



# ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

## Paediatric Population

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Committee

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# Transparency disclosures

- Independent Contractor (research grants) of significant value from Pfizer, Gilead, Enzon, Schering
- Scientific Advisor (Review Panel or Advisory Committee) of Schering, Gilead, Astellas, Pfizer
- Speaker's Bureau of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis

# Drug Development in Paediatric Patients

- clinical studies on pharmacokinetics, safety and tolerance are prerequisite
- if underlying conditions, cause of targeted disease and expected response to therapy are similar

➔ data from adults can be used to support documentation of efficacy

# A note about grading

- Potentially slightly different from adults
- We based our decisions on
  - Efficacy in paediatrics when available
  - If only adult efficacy data are available, then grading in paediatrics depends on availability of:
    - Quality PK study
    - Safety

# Outline

- Prophylaxis in NICU
- Treatment of neonatal candidiasis
- Prophylaxis in other paediatric patients
- Treatment of candidiasis in non-neonatal paediatric patients



# Prophylaxis in NICU

Recommendation	Literature	Comments
Non-absorbable oral agents (miconazole and nystatin): BI	4 RCTs (Austin Cochrane Review 2009, Aydemir 2010)	Reduction in fungal infection, but no change in mortality, potential gut damage & NEC
Fluconazole 3 or 6 mg/kg 2-3 times per week:  Recommendation: NICUs w/ high frequency of ICI (eg >2%), ALL neonates <1000 g (28 wks): BI	<b>5 RCTs</b> (Kicklighter 2001, Kaufman 2001, Kaufman 2005, Manzoni 2007, Aydemir 2010), <b>8 historical control studies</b> (Bertini 2005, Healy 2005, Manzoni 2006, Uko 2006, Aghai 2006, McCrossan 2008, Weitcamp 2008, Healy 2008), <b>1 metaanalysis</b> (Clerihew 2008)	Reduction in candida colonization, fungal infection, but no change in overall mortality. Concerns for neurodevelopmental toxicity, emergence of resistant species

# Prophylaxis in NICU - II

In NICUs w/ low frequency (eg <2%), decision for prophylaxis is on an individual basis and based on the presence of particular risk factors

Recommendation	Literature
Hand hygiene Treatment of maternal genital candidiasis before labor Avoiding use of broad spectrum antibiotics (3 <sup>rd</sup> gen ceph, carbapenems) Avoiding use of central iv lines	Kaufman 2010

Footnote: Administration of *Lactobacillus* prevents Enteric Colonization by *Candida* Species in Preterm Neonates but not infection by *Candida* (Manzoni 2006). Under study currently

Supplementation of lactoferrin +/- LGG has a significant effect on late-onset sepsis including an effect on fungal sepsis (Manzoni 2009)



## Treatment of candidaemia in neonates: no haematogenous *Candida* meningoencephalitis - I

Recommendation	Literature	Comments
Amphotericin B deoxycholate 1 mg/kg/day BII	Mora Duarte 2002, Fernandez 2000, Koren 1988, Benson 1989, Starke 1987, Baley 1990	Deoxycholate still used in NICU, relatively well tolerated, no direct NICU data
Liposomal amphotericin B 2.5-7 mg/kg/day BII	Kuse 2007, Juster-Reicher 2000, Juster-Reicher 2003, Scarcella 1998	Dose derived from several cohort studies. Definitive evidence from adults with candidaemia, no PK data
Fluconazole 12 mg/kg/day BII  Consider proposed loading of 24 mg/kg on day 1	Rex 1994, Rex 2003, Wade 2008, Wade 2009, Schwarze 1999, Schwarze 2000, Piper PIDJ 2011	Dose derived from several cohort studies, uncertainty about optimal dosage, no triazole pre-exposure, consider local epidemiology. Possibly a loading dose





## Treatment of candidaemia in neonates: no haematogenous *Candida* meningoencephalitis - II

Recommendation	Literature	Comments
Micafungin 4-10 mg/kg/day; 2 <sup>nd</sup> choice, BII	Heresi 2006, Hope 2007, Hope 2008, Hope 2010, Kuse 2007, Smith 2009, Benjamin 2010	Optimal dosage unclear, higher dosages may be indicated. Notice: EMA label
Caspofungin 25 mg/m <sup>2</sup> /day, 2 <sup>nd</sup> choice CII	Saez-Llorens 2009, Wahab Mohamed 2011	Very limited PK data; per m <sup>2</sup> a problematic measure of size, no clear idea whether this dosage gets into CNS
Amphotericin B lipid complex 5 mg/kg/day CII	Adler-Shohet 2001, Wurthwein 2005	Limited efficacy data, supportive laboratory animal data for HCME

## Candidaemia in neonates: HCME

- CNS infection relatively common (HCME)
  - Often subclinical involvement
  - Consider adding 5-FC to AmB, maximise dosages, favour fungicidal agents
- Examine all patients for endophthalmitis
- Catheter management
  - Remove intravenous catheter if possible
- Persistent candidaemia may require a fungicidal agent
- *C. parapsilosis* exhibits reduced susceptibility to echinocandins-uncertain if this is clinically relevant

# Treatment of candidaemia in neonates: HCME

Recommendation	Literature	Comments
Amphotericin B deoxycholate 1 mg/kg/day BII	Groll JID 2000	No definitive clinical data
Liposomal amphotericin B 2.5-7 mg/kg/day BII	Groll JID 2000	No definitive clinical data, good preclinical data
Micafungin 4-10 mg/kg/day; 2 <sup>nd</sup> choice, BII	Hope JID 2008	No definitive clinical data, good preclinical data, excellent paediatric PK

# Treatment of *Candida* of the renal tract (bezoars)



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Recommendation	Literature	Comments
Fluconazole 12 mg/kg/d, BII	Triolo 2002, Robinson 2009	No efficacy studies in this age
Amphotericin B deoxycolate 1 mg/kg/d, if flu-resistant <i>Candida</i> spp. BII	Robinson 2009	Lipid amphotericin B and echinocandins do not achieve good concentrations in kidneys although there are cases treated
Removal of urine catheter, if present Ultrasound searching for renal fungal balls with occlusive urine problems. If yes, combined surgery and antifungal therapy BIII	Robinson 2009	Surgery may not be necessary

# Prophylaxis in Paediatric Allo HSCT Patients - I

Recommendation	Literature	Comments
Fluconazole 8-12 mg/kgQD PO/IV until day +75 (AI)	Goodman 1992, Slavin 1995, Marr 2000; PedPK: Lee 1992; PedSaf: Ninane 1994	Uncertain dosage; no coverage of molds, therefore only when risk of IA is low or adequate diagnostics for IA available)
Micafungin 1mg/kgQD IV until day +30 (AI)	Van Burik 2006; PedPK: Seibel 2005; PedSaf: Arrieta PIDJ in press	RCT including Paediatrics; appropriate PedPK; indication EMA approved in Paediatrics
Posaconazole 200 mg TID PO for $\geq$ grade II GVHD in $\geq$ 13 year old (BI)	Ullmann 2008; PedPK: Krishna 2007	<b>TDM should be considered.</b> Not approved in <18 yrs; drug interactions



## Prophylaxis in Paediatric Allo HSCT Patients – II

Recommendation	Literature	Comments
Voriconazole PO/IV, at approved therapeutic dosages in $\geq 2$ years (BI)	Wingard 2010; PedPK; Walsh 2004; Karlsson 2009; EMA EPAR	<b>TDM should be considered.</b> No PK/dose < 2 yrs; drug interactions; controversial dosing in paedts although approved in 2 yrs and older
Itraconazole 2.5 mg/kg BID PO plus TDM in $\geq 2$ years (BI)	Winston 2003; Marr 2004; PedPK: de Repentigny 1998; Groll 2002; Foot 1999	Not approved in children; drug interactions; <b>TDM for absorption</b>

# Prophylaxis in Paediatric AML/ Recurrent Leukaemia Patients - I

Recommendation	Literature	Comments
Fluconazole 8-12 mg/kgQD IV/PO after last day of CTX until neutrophil recovery (AI)	Rotstein 1999; PedPK: Lee 1992; PedSaf: Ninane 1994	Uncertain dosage; no coverage of molds, therefore only when risk of IA is low or adequate diagnostics for IA available
Micafungin 1mg/kgQD IV BI	Van Burik 2006. PedPK: Seibel 2005; PedSaf: Arrieta PIDJ in press	RCT including Paediatrics; appropriate PedPK; indication EMA approved in Paediatrics; option for infants < 2 years or when azoles are contraindicated
Posaconazole 200 mg TID PO in $\geq$ 13 year old (BI)	Cornely 2008; PedPK: Krishna 2007	<b>TDM should be considered.</b> Not approved in <18; drug interactions

# Prophylaxis in Paediatric AML/ Recurrent Leukaemia Patients - II

Recommendation	Literature	Comments
Voriconazole PO/IV, at approved therapeutic dosages in $\geq 2$ years (BII)	Wingard 2010; Mattiuzzi 2011; PedPK: Walsh 2004; Karlsson 2009; EMA EPAR	<b>TDM should be considered.</b> No PK/dose < 2; drug interactions; controversial dosing in Paediatrics although approved in 2 and older
Itraconazole 2.5 mg/kg BID PO in $\geq 2$ years (BI)	Menichetti 1999; PedPK: de Repentigny 1998; Groll 2002; Foot 1999	Not approved in children; drug interactions; <b>TDM for absorption</b>
Liposomal amphotericin B 1 mg/kg QOD IV (BI)	Penack 2006; PedPK: Walsh ICAAC 2008; PedSaf: Kolve 2009	Option particular for <2 years or when azoles are contraindicated



## Prophylaxis in Paediatric Auto HSCT

with ANC <500 ≥10 days, severe mucosal toxicity, or no G-CSF

Recommendation	Literature	Comments
Fluconazole 8-12 mg/kgQD IV/PO until neutrophil recovery (BI)	Rotstein 1999; PedPK: Lee 1992; PedSaf: Ninane 1994	Uncertain dosage; coverage of molds relative, as frequency is low in this population
Micafungin 1mg/kgQD IV (AI)	Van Burik 06. PedPK: Seibel 2005; PedSaf: Arrieta PIDJ in press	RCT including Paediatrics; appropriate PedPK; indication EMA approved in Paediatrics; option for infants < 2yrs or when azoles are contraindicated
Itraconazole 2.5 mg/kg BID PO in ≥ 2 years (BI)	Menichetti 1999; PedPK: de Repentigny 1998; Groll 2002; Foot 1999	Not approved in children; drug interactions; <b>TDM for absorption</b>
Lipos. amphotericin B 1 mg/kg QOD IV (BI)	Penack 2006; PedPK: Walsh ICAAC 2008; PedSaf: Kolve 2009	Option particular for <2 years or when azoles are contraindicated



## Prophylaxis in Paediatric SOT Patients

- Data in paediatric patients on which to base sound recommendations are lacking
  - Overall incidence of IC and mortality in different SOT scenarios is unknown
  - Specific risk factors in individual SOTs are unknown / may be similar to those in adults / may correspond to those of ICU patients
- No separate recommendations feasible
- Need for paediatric multi-centre register studies and interventional trials, if warranted by incidence



## Prophylaxis in PICU Patients

- Data in paediatric patients on which to base sound recommendations are lacking
- Prophylaxis with fluconazole may be considered in PICU pts at increased risk similar to adults
- Need for paediatric multi-centre studies and interventional trials, if warranted by incidence



## Empirical therapy in cancer patients for fever during neutropenia - I

Recommendation	Literature	Comments
Liposomal amphotericin B 3 mg/kg/day IV AI	Maertens 2010, Prentice 1997, Walsh 2004, Walsh 1999; PedPK: Walsh ICAAC 2008; PedSaf: Kolve 2009	Similar efficacy compared to caspo and DAmB; less Toxicity as DAmB / more nephrotoxicity as Caspo. Broad antifungal coverage
Caspofungin 50 mg/m <sup>2</sup> /day IV AI	Maertens 2010, Walsh 2004; Ped PK: Walsh 2005; Ped safety: Zaoutis 2009	Similar efficacy compared to LAmB but less nephrotoxicity Broad antifungal coverage
Fluconazole 6 mg/kg/day IV/PO BII	Viscoli 1996; PedPK: Lee 1992; PedSaf: Ninane 1994	One study including children at low risk of IA, similar efficacy than ampho B, lower toxicity

## Empirical therapy in cancer patients for fever during neutropenia - II

Recommendation	Literature	Comments
Amphotericin B deoxycholate 0.7 – 0.8 mg/kg/day IV BII	Viscoli 1996, Prentice 1997, Walsh 1999	One study including children at low risk of IA, similar efficacy than fluco, higher toxicity
Micafungin 4-10 mg/kg/day IV; 2 <sup>nd</sup> choice, BII	Kubiak 2010; PedPK: Seibel 2005; PedSaf: Arrieta PIDJ in press	No paediatric data in this indication; not significantly different of caspo in large retrospective adult cohort study
Amphotericin B lipid complex 5 mg/kg/day IV CII	Wingard 2000; PedPK: Walsh 1997; PedSaf: Wiley 2005	No paediatric data in this indication; more toxic as LAmB in randomized study in adults

No paediatric data on feasibility of pre-emptive therapy

# Treatment of invasive candidiasis/candidaemia- non neonate - I

Recommendation	Literature	Comments
<b>1st line</b>		
Liposomal amphotericin B 3 mg/kg AI	Queiroz-Telles 2008	
Fluconazole 8-12 mg/kg BI	Rex 1994, Rex 2003	Optimal dosage not defined; Avoid if previous exposures to triazoles; If allowed by local epidemiology; Not critically ill
Voriconazole 7 mg/kg q12 BI >12 years as adults	Neely 2010, Walsh 2004	Optimal dosage not defined; Need for TDM; Variable pharmacokinetics; Risk of drug interactions; No data in children < 2 years
Posaconazole		No advantages for <i>Candida</i>
Isavuconazole / itraconazole		No data



## Treatment of invasive candidiasis/candidaemia- non neonate - II

Recommendation	Literature	Comments
Caspofungin 50 mg/m <sup>2</sup> AI	Walsh 2005, Neely 2009	No loading dose; maximum 70 mg/day
Micafungin < 40 kg 2-4 mg/kg AI > 40 kg 100-200 mg	Queiroz-Telles 2008, Hope 2007	EMA warning
Anidulafungin 3 mg/kg loading dose, 1.5 mg/kg maintenance BIII	Benjamin 2006	Possible paediatric dosages, more studies in progress
<b>2nd line</b>		
ABLC 5 mg/kg AI	Wiley 2005	Infusion toxicity



# Treatment of invasive candidiasis/candidaemia- non neonate - I

Recommendation	Literature	Comments
Neutropenic vs. non neutropenic: use fungicidal agent		No specific studies in children; recommendations extrapolated from adult studies, no availability of paediatric PK data
Catheter management: removal etc		
Surveillance of local epidemiology		
Combined therapy includes 5-FC with other agents, no advantages combining fluconazole and amphotericin B: use in meningitis, peritonitis, septic arthritis, severe urinary tract infections		



# Treatment of invasive candidiasis/candidaemia- non neonate - II



Recommendation	Literature	Comments
Eye examination in all patients <i>Candida</i> species		No specific studies in children; recommendations extrapolated from adult studies, no availability of paediatric PK data
Amphotericin B or echinocandins for <i>C. glabrata</i> or <i>C. krusei</i>		
Increased MIC of echinocandins against <i>C. parapsilosis</i> may be present, but no clinical differences demonstrated		

MIC: minimum inhibitory concentration



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Thank you



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