

Studies in Neonatal Fungal Infections

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Background

- Invasive fungal infections in neonates are very rare
- Fungal infections in neonates are predominately caused by *Candida* spp.
- Fungal infections mainly affect very and extremely premature neonates
- *Candida* infections in neonates have poor prognosis affecting neurodevelopmental outcome
- Fungal infections in children <1 year are decreasing or there is no change
- Bridging studies in rabbits show that neonates would require much greater doses than adults with candidaemia provided that CNS penetration of antifungals is essential
- No RCT in treatment of neonatal candidiasis

Antifungals in clinical use and in development

- Amphotericin B & lipid formulations –
 - never studied but used
- Fluconazole –
 - well studied and widely used for **prophylaxis**
 - therapeutic dose should be higher based on the modelling but has been not studied in humans and rarely used in practice
- Voriconazole
 - Full waiver < 2years granted by the EMA
- Echinocandins
 - Caspofungin – approved with limited data in neonates
 - Micafungin – approved but dose might be too low according to bridging studies
 - Anidulafungin – high content of polysorbate 80, applicant is seeking for a full waiver

How to fill the caps?

- Via paediatric regulation (PDCO)
 - Request for neonatal studies with not approved agents or with new indication
 - Anidulafungin
 - New antifungals
- Via other sources
 - FP7 or alternatives
 - Horizon 2020
 - National grant schemes

Development of antifungals for neonates - options

- Full development – PK, appropriately powered efficacy and safety studies
 - May not be feasible due to small and decreasing number of patients
- PK/PD based development
 - What is the appropriate PD target – extrapolated from animals?
 - Do all neonates need to be treated with high doses of antifungals to reach brain tissue?
 - How many neonates to be included to address safety concerns?
- PK only + extrapolation of efficacy from adults/older children
 - Not sufficient
- Postmarketing registry in sentinel sites - safety