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Antifungals and current treatment guidelines in pediatrics and neonatology

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- **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

All children
Only candida
A B C / I II III + D supports
recommendation against use

ECIL

IFI in pediatric hematological and
oncological patients
A B C / I II III

IDSA

Neonates
A B C / I II III

DMyKG

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 pathogen) resistance to fluconazole
- Far less prevalent *C. guilliermondii* to echinocandines, *C. lusitanae* to AMB

Candida IFI diagnosis

- IDSA (neonates)
 - CSF + dilated retinal exam in pts with + BC and/or urinoculture B-III
 - Imaging of liver, spleen and GU tract in case of persistently + cultures from sterile body fluids A-III
 - Meningoencephalitis often, also liver, spleen, joints, eye, lungs
 - Septic shock NO
- ESCMID, ECIL, DMyKG
 - Culture/microscopic exam, susceptibility testing YES
 - Non/culture assays NO
 - Search for endocarditis, endophthalmitis, chorioretinitis

Treatment of IC: D-AMB, L-AMB and ABLC

ESCMID

D-AMB: C-I
L-AMB: A-I
ABLC: B-II

ECIL

D-AMB: /
L-AMB: /
ABLC: C-II

IDSA

D-AMB: A-I
L-AMB: A-I
ABLC: /

DMyKG

D-AMB: C-III
L-AMB: A-I
ABLC: A-II

Treatment of IC: caspofungin, micafungin and anidulafungin

ESCMID

caspofungin : A-I
micafungin : A-I
anidulafungin: B-II

ECIL

caspofungin : B-II
micafungin : B-II
anidulafungin: /

IDSA

caspofungin : A-I/A-III*
micafungin : A-I/A-III*
anidulafungin: /

DMyKG

caspofungin : A-II
micafungin : A-I
anidulafungin: /

Treatment of IC: 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

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: /

IDSA

D-AMB: A-II

L-AMB: B-III

ABLC: B-III

ABCD: B-III

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

IDSA

caspofungin: /
micafungin: B-III
fluconazole B-II

DMyKG

caspofungin: A-II
micafungin: A-II
fluconazole B-II

Remove CVC or not? Duration of therapy?

ESCMID

Remove indwelling when possible
A-II

When CVC cannot be removed do
not use D-AMB and azoles D-II

Treat at least 14d after the last +
BC. If still neutropenic evaluate for
resolution of signs and symptoms
including exclusion of endocarditis
and endophthalmitis

IDSA

Remove CVC A-II

Treat neonates for 3w B-II

Replace CVC on an anatomically
distinct site when treating
with antifungals

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

ESCMID, IDSA

Treatment of maternal vaginal
candidiasis to prevent neonatal
colonization

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JAMA. 2014 May 7; 311(17): 1742–1749. doi:10.1001/jama.2014.2624.

Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: A randomized clinical trial

Daniel K. Benjamin Jr., MD, PhD, Mark L. Hudak, MD, Shahnaz Duara, MD, David A. Randolph, MD, PhD, Margarita Bidegain, MD, MHS-CL, Gratias T. Mundakel, MD, Girija

CONCLUSIONS AND RELEVANCE—Among infants with a birth weight of less 750 g, 42 days of fluconazole prophylaxis compared with placebo did not result in a lower incidence of the composite of death or invasive candidiasis. These findings do not support the universal use of prophylactic fluconazole in extremely-low-birth-weight infants.

ECIL recommendation for diagnostics of IFI

Galactomannan in serum:

- Prospective monitoring and serial screening of galactomannan 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:

- Threshold > 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.

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

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

casprofungin: B-II

Voriconazole TDM (B-III) and
change to i.v. therapy is an option.

Combination therapy: B-II

ECIL

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

casprofungin: A-II

ABLC: B-II

Combination echinocandin +
polyene/triazole: C-II