Antifungals and current treatment guidelines in pediatrics and neonatology

Dragana Janic. University Children`s Hospital, Belgrade, Serbia

- **Infectious Diseases Society of America (IDSA), 2016**

Pappas PG et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4)

- **The European Conference on Infection in Leukaemia (ECIL-4), 2014**

Groll AH et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol. 2014 Jul;15(8):e327-40

- **The European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 2012**

Hope WW et al. 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. Clin Microbiol Infect. 2012 Dec;18 Suppl 7:38-52*

Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy (DMyKG), 2011

Ruhnke M et al. Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. Mycoses. 2011 Jul;54(4):279-310

Characteristics of the guidelines

ESCMID	ECIL
All children Only candida A B C / I II III + D supports recommendation against use	IFI in pediatric hematological and oncological patients A B C / I II III

IDSA	DMyKG
Specific for neonates, otherwise extrapolation of adult guidelines A B C / I II III	All children Only candida A B C / I II III

Candida IFI facts

- 10% nosocomial BSIs, 50% of CVC infections, 50% non-albicans spp, 1.5 to 5 times more prevalent in children than in adults, mortality 50% in neonates, frequent meningoencephalitis in neonates
- Susceptibility: C. albicans, C. parapsilosis, C. tropicalis to fluconazole and other azoles, AMB and echinocandines
- Resistance: C. crusei and C. glabrata to fluconazole and variably to other azoles
- Emerging: C. parapsilosis (neonatal patogen) resistance to fluconazole
- Far less prevalent C. guillermondi to echinocandines, C. lusitaniae resistance to AMB

Candida IFI diagnosis

- IDSA (neonates)
  - CSF + dilated retinal exam in pts with + BC and/or urinoculture A-III
  - Imaging of liver, spleen and genitoutinaty tract in case of persistently + cultures from sterile body fluids A-III
  - Meningoencephalitis often, also liver, spleen, joints, eye, lungs, endocarditis rarely
  - Septic shock not often as in older children
- ESCMID, ECIL, DMyKG
  - Culture/microscopic exam, susceptibility testing YES
  - Non/culture assays NO
  - Search for endocarditis, endophtalmitis, chorioretinitis

Treatment of IC non-neutropenic pts: D-AMB, L-AMB and ABLC

ESCMID	ECIL
D-AMB: C-I **L-AMB: A-I** ABLC: B-II	D-AMB: / **L-AMB: /** ABLC: C-II

IDSA	DMyKG
D-AMB: A-I **L-AMB: A-I** ABLC: /	D-AMB: C-III **L-AMB: A-I** ABLC: A-II

Treatment of IC non-neutropenic pts : caspofungin, micafungin and anidulafungin

ESCMID	ECIL
caspofungin : A-I micafungin : A-I anidulafungin: B-II	caspofungin : B-II micafungin : B-II anidulafungin: /

IDSA	DMyKG
caspofungin : A-I/A-III* micafungin : A-I/A-III* anidulafungin: /	caspofungin : A-II micafungin : A-I anidulafungin: /

Treatment of IC non-neutropenic pts: fluconazole and voriconazole

ESCMID

fluconazole: B-I
voriconazole : B-I

ECIL

fluconazole: B-II
voriconazole: B-II

IDSA

fluconazole: A-I/A-III*
voriconazole: A-I

DMyKG

fluconazole: A-II
voriconazole : A-II
for second line therapy

Treatment of IC in neonates: D-AMB, L-AMB, ABLC and ABCD

ESCMID
D-AMB: B-II **L-AMB: B-II** ABLC: C-II ABCD: /

- L AMB – lack of randomized studies in this population

IDSA
D-AMB: A-II **L-AMB: B-III** kidney concentration low

DMyKG
D-AMB: C-III **L-AMB: A-II** ABLC: A-II ABCD: /

Treatment of IC in neonates: caspofungin and micafungin, fluconazole

ESCMID

caspofungin: C-II
micafungin: B-II
fluconazole B-II

Flucytosine combination with L-AMB or fluconazole for meningoencephalitis in IDSA and DMyKG C-III if not used in prophylaxis

IDSA

caspofungin: /
micafungin: B-IIIkidney and CSF penetration low, not for meningoencefalitis
fluconazole B-II for continuation therapy

DMyKG

caspofungin: A-II
micafungin: A-II
fluconazole A-III

Remove CVC or not?
Duration of therapy?

ESCMID
Remove indwelling lines when possible A-II If not use **L AMB** and echinocandines C II When CVC cannot be removed do not use D-AMB and azoles D-II
Treat at least 14d after the last + BC A III. If still neutropenic evaluate for resolution of signs and symptoms including exclusion of endocarditis and endophtalmitis

IDSA
Remove CVC A-II Treat neonates for 3w B-II Replace on an anatomicaly distinct site when treating with antifungals In chronic disseminated candidiasis (hepatosplenic) **L AMB** has highest recommendation. Treat until lesions resolve on imaging (several months). Do not delay further chemo od SCT

Prevention of IC in neonates

ESCMID
Nystatin > 1500gr B-II *Lactobacillus* and lactoferrin B-II Fluconazole for all high-risk NICUs and BW<1000gr A-I
When Nystatine beware of NEC risk When Fluconazole beware of theoretical concern of neurodevelopmental toxicity and of drug resistance

IDSA
Idem for Fluconazole A I, Nystatin and lactoferin C II ESCMID, IDSA Treatment of maternal vaginal candidiasis to prevent neonatal colonization

High risk NICU has more than 10% IFI

ECIL recommendation for diagnostics of IFI

Galactomannan in serum:

- Prospective monitoring and serial screening of galctomannan twice weekly in children at high risk for IFI (A-II)
- Threshold >0.5 (B-III)

Galactomannan in bronchoalveolar lavage:

- Threshold > 1 is adjunctive method for diagnosis if invasive pulmonary aspergilosis (B-III)

Galactomannan in cerebrospinal fluid:

- Threshhold > 0.5 is adjunctive method for diagnosis if invasive aspergilosis of CNS (B-III)

β-D-glucan:

- No specific recommendations and grading

Detection of fungal nucleic acids in body fluids and tissues:

- No specific recommendations and grading

Imaging:

- Perform CT of the lung or adequate imaging of the symptomatic region in high-risk patients with febrile neutropenia that persists beyond 96h or with focal clinical findings (B-II)

Empiric antifungal treatment in neutropenic children: D-AMB, L-AMB, caspofungin and fluconazole

ESCMID
D-AMB: B-II if available and if higher toxicity acceptable **L-AMB: A-I** Caspofungin: A-I Fluconazole: B-II in case of low incidence of aspergillosis or using a mould-specific diagnostic algorithm

IDSA
D-AMB: / **L-AMB: /** Caspofungin: / Fluconazole: /

ECIL
D-AMB: / **L-AMB: A-I** Caspofungin: A-I Fluconazole: /

Empiric and preemptive antifungal treatment

ESCMID
ANC<500 for 10d + refractory or new fever despite broad spectrum antibiotics

ECIL
For AL and HSCT: After four day of fever unresponsive to broad spectrum antibiotics (B-II) and should be continued until resolution of neutropenia (B-II). No grading for preemptive but can be applied if rapid lung CT, bronchoscopy and galactomannan available. Discouraged for candida

Empirical antifungal therapy – risk stratification

- High risk of IFD: patients with AML, high-risk ALL, relapsed acute leukemia, children undergoing allogeneic HSCT
- Children with prolonged neutropenia and children receiving high-dose corticosteroids
- All others should be categorized as low risk (A-III)
- In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or **liposomal amphotericin B** for empirical antifungal therapy A-I
- In IFD low-risk patients with prolonged (≥ 96 hours) FN, consider withholding empirical antifungal therapy C-III*

Initial treatment of IA and salvage therapy

IDSA	ECIL
Initial: voriconazole: A-I **L-AMB: A-I** Combination therapy not reccomended: B-II **Salvage:** **L-AMB: A-II** posaconazole: B-II itraconazole: B-II caspofungin: B-II voriconazole TDM (B-III) and change to i.v. therapy is an option. Combination therapy: B-II	**Initial:** voriconazole: A-I **L-AMB: B-I** ABLC: B-II Combination echinocandin + polyene/triazole: C-III **Salvage:** voriconazole: A-I **L-AMB: B-I** caspofungin: A-II ABLC: B-II Combination echinocandin + polyene/triazole: C-II