high dose regimen for treatment of infants with IC. Unfortunately, however, inherent difficulties in conducting neonatal trials and the general decrease in the incidence of neonatal candidiasis resulted in early termination of one of the studies after the enrollment of only 30 infants with the primary and safety results reported elsewhere ([17](#_ENREF_17)).

Ideally, predictions from preclinical models should be tested clinically to prospectively validate the PK-PD relationships. Establishing preclinical-to-clinical linkages are increasingly viewed as fundamental for the establishment of effective antimicrobial therapies. In this study, we examined the clinical relevance of reaching the PD target established in preclinical models. We combined micafungin plasma concentrations from four neonatal clinical trials to construct a population PK (PPK) model and then explored whether increasing micafungin drug exposures resulted in improved clinical outcomes in infants with IC.

**METHODS**

**Study Design**

Micafungin plasma concentrations from four pediatric clinical trials were available for population PK modeling. Each study has been described in detail elsewhere ([16-20](#_ENREF_16)). Briefly, the dataset consists of two PK and safety studies with dosages ranging from 0.75 to 10 mg/kg and two efficacy, safety, and PK studies with dosages ranging from 2 to 10 mg/kg/day. The local Institutional Review Board/Ethics Committee at each site approved the studies and parental consent was obtained for each infant prior to initiation of study procedures within each study. Plasma sampling is described in the respective publications. The micafungin concentrations were analyzed using high performance liquid chromatography (HPLC), as detailed in the individual publications ([16](#_ENREF_16), [18](#_ENREF_18), [19](#_ENREF_19)). Estimated gestational age was not available for all clinical trials so we were unable to incorporate this variable in the analysis or to use it to calculate other age descriptions such as post-menstrual age.

**PPK modeling**

A PPK model was constructed using the population PK program Pmetrics (v1.5.1, University of Southern California, Los Angeles, CA, USA) ([21](#_ENREF_21)). The observations were weighted by the inverse of the estimated assay variance. Initial parameter estimates were anchored on two prior population PK models. The first study included 47 infants < 4 months which used prior knowledge from adult population PK modeling and standardized estimates of clearance and volume in the central compartment to a 70-kg adult weight ([22](#_ENREF_22)). The second study utilized 293 pediatric patients including the 64 infants in the present analysis (unpublished data). This population PK model normalized the clearance and volume to the mean weight of the 293 pediatric patients based on prior knowledge from previous pediatric population PK analysis ([23](#_ENREF_23)). The structural model included allometric scaling of clearance, as previously described (21). Clearance and volume were also standardized to the mean body weight of the population (1.8 kg). The differential equations for the final structural model with allometric scaling are as follows:

Eq. 1

Eq. 2

where CLstd and Vstd represent the normalized clearance and volume values using the mean body weight of the population, R represents the infusion of micafungin into compartment 1, Kcp and Kpc represent the rate of drug transfer to and from the central (compartment 1) and peripheral (compartment 2) compartments, respectively.

The fit of the model to the data was evaluated by visual inspection of the observed-versus-predicted concentrations before and after the Bayesian step, and the coefficient of determination (*r2*) from the linear regression of the observed-versus-predicted values. In addition, the estimates for bias (mean weighted error), imprecision (adjusted mean weighted squared error), objective function, and log likelihood were assessed. Non-compartmental analyses were conducted for the infants with 4 or more samples in a 24-hour period to generate NCA AUC0-24s and compared to the population model-predicted AUC0-24s.

Bayesian posterior estimates from the final model were used to estimate area-under-the concentration-time curve (AUC) for each patient for the entire dosing interval. The average daily AUC was then determined by dividing the total AUC for the treatment course by the number of days of micafungin therapy. Using daily average AUC avoids the issue of having to define what time in the course of therapy that AUC is important for efficacy (e.g. AUC at the end of dosing or on a specific day during therapy).

**Exposure-Response Analysis**

A subset of 29 infants who received micafungin for the treatment of proven invasive candidiasis was used for the exposure-response analysis. Mycological response was used as an outcome measure. Successful mycological response was defined as eradication (documented by negative fungal cultures) through 1 week post the receipt of the last dose of micafungin. In most patients, after documentation of eradication during therapy, follow-up cultures were sparse or not performed due to lack of clinical need (i.e. a successful response). Therefore, an additional part of the definition of “successful response” was that no new antifungal therapy was required after completion of micafungin. Failure (persistence of infection) was defined as continued positive cultures or in the absence of repeat cultures, there was a requirement to switch to an alternative antifungal therapy for further treatment. Survival reported anytime during the course of the study was used in the analysis.

The relationship of AUCave and AUCave:MIC to mycological response (binary data) was analyzed using logistic regression in SAS® (version 9.3, SAS Institute Inc., Cary, NC, USA). The logit function was used without covariates illustrated by the following equation:

where Y is response, β0 is the intercept parameter and β is the vector of slope parameters.

The exposure parameters were added in an automated stepwise approach with α=0.3 for model inclusion and α=0.05 for model retention. Additional statistical comparisons were performed in MYSTAT 12 (version 12.02, <http://www.systat.com>).

**Attainment of Pharmacodynamic Targets**

Drug exposures from the 29 infants with IC were used to verify if the 10 mg/kg dosage ensured attainment of the PD target (AUC and AUC:MIC ratio) representing the near-maximal effect determined in the *in vivo* rabbit model of *Candida* meningoencephalitis ([15](#_ENREF_15), [22](#_ENREF_22)) and to assess if achieving this target improved survival and/or mycological response.

**RESULTS**

**Study Population for PPK**

A summary of the demographics of patients enrolled included from the 4 studies is provided in **Table 1.** Four micafungin clinical trials with a combined total of 64 infants aged 3 to 119 days were available. There were slightly more males than females (n=35 males, 55%), the mean (SD) age was 35 days (27 days), and the mean (SD; range) weight was 1.8 kg (1.1 kg; 0.5-4.8 kg). The treatment duration ranged from 1 to 34 days, with a mean (SD) of 6.8 days (7.9 days).

**Population PK model**

A total of 287 micafungin concentrations from 64 infants were retrieved for the population PK analysis. Forty infants had multiple samples over a 24-hour dosing interval with an average of 5 samples each (range 3-9). A description of the 4 studies is included in **Table 1**. A two-compartment model with allometric scaling fit the data well. A visual inspection of the observed-versus-predicted concentrations after the Bayesian step was acceptable with a coefficient of determination (*r2*) of 0.945 (**Figure 1**) using the median parameter values. Similar results were observed for the mean posterior predicted values (*r2* = 0.941 for the linear regression of the observed-versus-predicted values). Estimates of bias and imprecision were also acceptable (-0.126 and 0.902, respectively). The mean parameter estimates are included in **Table 2**. The mean (SD) clearance and volume in the central compartment were 0.07 (0.05) L/h/1.8 kg and 0.61 (0.53) L/1.8 kg, respectively.

Thirty-seven infants had 4 or more samples in the 24-hour period. AUC0-24 calculated using NCA analyses for these 37 subjects were compared to AUC0-24 calculated from the model predictions. Spearman correlation rank order test demonstrated the results were not significantly different (S = 140, p-value < 2.2e-16, Rho=0.983).

**Exposure-Response Population and Analysis**

Twenty-nine infants ranging in age from 4 to 117 days received micafungin for the treatment of proven invasive candidiasis or candidemia; 17 infants received a dose of 2 mg/kg in a trial comparing micafungin to liposomal amphotericin B ([20](#_ENREF_20)) and 12 infants received a dose of 10 mg/kg in a trial comparing micafungin to conventional amphotericin B ([17](#_ENREF_17)). The median (range) body weight of the 29 infants was 1.95 kg (0.68 to 4.85 kg). The median (range) treatment duration was 14 days (1-34 days). Minimum inhibitory concentration (MIC) values from the 2 mg/kg and 10 mg/kg studies were available for all but 2 infants with values ranging from 0.004-2 mg/L and 0.03-2 mg/L, respectively. All but 3 patients had candidemia. The other 3 patients had proven infections in the urinary tract (n=2) and disseminated disease (n=1; eye, CSF, blood). Seventy-six percent and 92% of infants receiving 2 and 10 mg/kg survived, respectively. Of the five patients that died, 3 deaths occurred in the first week of starting micafungin (2 at 2 mg/kg and 1 at 10 mg/kg), 1 infant (2 mg/kg) died during the first week after the last dose of micafungin, and 2 infants (2 mg/kg) died within the 30 days after the last dose of study drug. Successful mycological response was achieved in 76% and 83% of patients receiving 2 and 10 mg/kg, respectively. Both infants with urinary tract infections administered 10 mg/kg/day had a successful mycological response. The infant with a disseminated infection (2 mg/kg/day) failed mycologically; however, all 3 survived. **Table 3** summarizes the exposure estimates (AUCave and AUCave:MIC) for the 2 and 10 mg/kg dosages from each study.

The CNS PD target AUC for near-maximal effect that was demonstrated in the rabbit model of HCME was approximately 166.5 mgh/L ([15](#_ENREF_15), [22](#_ENREF_22)). All infants treated at a dose of 10 mg/kg achieved the CNS PD target, while only two (12%) of the infants receiving 2 mg/kg achieved the CNS PD target (**Table 4**). Successful mycological response was achieved by 86% of patients who reached the PD target as compared to 73% of patients who did not meet the PD target, but this difference was not statistically significant (p=0.396). Of those infants reaching the AUC:MIC ratio PD target for near-maximal effect of 1332, successful mycological response was achieved by 73% and 83% of those who reached and did not reach the target, respectively. There was no clear relationship between mycological response (success or failure) and either AUCave and AUCave:MIC when examined using logistic regression (p > 0.3). **Figure 2a and 2b** illustrates the similarity in the drug exposure measures for those patients with successful and failure of mycological response.

**DISCUSSION**

In the current population PK analysis, robust estimates of drug exposures for individual patients were obtained. However, no statistically significant relationship between drug exposure and treatment outcomes was demonstrated. There are several potential reasons for this observation. First, the number of infants (n=29) was small, and therefore, the study lacked adequate power to detect a difference despite the numerically better response rate in the group with higher exposures [86% versus 73%, p=0.396]. Assuming the mycological responses rates of 86% and 73% from the two groups, the study would require a sample size of approximately 142 to yield at least 80% power (two-sided, 5% significance level). Second, there is extreme heterogeneity in the clinical characteristics of neonates and young infants with many factors that are extraneous to the infection that potentially confound outcome measures (e.g. gestational age, birth weight, and other concomitant co-morbidities). Third, there is significant heterogeneity in the clinical presentation and prognosis of *Candida* infections in this population. Disease may range from simple colonization to dissemination and devastating involvement of the brain. It may be possible to stratify patients to more effectively account for the heterogeneity; however, there simply are not adequate laboratory and clinical tools to do this accurately.

Outcome measures used in these studies have a number of inherent limitations. Previous studies have demonstrated that infants that survive IC have poorer neurodevelopment outcomes compared to those without IC regardless of the presence of candidemia or confirmed CNS infection ([7](#_ENREF_7)). The extent of correlation between short-term outcome measures and longer-term neurodevelopment outcomes is not known. The demonstration of negative fungal cultures is central to definitions of disease resolution. However, the lack of sensitivity of fungal cultures (<50%) ([24](#_ENREF_24)) impairs the clinical utility of this metric. Clinical signs and symptoms are neither sensitive nor specific enough to assess therapeutic response ([25](#_ENREF_25)). The strongest predictor of septicemia in one study was hypotension, present in less than 5% of the infants, which had only a 31% positive predictive value ([26](#_ENREF_26)). All-cause mortality is obviously an important endpoint, but is invariably confounded by comorbidities that may overwhelm the signal coming from the drug-pathogen interaction. The use biomarkers such as (1→3)-β–D-glucan could aid in the objective assessment of the response to therapy ([27](#_ENREF_27), [28](#_ENREF_28)). These data and others suggest that fungal biomarkers be included for assessment of therapeutic response in future clinical trials ([29](#_ENREF_29)).

A further problem resides in substantial difficulties in conducting clinical trials in this patient population. Enrollment in the micafungin clinical trials was extremely slow. For example, a recently terminated study enrolled only 30 of the 225 planned patients in 2 and a half years ([17](#_ENREF_17)). Reasons for such slow recruitment may be related to the decreased incidence of invasive candidiasis in this population ([30](#_ENREF_30)). A recent study reported in 2014 that the annual US incidence of invasive candidiasis decreased dramatically ([30](#_ENREF_30)). The terminated study provides a recent example of the difficulty of conducting these studies ([17](#_ENREF_17)). This study had 70 sites from 23 countries available to screen patients. Only half of the sites found appropriate infants to screen and only 22% of them were able to enroll at least one infant.

Clinical trials may not be the most efficient way to identify safe and effective regimens for relatively rare fungal infections. Preclinical-to-clinical bridging studies represent one of the few ways regimens can be de-risked for clinical study. Importantly, however, there is relatively little experience with this approach and certainly no consensus on the type of studies that are required. We have recently reflected and summarized some of the necessary factors in a PK-PD package for the development of new antifungal agents in adults ([31](#_ENREF_31)). The same exercise now needs to be performed for infants. This topic was discussed in detail at a recent FDA workshop (<http://www.fda.gov/Drugs/NewsEvents/ucm507958.htm>). Some important considerations include: (1) using preclinical models that are a faithful mimic of human neonatal disease. Such an approach enables pharmacodynamic idiosyncrasies in infants to be examined; (2) using neonatal strains and studying more than one strain; (3) cross validating findings in several experimental model systems; (4) using compounds for which there is an established regimen and indication to enable the outcomes from new agents to be benchmarked; (5) setting up experimental models that produce “on scale” readouts. Model behavior is governed by the chosen experimental conditions, such as strain, inoculum, background immunosuppression, delay in initiation of treatment, and treatment duration. The key idea is that clinically relevant exposures of a positive control should induce a response in the middle of the drug exposure-response relationship.

Clinical data remains central to establishing safe and effective anti-infective regimens for neonates. A toxicodynamic relationship was not established in the current dataset, which was too small to enable meaningful analyses. Clear relationships between drug exposure and toxicity have not been established for the echinocandins in any clinical context. The safety of neonatal dosages as high 15 mg/kg is published elsewhere ([16](#_ENREF_16), [17](#_ENREF_17), [32](#_ENREF_32), [33](#_ENREF_33)).

Regarding the population PK model employed for the current analysis, we used a previously described PPK model for micafungin which applied a an exponent of 0.75 on clearance estimates. A recent report suggests that allometric scaling for neonatal data of 0.75 may not be appropriate ([34](#_ENREF_34)). To check our results, we performed a sensitivity analysis using 1 as the allometric scaling exponent. However, the resulting estimates for clearance and AUCave did not differ from the model describe herein.

In conclusion, we could not establish a statistically significant relationship between micafungin exposure and the clinical outcome of neonatal candidiasis. However, prior PK-PD studies suggest that relatively high drug exposures are required for the effective treatment of CNS candidiasis. Without larger numbers of patients and more accurate clinical outcome measures, there will be persistent problems in establishing direct preclinical to clinical linkages. At the present time carefully designed experimental programs coupled with PK-PD bridging studies provide the best way to develop new drugs for premature infants.

**Reference**

1. **Manzoni P, Mostert M, Castagnola E.** 2015. Update on the management of Candida infections in preterm neonates. Arch Dis Child Fetal Neonatal Ed **100:**F454-459.

2. **Arsenault A, Bliss J.** 2015 Neonatal Candidiasis: New Insights into an Old Problem at a Unique Host-Pathogen Interface. Curr Fung Infect Rep **9:**246-252.

3. **Smith P, Steinbach W, Benjamin D, Jr.** 2005. Neonatal Candidiasis. Infect Dis Clin North Am **19:**603-615.

4. **Benjamin D, DeLong E, Cotten C, Garges H, Steinbach W, Clark R.** 2004. Mortality following blood culture in premature infants: increased with Gram-negative bacteremia and candidemia, but not Gram-positive bacteremia. J Perinatol **24:**175-180.

5. **Watt K, Cohen-Wolkowiez M, Ward R, Benjamin D.** 2012. Pediatric antifungal drug development: lessons learned and recommendations for the future. Pediatric Infectious Disease Journal **31:**635-637.

6. **Stoll B, Hansen N, Adams-Chapman I, Fanaroff A, Hintz S, Vohr B.** 2004. Neurodevelopmental and Growth Impairment Among Extremely Low-Birth-Weight Infants With Neonatal Infection. JAMA **292:**2357-2365.

7. **Benjamin D, Jr, , Stoll B, Fanaroff A, McDonald S, Oh W, Higgins R, Duara S, Poole K, Laptook A, Goldberg R, Network NIoCHaHDNR.** 2006. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics **117:**84-92.

8. **Pappas P, Kauffman C, Andes D, Clancy C, Marr K, Ostrosky-Zeichner L, Reboli A, Schuster M, Vazquez J, Walsh T, Zaoutis T, Sobel J.** 2016. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis doi:10.1093/cid/civ933.

9. **Ullmann A, Akova M, Herbrecht R, Viscoli C, Arendrup M, Arikan-Akdagli S, Bassetti M, Bille J, Calandra T, Castagnola E, Cornely O, Donnelly J, Garbino J, Groll A, Hope W, Jensen H, Kullberg B, Lass-Flörl C, Lortholary O, Meersseman W, Petrikkos G, Richardson M, Roilides E, Verweij P, Cuenca-Estrella M, Group EFIS.** 2012. ESCMID\* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect **18:**53-67.

10. **Cornely O, Bassetti M, Calandra T, Garbino J, Kullberg B, Lortholary O, Meersseman W, Akova M, Arendrup M, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly J, Groll A, Herbrecht R, Hope W, Jensen H, Lass-Flörl C, Petrikkos G, Richardson M, Roilides E, Verweij P, Viscoli C, Ullmann A, Group EFIS.** 2012. ESCMID\* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect **18:**19-37.

11. **Hope W, Castagnola E, Groll A, Roilides E, Akova M, Arendrup M, Arikan-Akdagli S, Bassetti M, Bille J, Cornely O, Cuenca-Estrella M, Donnelly J, Garbino J, Herbrecht R, Jensen H, Kullberg B, Lass-Florl C, Lortholary O, Meersseman W, Petrikkos G, Richardson M, Verweij P, Viscoli C, Ullmann A, Group EFIS.** 2012. ESCMID\* guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp. Clinical Microbiology and Infection **18 Suppl 7:**38-52.

12. **Cornely O, Pappas P, Young J, Maddison P, Ullmann A.** 2011. Accumulated safety data of micafungin in therapy and prophylaxis in fungal diseases. Expert Opin Drug Saf **10:**171-183.

13. **Arrieta A, Maddison P, Groll A.** 2011. Safety of micafungin in pediatric clinical trials. Pediatr Infect Dis J **30:**e97-e102.

14. **Astellas Pharma US I.** 2016. MYCAMINE® (micafungin sodium) prescribing information. <https://www.mycamine.com>. Accessed

15. **Hope W, Mickiene D, Petraitis V, Petraitiene R, Kelaher A, Hughes J, Cotton M, Bacher J, Keirns J, Buell D, Heresi G, Benjamin D, Jr, , Groll A, Drusano G, Walsh T.** 2008. The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous *Candida* meningoencephalitis: implications for echinocandin therapy in neonates. J Infect Dis **197:**163-171.

16. **Benjamin D, Jr, , Smith P, Arrieta A, Castro L, Sánchez P, Kaufman D, Arnold L, Kovanda L, Sawamoto T, Buell D, Hope W, Walsh T.** 2010. Safety and pharmacokinetics of repeat-dose micafungin in young infants. Clin Pharmacol Ther **87:**93-99.

17. **Benjamin D, Jr,, Kaufman D, Hope W, Smith P, Arrieta A, Manzoni P, Kovanda L, Lademacher C, Isaacson B, Jednachowski D, Wu C, Walsh T.** 2015. Micafungin versus Conventional Amphotericin B in the Treatment of Invasive Candidiasis in Infants, abstr Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, USA,

18. **Heresi G, Gerstmann D, Reed M, van den Anker J, Blumer J, Kovanda L, Keirns J, Buell D, Kearns G.** 2006. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. Pediatr Infect Dis J **25:**1110-1115.

19. **Undre N, Stevenson P, Freire A, Arrieta A.** 2012. Pharmacokinetics of micafungin in pediatric patients with invasive candidiasis and candidemia. Pediatr Infect Dis J **31:**630-632.

20. **Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, Konja J, Diekmann-Berndt H, Koblinger S, Groll A, Arrieta A, Group MICS.** 2008. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. Pediatr Infect Dis J **27:**820-826.

21. **Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW.** 2012. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit **34:**467-476.

22. **Hope W, Smith P, Arrieta A, Buell D, Roy M, Kaibara A, Walsh T, Cohen-Wolkowiez M, Benjamin DJ.** 2010. Population pharmacokinetics of micafungin in neonates and young infants. Antimicrob Agents Chemother **54:**2633-2637.

23. **Hope WW, Kaibara A, Roy M, Arrieta A, Azie N, Kovanda LL, Benjamin DK, Jr.** 2015. Population pharmacokinetics of micafungin and its metabolites M1 and M5 in children and adolescents. Antimicrob Agents Chemother **59:**905-913.

24. **Berenguer J, Buck M, Witebsky F, Stock F, Pizzo P, Walsh T.** 1993. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis. Disseminated versus single-organ infection. Diagnostic microbiology and infectious disease **17:**103–109.

25. **Kelly M, Benjamin D, Smith P.** 2015. The Epidemiology and Diagnosis of Invasive Candidiasis Among Premature Infants. Clin Perinatol **42:**105–117.

26. **Fanaroff A, Korones S, Wright L, Verter J, Poland R, Bauer C, Tyson J, Philips Jr, Edwards W, Lucey J, Catz C, Shankaran S, Oh W.** 1998. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. Pediatr Infect Dis J **17:**593-598.

27. **Salvatore C, Chen T, Toussi S, DeLaMora P, Petraitiene R, Finkelman M, Walsh T.** 2016. (1→3)-β-D-glucan in cerebrospinal fluid as a biomarker for Candida and Aspergillus infections of the central nervous system in pediatric patients. J Pediatr Infect Dis Soc **5:**277-286.

28. **Salvatore C, Petraitiene R, Sitaras L, Hammad H, Leimena P, Toussi S, Finkelman M, Walsh T.** Prospective study and analytical performance of serum (1->3)-β-D-glucan in pediatric patients, p. *In* (ed),

29. **Benjamin DJ, Stoll B, Gantz M, Walsh M, Sánchez P, Das A, Shankaran S, Higgins R, Auten K, Miller N, Walsh T, Laptook A, Carlo W, Kennedy K, Finer N, Duara S, Schibler K, Chapman R, Van Meurs K, Frantz Ir, Phelps D, Poindexter B, Bell E, O'Shea T, Watterberg K, Goldberg R, NICHD N.** 2010. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics **126:**e865-873.

30. **Aliaga S, Clark R, Laughon M, Walsh T, Hope W, Benjamin D, Kaufman D, Arrieta A, Benjamin DJ, Smith P.** 2014. Changes in the Incidence of Candidiasis in Neonatal Intensive Care Units. Pediatrics **133:**236-242.

31. **Hope W, Drusano G, Rex J.** 2016. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. J Antimicrob Chemother **71:**3008-3019.

32. **Smith P, Walsh T, Hope W, Arrieta A, Takada A, Kovanda L, Kearns G, Kaufman D, Sawamoto T, Buell D, Benjamin DJ.** 2009. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Pediatr Infect Dis J **28:**412-415.

33. **Auriti C, Falcone M, Ronchetti M, Goffredo B, Cairoli S, Crisafulli R, Piersigilli F, Corsetti T, Dotta A, Pai M.** 2016. High-Dose Micafungin for Preterm Neonates and Infants with Invasive and Central Nervous System Candidiasis. Antimicrob Agents Chemother **60:**7333-7339.

34. **Calvier E, Krekels E, Välitalo P, Rostami-Hodjegan A, Tibboel D, Danhof M, Knibbe C.** 2017. Allometric Scaling of Clearance in Paediatric Patients: When Does the Magic of 0.75 Fade? Clin Pharmacokinet **56:**273-285.

**Figure 1.** Observed versus posterior predicted concentrations (mg/L) from the final model after the Bayesian step on a linear scale (upper) (*r2*= 0.945, slope = 0.995 [95%CI 0.967 to 1.02], intercept = 0.24 [95%CI −0.104 to 0.584]) and on a log scale (lower) (*r2*= 0.947, slope = 0.946 [95%CI 0.92 to 0.972], intercept = 0.0496 [95%CI 0.0284 to 0.0709]). Dotted line is line of unity where observed concentrations equal predicted concentrations.

**Figure 2.** Boxplot illustrating the relationship between mycological response and AUCave (a) and AUCave:MIC (b) (The box represents the interquartile range of AUCave and AUCave:MIC, respectively, with the median displayed as the band inside the box, the lines extending from the boxes represent the overall range of values.)