# Treatment and Prophylaxis

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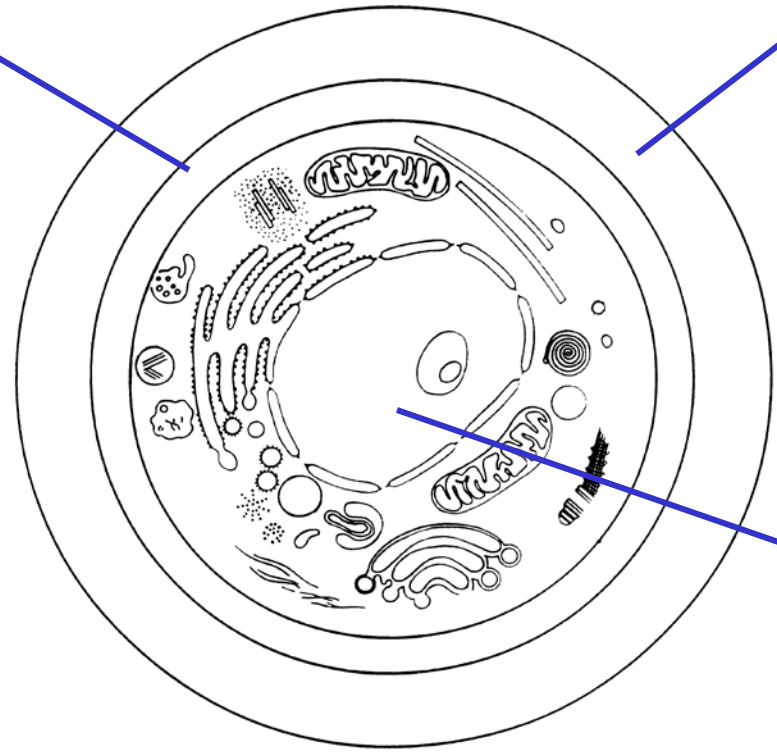
# Pediatric Antifungal Armamentarium

## ***Cell membrane***

- **Polyenes**
  - > DAMB
  - > LAMB
  - > ABLC

- **Triazoles**
  - > Fluconazole
  - > Itraconazole
  - > Voriconazole *
  - > Posaconazole



## ***Cell wall***

- **Echinocandins**
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

## ***Nucleic acid synthesis***

- > Flucytosine

# EMA Guidance for Pediatric Drug Development

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

➡ **data generated in adults can be used to support documentation of efficacy**

However, the regulations stress the importance of post-marketing surveillance to increase the pediatric database

European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION(CPMP/ICH/2711/99).

# Algorithms of Antifungal Interventions

- **Primary prophylaxis**
- **Empirical therapy**
- **Pre-emptive therapy**
- **Treatment of documented infections**
- **Secondary prophylaxis**

➢ ***Focus on cancer/HSCT patients and recommendations of the ECIL Pediatric Group***

# ECIL 4 - A Note about Grading

- Guided by concepts of pediatric drug development
- Decisions based on
  - efficacy in pediatric patient when available
  - if only adult efficacy data are available, then grading in pediatrics depends on availability of:
    - quality PK study
    - safety data
  - regulatory approval also considered

# Treatment Algorithms for Invasive Fungal Diseases

# Overriding Principle

- **In practice, treatment often needs to be started pre-emptively on the basis of clinical findings, imaging results and/or antigen markers**
- **Despite this situation, however, all efforts should be made to perform the necessary procedures to**
  - **identify the causative agent**
  - **to allow for resistance testing**

# Candidemia:
# First-line Clinical Trial Data

| Treatment | Success at EOT |
|---|---|
| D-AMB 0.7-0.9 mg/kg/d | 62 – 79% [1-4] |
| Fluconazole 400 mg/d | 72% [1] |
| Flu 800 + D-AMB 0.7 * | 68% [5] |
| ABLC 5 mg/kg/d * | 65% [4] |
| L-AMB 3 mg/kg/d | 89.5% [6] |
| Caspofungin 70/50 mg/d | 74% [2] |
| **Voriconazole 12/6 mg/kg/d** | 70% [3] |
| Micafungin 100 mg/d | 89.6% [6] |
| **Anidulafungin 200/100 mg/d **** | 75,6% [7] |

*Rex 94; 2, Mora 02; 3, Kullberg 04; 4, Anaissie 95; 5, Rex 01; 6, Kuse 07; 7, Pappas 07; 8, Reboli 07*

# ECIL 4 Recommendations: Candidemia and Invasive Candidiasis

Management includes antifungal therapy, control of underlying condition(s), surgery, removal of central venous line (no grading)

*Antifungal therapy*: *

| | |
|---|---|
| Amphotericin B Lipid Complex | C II |
| Caspofungin [2] | B II |
| Fluconazole [2] | B II |
| Liposomal Amphotericin B | B II |
| Micafungin [1,2] | B II |
| Voriconazole +TDM [2] | B II |

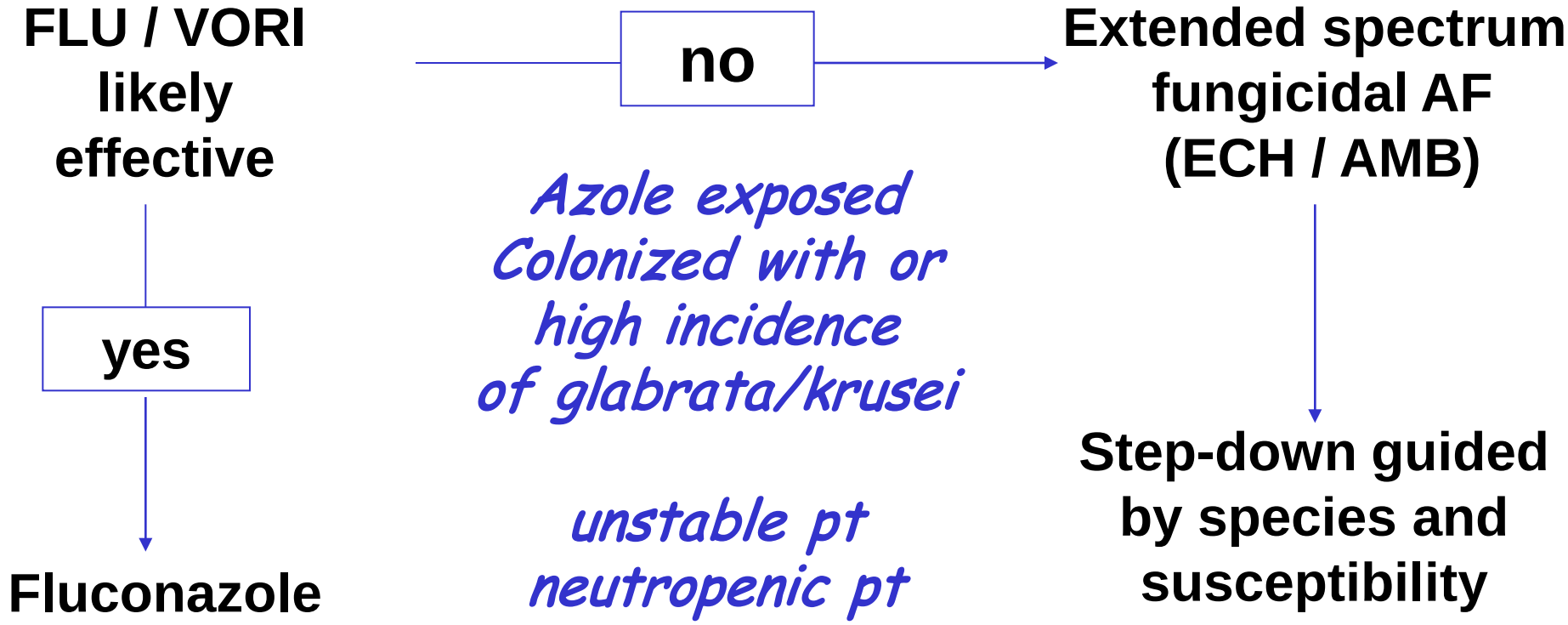
[1] note EMA Black Box Warning for micafungin; implications for other echinocandins not clear

[2] C.krusei is inherently resistant to fluconazole; C.glabrata has variable susceptibility to fluconazole, and treatment with fluconazole is not advised; echinocandins have higher MICs against C.parapsilosis, however, the clinical implications are unknown.



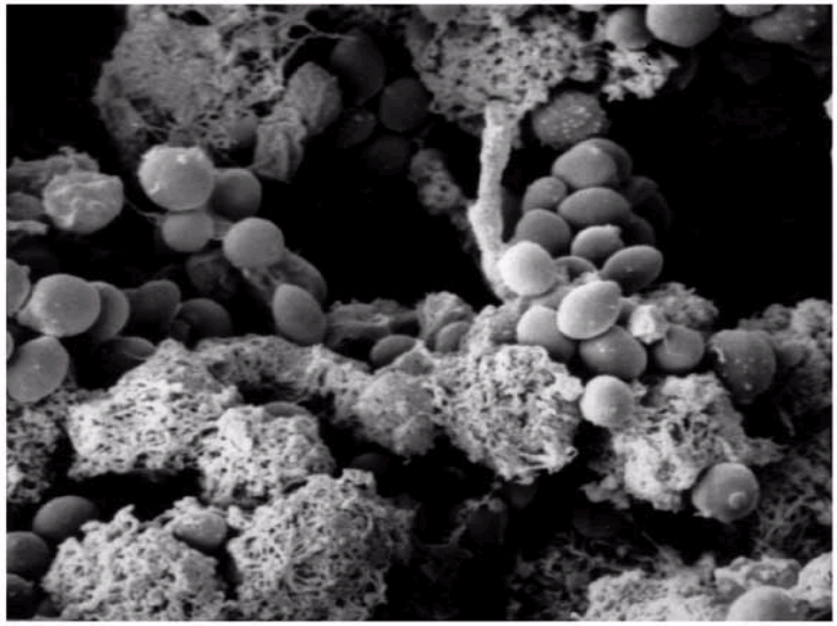
* *in alphabetical order*

# Initial Treatment Algorithm




*modified from Kullberg 05*

# General Management Issues



*Maki EID 01*

## ! Consider catheter removal

- **CSFs in neutropenic patients, discontinuation of steroids in immunosuppressed patients**
- **Therapy for 14 days after last pos. blood culture and resolution of all clinical symptoms**
- **Fundoscopy (ultrasound) prior to end of treatment**

*Pappas PG et al. Clin Infect Dis 2009;48:503–35; Nucci M et al. Clin Infect Dis 2010;51:295–303*

# Invasive Aspergillosis: First Line Clinical Trial Data

| Treatment | CR/PR at 3 mo | Surv. at 3 mo |
|---|---|---|
| Voriconazole 12/8 mg/kg | **52.8 %** | **70.8 %** |
| **D-AMB 1.0 mg/kg + OLAT** | **31.6 %** | **57.9 %** |

| | CR/PR at EOT | Surv. at 3 mo |
|---|---|---|
| **L-AMB 3 mg/kg** | **50.0 %** | **72 %** |
| **L-AMB 10 / 3 mg/kg** | **46.0 %** | **59 %** |

*Herbrecht 02; Cornely 05*

# ECIL 4 Recommendations: 1st line Therapy of Invasive Aspergillosis

*Antifungal therapy*: *

| | |
|---|---|
| ABLC | B II[1] |
| Liposomal AmB | B I [1] |
| Voriconazole i.v. +TDM | A I [1] |
| Combination therapy | C III |

[1] voriconazole should be preferred in CNS infection.

[2] oral voriconazole should be used in presence of renal failure because of potential for accumulation of the cyclodextrin excipient

* *in alphabetical order*

# Initial Treatment Algorithm in Pediatric Patients

**Voriconazole susceptible strain likely**

**yes**

**Voriconazole**

**no**

***VCZ exposed***
***PCZ exposed***
***high incidence of zygomycosis***
***<u>or</u>***
***no TDM available***
***age < 2 years***
***contraindications***

**Liposomal Amphotericin**

**Modification guided by species, response and tolerance**

*references in Groll AH, EHD 2011*

# Voriconazole:
# Current Dosage Recommendation

***Children 2 to 11 years and***
***adolescents 12-14 years and <50 kg***

- **2x8 mg/kg IV (day 1: 2x9 mg/kg)**
- **2x9 mg/kg PO (max: 2x350mg)**

***Adolescents*** **≥12 to 14 years and > 50 kg**
**and those 15 years and beyond:**

- **2x4 mg/kg IV (2x6 mg day 1)**
- **2x200 mg PO (2x400 mg day 1) (adult dose)**

# Is TDM Indicated to Guide VCZ Treatment ?

**The pharmacology of VCZ makes it a candidate for TDM**

- Interpretation of concentrations requires achievement of steady state – achivement of steady state, however, uncertain in a non-linear drug
  - Start monitoring early to avoid subtherapeutic exposure early during therapy

- Current boundaries for the therapeutic use range between 2 to 6 ug/mL at trough
  - Increments/decrement not defined – suggestion: 50 and 100 mg per dose in children and adolescents, respectively

# General Management Issues

- ***Adjunctive surgery:*** **skin and soft tissue infections; impeding arrosion of pulmonary arteries; operable CNS or lung lesions**
- **CSFs in neutropenic patients**
- **D/c of steroids immunosuppressed pts**
- **Evaluation for further sites of infection (CNS)**
- **Duration of therapy determined response and reversal of deficit in host defenses**

*Groll & Ritter Klin Padiatr 2005;217 S1: S37; Walsh et al. Clin Infect Dis 2008;46:327*

# Options for Non-*Aspergillus* Mould Infections

| | AMB | CAS | VCZ | ITC | PCZ |
|---|---|---|---|---|---|
| *A.fumigatus* | S | S | S | S | S |
| *A.flavus* | S | S | S | S | S |
| *A.niger* | S | S | S | S | S |
| *A.terreus* | I-R | S | S | S | S |
| ***Zygomycetes*** | **S** | **R** | **R** | **S-I** | **S-I** |
| ***Hyalohyphomyc*** | **I-R** | **R** | **I-R** | **I-R** | **I-R** |
| ***Phaeohyphomyc*** | **S-I** | **I-R** | **S-I** | **S-I** | **S-I** |

*Pfaller MA & Diekema DJ. J Clin Microbiol 2002;40:3551–7; Johnson LB & Kauffman CA. Clin Infect Dis 2003;36:630–7; Lass-Floerl C et al. ICAAC 2007*

# Empirical / Pre-emptive Therapy and Primary Chemoprophylaxis

# Antifungal Prevention: Rationale / Strategies

- **Difficulties in diagnosis and prognostic impact of early treatment provide rationale for initiation of treatment before a definite microbiological diagnosis**
  - **Empirical therapy *(fever criterion*)**
  - **Pre-emptive therapy *(CT, galactomannan)***
- **Also available: Primary prophylaxis**

# ECIL 4 Recommendations:
## Empirical and Pre-emptive Therapy

- If chosen as strategy, empirical therapy should be initiated after 96 hours of fever with unclear origin unresponsive to broad-spectrum antibacterial agents (BII)
- Both caspofungin and liposomal amphotericin B (1-3 mg/kg/d) can be recommended for empirical antifungal therapy in children (AI)
- Although there are no for patients already receiving mold-active antifungal prophylaxis, however, switching to a different class of mold-active antifungal agent seems reasonable (no grading)
- Therapy should be continued until resolution of neutropenia (BII)
- Although there are no data on pre-emptive strategies in children, it may be an alternative to empirical therapy (no grading)

# Primary Chemoprophylaxis: Targets and Intention

- ***Target:***
  - **Populations at high risk (≥ 10%)**
    - **AML, recurrent leukemia's, ? high risk ALL**
    - **Allogeneic HSCT**
      - **ANC ≤500**
      - **grade III/IV GVHD**
- ***Intention:***
  - **Reduction of invasive fungal diseases**
  - **Reduction of overall patient mortality**

# Primary Chemoprophylaxis: Strategies in Adults and Impact

| | Impact on | |
|---|---|---|
| | invasive infections | overall mortality |
| Topical azoles / polyenes | 0 | 0 |
| Aerosolized DAMB | 0 | 0 |
| Aerosolized LAMB | + (IA) | 0 |
| Low-dose DAMB / ABLC | ? | 0 |
| Low-dose LAMB | + | 0 |
| Fluconazole 400mg | + | + |
| Itraconazole (≥0.5µg/mL) | + (+IA) | 0 |
| Micafungin | + | 0 |
| Posaconazole | + (+ IA) | + |
| Voriconazole | + | 0 |

*References in Groll & Tragiannidis Sem Hematol 2009; 46: 212*

# ECIL 4 Recommendations:
## Primary Chemoprophylaxis in Leukemia Patients

- **Primary antifungal prophylaxis against IFDs should be considered in high risk patients (BII)**

- ***Options include (alphabetical order):***
  - fluconazole (CI) (active only against yeast)
  - itraconazole (BI), TDM recommended
  - liposomal amphotericin (BII)
  - Posaconazole (BI for children >12 years), TDM recommended

  - other options include voriconazole +TDM, micafungin, and aerosolized liposomal amphotericin B (no grading)
  - note: caution should be used with the concurrent use of itraconazole, posaconazole, voriconazole with vincristin

*TDM, therapeutic drug monitoring*

# ECIL 4 Recommendations:
## Primary Chemoprophylaxis in allo HSCT: Neutropenic Phase

- **Primary prophylaxis against IFDs is recommended during the neutropenic phase until engraftment (BII)**
- ***Options include (alphabetical order)***
  - *fluconazole (AI) (active only against yeast)*
  - *Itraconazole (BI), TDM recommended*
  - *liposomal amphotericin (CIII)*
  - *micafungin (CI)*
  - *Voriconazole (BI), TDM recommended*
  - *other options include aerosolized LAMB and posaconazole +TDM (no grading)*

*TDM, therapeutic drug monitoring*

# ECIL 4 Recommendations:
## Primary Chemoprophylaxis in allo HSCT: Post Engraftment

- **<u>No GVHD, standard immunosuppression:</u>**
  - **continue prophylaxis until immune recovery (no grading)**
- **<u>GVHD, augmented immunosuppression:</u>**
  - **primary prophylaxis against mould and yeast infections is recommended (AII); options include *(in alph. order):***

    - itraconazole (CII), TDM recommended
    - posaconazole (BI for children >12 years), TDM recommended
    - voriconazole (BI), TDM recommended

  other options include liposomal amphotericin B and micafungin (no grading)

*TDM, therapeutic drug monitoring*

# Algorithm for Persistently Febrile Neutropenic or for Symptomatic Patients

**Diagnostic work up including blood cultures, galactomannan antigen x3, chest CT and other imaging as indicated**

- **All studies negative:**
  - ***Continue prophylaxis or start empirical therapy (change of class)***
- **Positive blood cultures:**
  - ***Treat according to species/in vitro susceptibility (change of class)***
- **Galactomannan positive, chest CT negative:**
  - ***Start pre-emptive antifungal therapy (change of class)***
- **Positive chest CT / positive imaging:**
  - ***Start pre-emptive therapy (change of class) and pursue invasive diagnostic procedures***

# Conclusions

# Invasive Fungal Infections

**Continue to be important causes of morbidity and mortality**

**Further research needed**

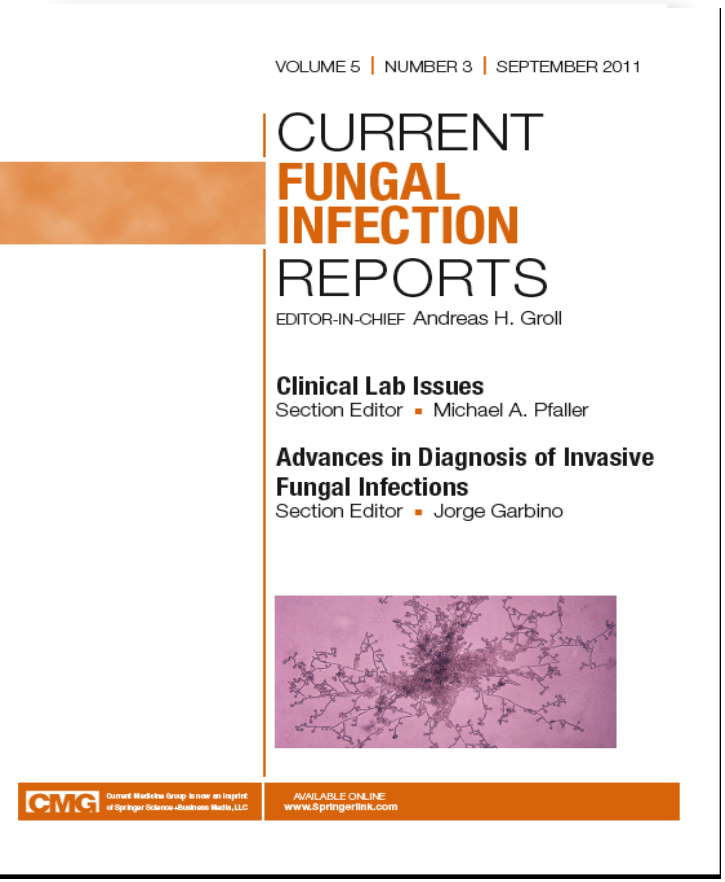
- **Epidemiology and outcome**
- **Imaging and molecular diagnostics**
- **Phase IV clinical programs**
- **Education and procedural auditing**

# ECIL 4 – Pediatric Group Considerations for Fungal Diseases and Antifungal Treatment in Children

Elio Castagnola (Italy); Simone Cesaro (Italy); Jean-Hugues Dalle (France); Dan Engelhard (Israel); William Hope (United Kingdom); Thomas Lehrnbecher (Germany); Emmanuel Roilides (Greece); Jan Styczynski (Poland), Adilia Warris (The Netherlands)

Co-ordinator: Andreas H. Groll (Germany)

European Conference on Infections in Leukemia
- a joint initiative of EBMT, ICHS, EORTC and European LeukemiaNet

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Editor-in-Chief: Andreas H. Groll

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