Antifungal Treatment in Neonates

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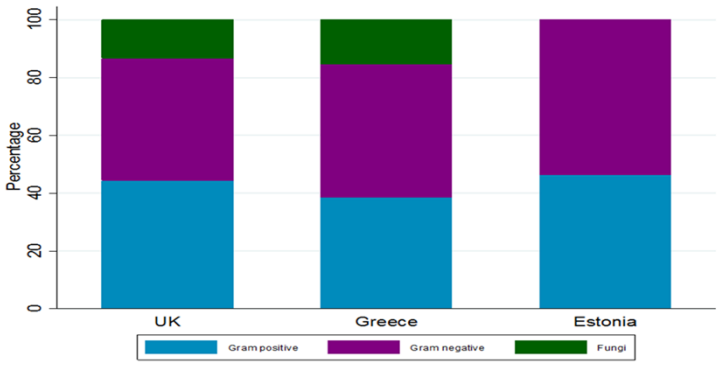
Prevalence of invasive fungal infections in NeoINN database



2005-2014 – UK; 2012-2014 – Estonia & Greece

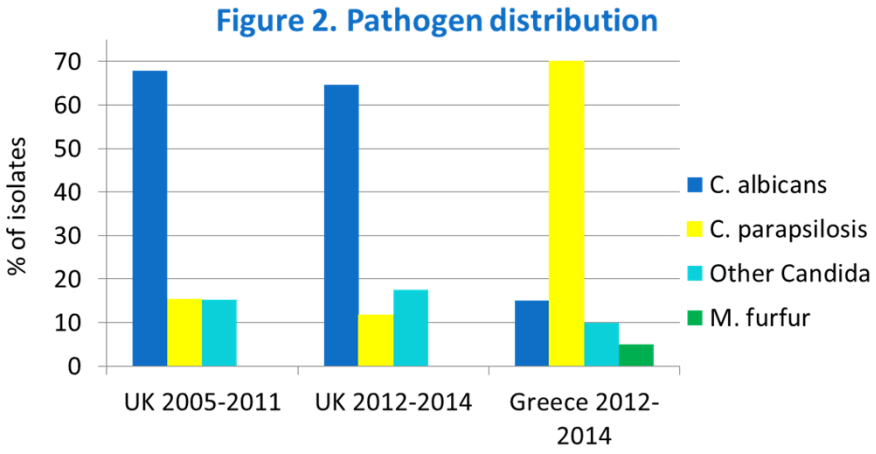
Patient with fungal infection in NICU

- Is extremely or very premature – BW<1000g
- Has received antibiotics
- Has received parenteral nutrition
- Has central venous or arterial catheter(s)

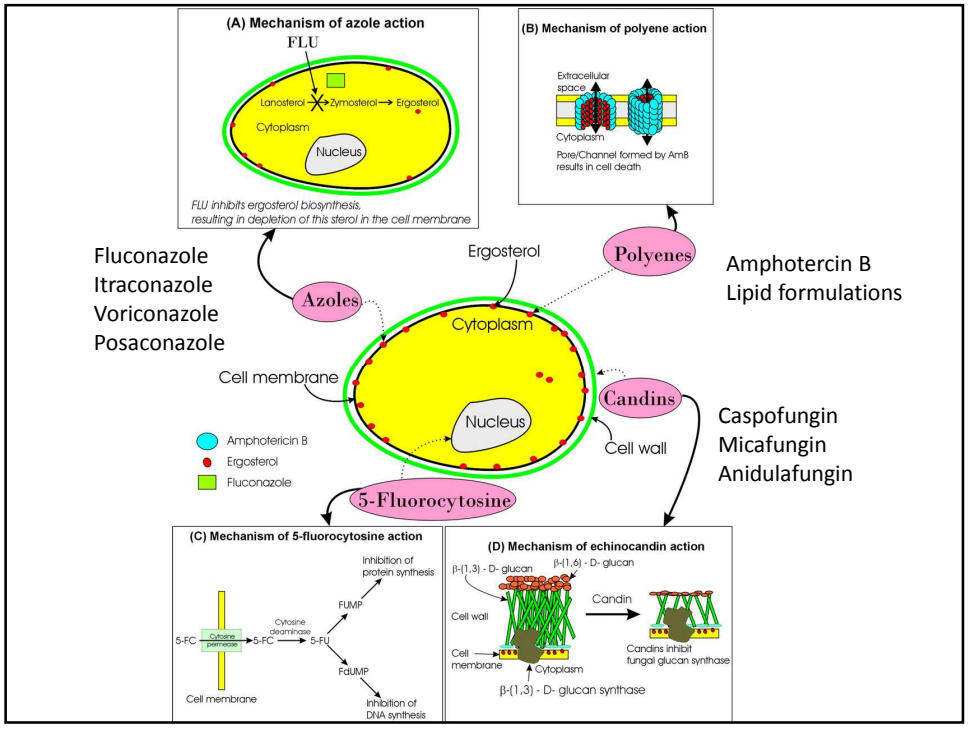
Questions

- What is potential etiology of fungal infection?
- What is the susceptibility of microorganisms to antifungal agents
- Which antifungal agent is the best?
  - What is the evidence?
- Which dose should be used?
- Where do find correct information?

Vast majority of fungal infections in neonates are caused by *Candida* spp.



ESPID poster 2015; NeoINN database



In Vitro Activity of Currently Used Antifungal Agents

Fungal species	FLU	ITRA	POSA	VOR	AMB	Echinocandins[a]
Aspergillus fumigatus	–	+	+	+	+	+
Aspergillus flavus	–	+	+	+	+	+
Aspergillus terreus	–	+/–	+	+	+/–	+
Candida albicans	+	+	+	+	+	+
Candida krusei	–	+/–	+	+	+/–	+
Candida glabrata	+/–	+/–	+/–	+/–	+	+
Other *Candida* species[b]	+	+	+	+	+	+/–
Cryptococcus neoformans	+	+	+	+	+	–
Coccidioides species	+	+	+	+	+	–
Blastomyces dermatitidis	+/–	+	+	+	+	–
Histoplasma capsulatum	+	+	+	+	+	–
Fusarium species	–	–	+/–	+/–	+/–	–
Zygomycetes	–	+/–	+	–	+	–
Scedosporium apiospermum	–	–	+	+	+/–	–
Scedosporium prolificans	–	–	–	–	–	–
Trichosporon	–	–	ND	+	+/–	–

NOTE. +, in vitro activity; –, no in vitro activity; +/– modest in vitro activity; AMB, amphotericin B; FLU, fluconazole; ITRA, itraconazole; ND, no data; POSA, posaconazole; VOR, voriconazole.

[a] Caspofungin, micafungin, and anidulafungin.

[b] *Candida parapsilosis* is less susceptible in vitro to the echinocandins.

Leventakos K et al. Clin Infect Dis. 2010;50:405-415

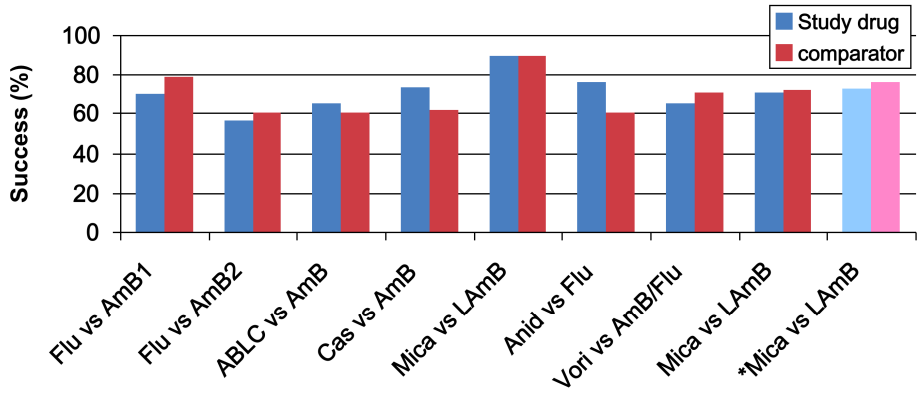
Percent of resistance of yeasts in paediatric patients in Spain

Antifungal	% of resistance N = 203
Anidulafungin	2.5
Caspofungin	1
Micafungin	2
Fluconazole	3*
Itraconazole	2
Voriconazole	1.5*
Posaconazole	1.5
Amphotericin	0.5*

J Clin Microbiol 2011; 49: 4158-63

**C.krusei*

Candidaemia: randomised trials, non-neutropenic patients (EOT)



Rex, 1994; Phillips 1997; Nguyen, 1995; Anaissie, 1995; Perfect, 2002; Queiroz-Telles, 2008; Pappas, 2007

*Paediatric study

Treatment of invasive candidiasis in neonates

Agent	Dose	Comment
Grade A		
		None
Grade B II		
AmphoB	1 mg/kg/day	PK trials in neonates but no efficacy
L-AMB	2.5 – 7 mg/kg/day	
Fluconazole	25 mg/kg loading 12 mg/kg/day	Limited data on efficacy in neonates
Micafungin	4-10 mg/kg/day	Evidence for efficacy from preclinical models Labelled dose 2-4 mg/kg/day
Grade C II		
Caspofungin	25 mg/m^2/day	Limited PK
ABLC	2.5-5 mg/kg/day	Preclinical data suggest efficacy

Clin Microbiol Infect 2012; **18** (Suppl. 7): 38–52

Fluconazole and micafungin dosing recommendations in various guiding documents (mg/kg/day)

	SPC	Blue Book	Red Book	ESCMID guidelines
Fluconazole				
Neonates	0-14d 3-12 q72h 15-17d 3-12 q48h	12 q24h	None	25 loading dose 12 q24h
Children	6-12	12	6-12	8-12
Micafungin				
Neonates	2-4	8	None	4-10
Children	2-4	2-8	4-12	2-4

Clin Microbiol Infect 2012; **18** (Suppl. 7): 38–52

Number of studies with antifungals in different age groups

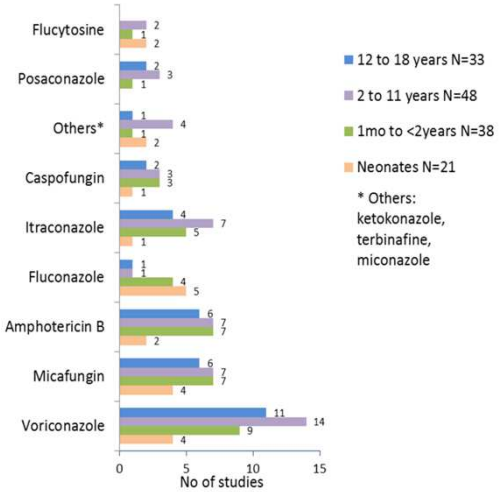
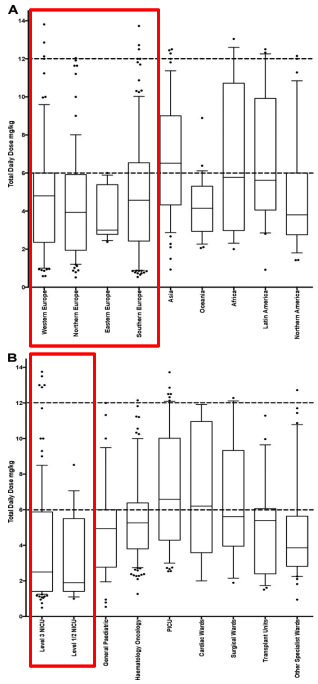


Figure 2. Number of times age groups were included in different studies

Sõnajalg K, 2015



Total daily dose of fluconazole for treatment of invasive fungal infections: ARPEC study

J. M. Lestner et al. Antimicrob. Agents Chemother. 2015;59:782-789

Dosing: neonates vs other populations

Meningitis in neonates with candidiasis is common

Characteristic	N (%)
N	223
Male, N (%)	134 (60.1)
Mode of Delivery	
Vaginal, N (%)	101 (45.3)
Cesarean, N (%)	122 (54.7)
Gestational age in weeks, mean ± standard deviation	31.4 ± 2.4
BW in grams, median (range)	1410 (750–3540)
Age at diagnosis of candidiasis in days, median (range)	15 (1–86)
Previous antibiotic therapy, N (%)	201 (90.1)
Previous postnatal steroid therapy, N (%)	50 (22.4)
Previous ventilation, N (%)	135 (60.5)
Previous peripherally inserted central venous catheter, N (%)	155 (69.5)
Length of parenteral nutrition in days, median (range)	19 (0–74)
Antifungal prevention, N (%)	62 (27.8)
Positive culture	
Blood, N (%)	214 (96.0)
Urine, N (%)	5 (2.2)
Spinal fluid, N (%)	3 (1.3)
Others, N (%)	1 (0.5)
Fungal meningitis occurred in candidemia, N (%)	48 (22.4)
Other organ fungal infection, N (%)	12 (5.4)
Antifungal therapy types	
Fluconazole only, N (%)	189 (84.8)
Fluconazole + amphotericin B, N (%)	32 (14.3)
Amphotericin B only, N (%)	2 (0.9)
Others, N (%)	2 (0.9)
Outcome	
Recovery, N (%)	174 (78.0)
Antifungal therapy days, median (range)	21.5 (5–69)
Hospitalization days, median (range)	49.5 (5–197)
Mortality (including stopping therapy), N (%)	43 (19.3)
Unknown outcome after stopping therapy, N (%)	6 (2.7)

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

Wolters Kluwer

The Pediatric Infectious Disease Journal. 33(1):106-109, January 2014.

15

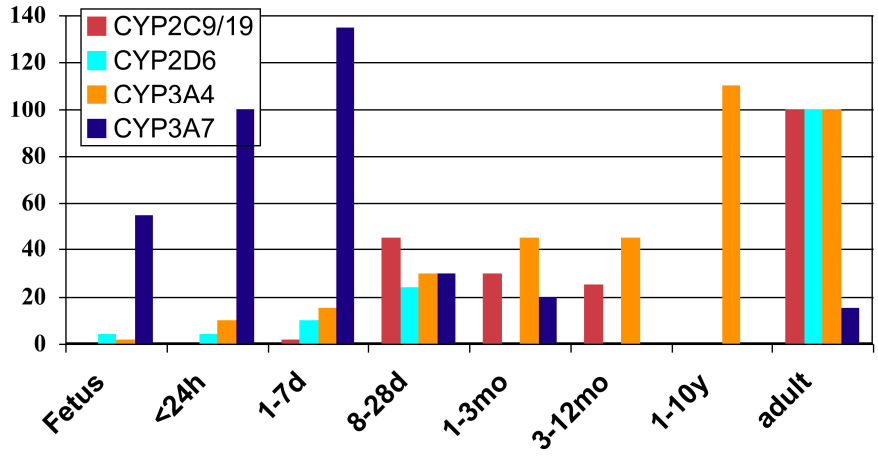
Outcome of *Candida* infection in neonates is poor

Logistic Regression Models of Death and NDI by Infection Status

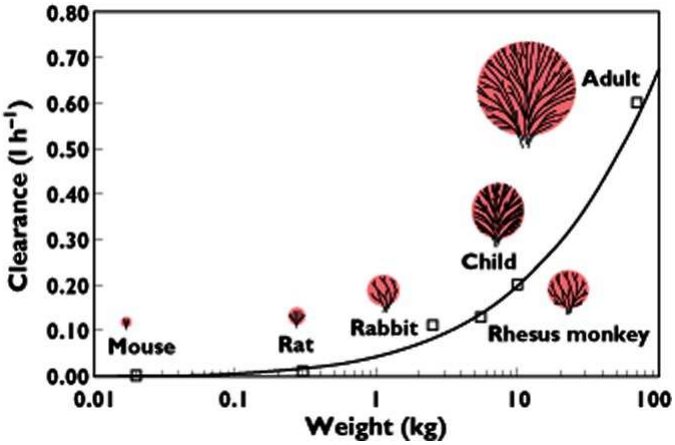
Variable	Death		NDI		Death/NDI	
	Adj OR (95% CI)	p	Adj OR (95% CI)	P	Adj OR (95% CI)	p
Infection Status: Candida vs. Groups from Candida Study						
Candida vs. Uninfected (Candida study)	4.76 (2.24, 10.14)	<0.001	1.37 (0.72, 2.63)	0.339	2.47 (1.47, 4.13)	0.001
Candida vs. LOS-Other	1.62 (0.96, 2.75)	0.073	0.79 (0.44, 1.43)	0.441	1.19 (0.76, 1.85)	0.457
Candida vs. Clinical infection	2.59 (1.47, 4.55)	0.001	0.83 (0.45, 1.53)	0.559	1.57 (0.99, 2.49)	0.057
Infection Status: Candida vs. Group from NRN registry						
Candida vs. Uninfected (NRN registry)	0.85 (0.51, 1.43)	0.545	1.83 (1.01, 3.33)	0.047	1.54 (0.99, 2.38)	0.054
Epoch 1	1.14 (0.88, 1.46)	0.325	6.22 (4.59, 8.43)	<0.001	3.35 (2.69, 4.17)	<0.001
Male	2.08 (1.62, 2.67)	<0.001	1.54 (1.19, 1.99)	0.001	1.93 (1.57, 2.37)	<0.001
Birth weight < 750g	5.41 (4.17, 7.02)	<0.001	1.66 (1.27, 2.18)	<0.001	3.20 (2.59, 3.95)	<0.001
Nonwhite race	1.07 (0.84, 1.37)	0.587	1.56 (1.21, 2.01)	0.001	1.40 (1.14, 1.72)	0.001
High school or less	1.84 (1.35, 2.52)	<0.001	1.44 (1.12, 1.86)	0.005	1.70 (1.35, 2.13)	<0.001
Postnatal corticosteroids	1.19 (0.75, 1.89)	0.452	2.24 (1.45, 3.45)	<0.001	2.00 (1.36, 2.93)	<0.001
IVH/PVL	4.84 (3.70, 6.31)	<0.001	3.08 (2.19, 4.33)	<0.001	5.45 (4.17, 7.10)	<0.001
NEC	5.20 (3.38, 8.02)	<0.001	1.26 (0.75, 2.12)	0.377	2.82 (1.90, 4.18)	<0.001

J Pediatr. 2013 October ; 163(4): 961–967

Ontogenesis of CYP450 isoenzyme activities in children compared with adults



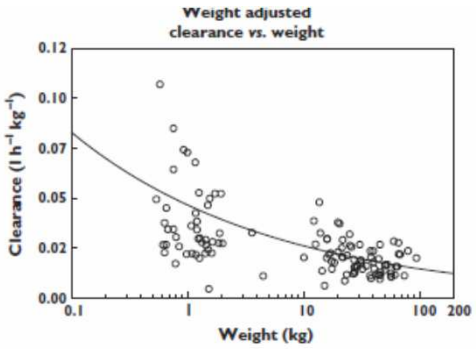
Clearance of caspofungin depending on species



Lestner et al. 2013

Weight adjusted clearance of micafungin

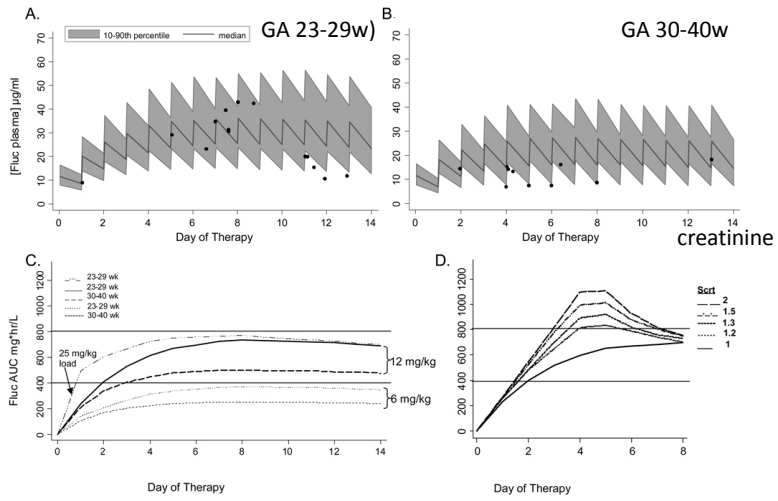
Panel B. The estimates for clearance have now been adjusted for weight. Because of the non-linear relationship between clearance and weight, adjusting for weight does not provide a correction. Neonates have higher weight adjusted clearances compared with heavier children (even though their absolute estimates for clearance are much lower, as shown in A.



AUC(0, 24 h) vs. weight

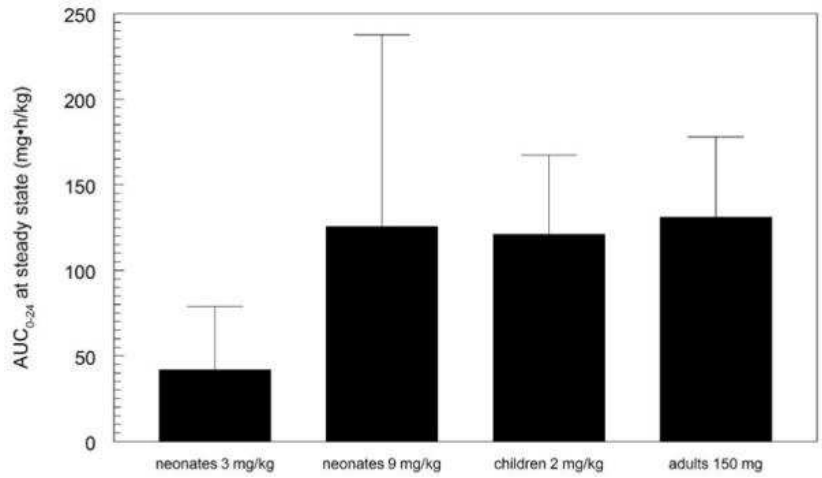
Br J Clin Pharmacol 2012 / **75**:6 / 1381–1395

Predicted medians and variability of fluconazole plasma concentrations in neonates



The Pediatric infectious disease journal. 2009;28(8):717-723

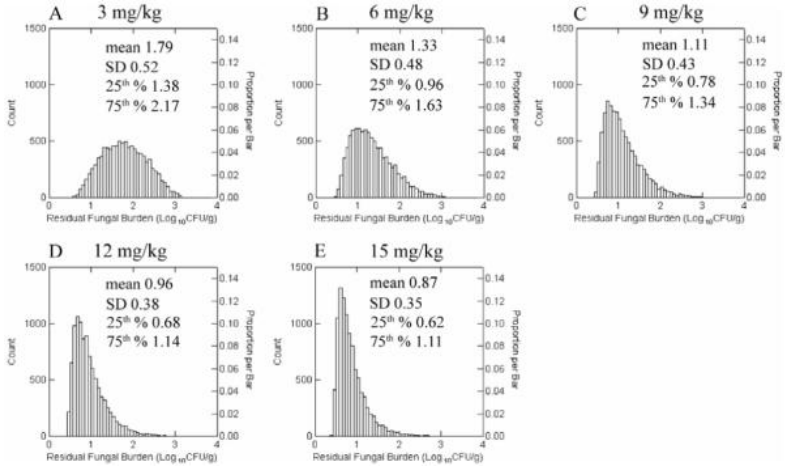
Predicted mean ± SD AUC of micafungin



J Infect Dis. 2008 Jan 1; 197(1): 163–171.

No safety concerns with high dose in small neonatal studies

Predicted residual fungal burden in CNS in simulated neonates receiving micafungin



J Infect Dis. 2008 Jan 1; 197(1): 163–171.

Future: studies for neonates

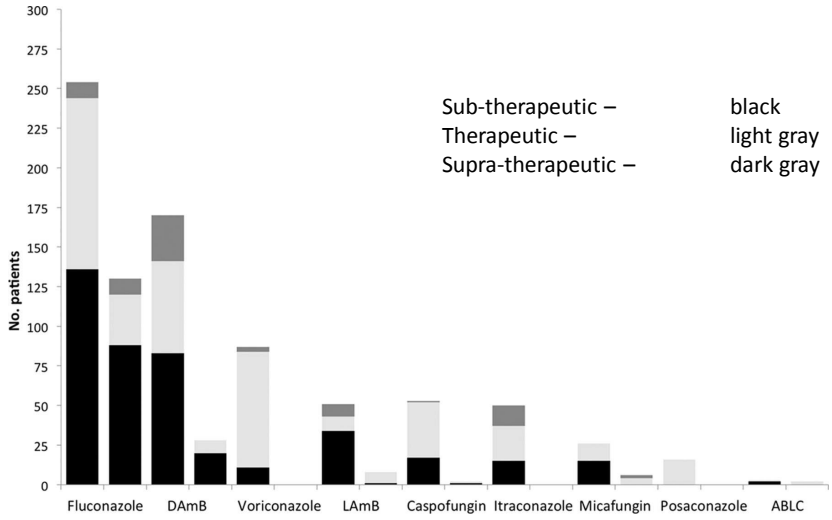
- Amphotericin formulations
  - PK studies have been completed but not reported
- Voriconazole – full waiver
- Posaconazole – no neonatal studies
- Caspofungin
  - Casp 2 mg/kg vs amphoB 1 mg/kg in culture proven infection (n =90) – recruiting
- Micafungin
  - Mica vs ampho B – terminated due to recruitment issues (n= 30)
  - Mica 15 mg/kg → 10 mg/kg/day vs fluc 25 mg/kg/day → 12 mg/kg/day or 20 mg/kg/day in candidiasis (n = 100) – ongoing
- Anidulafungin –
  - no neonatal studies planned due to excipients

www.clinicaltrials.gov

Conclusion

- Amphotericins, Fluconazole and Micafungin (caspofungin) are treatment of choice for neonatal candidiasis
- Higher doses of antifungals than recommended in the SPC and some guidelines may be needed for neonates to achieve maximum efficacy
- Current dosing recommendations mostly originate from simulation/modeling studies
- RCT may not be feasible in neonates, thus registry data will be very valuable

Numbers of patients receiving individual antifungal agents



J. M. Lestner et al. **Antimicrob. Agents Chemother. 2015;59:782-789**