Antifungal Therapy for Children

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Invasive fungal infections

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- Important causes of infectious morbidity and mortality in immunocompromised children
- Display constant epidemiological shifts that follow the evolution of clinical medicine
- Remain difficult to diagnose, and newer diagnostic tools seem to have different validity in the pediatric population

Algorithms of antifungal interventions

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- Primary prophylaxis
- Empirical therapy
- Pre-emptive therapy
- Treatment of documented infections
  - induction
  - consolidation / maintenance
  - salvage therapy
- Sekundary prophylaxis

Pediatric Antifungal Arsenal

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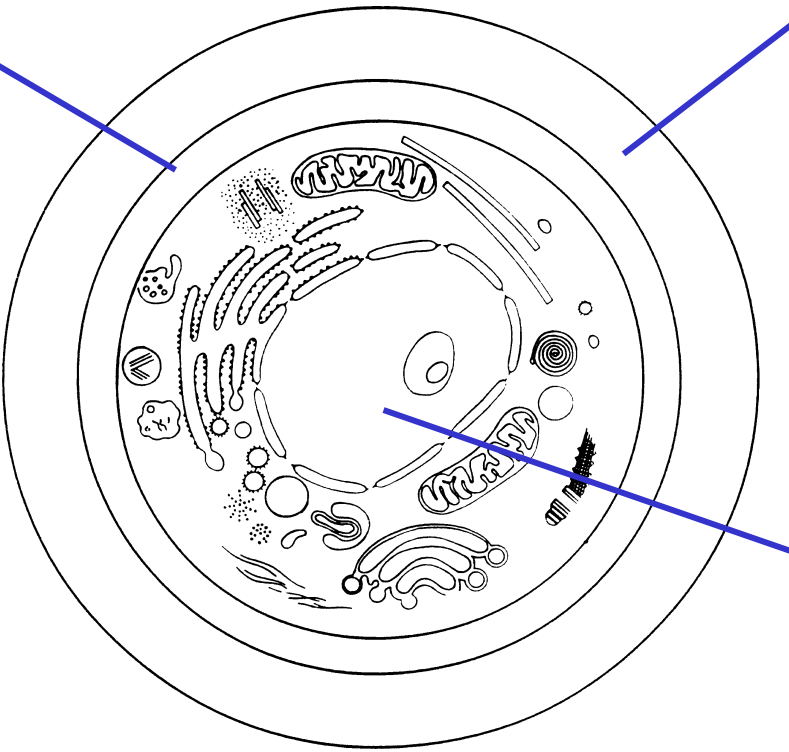
Cell membrane

- Polyenes
  - > D-AmB
  - > L-AmB
  - > ABLC
- Triazoles
  - > Fluconazole
  - > Itraconazole
  - > Voriconazole
  - > Posaconazole



Cell wall

- Echinocandins
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

Nucleic acid synthesis

- > Flucytosine

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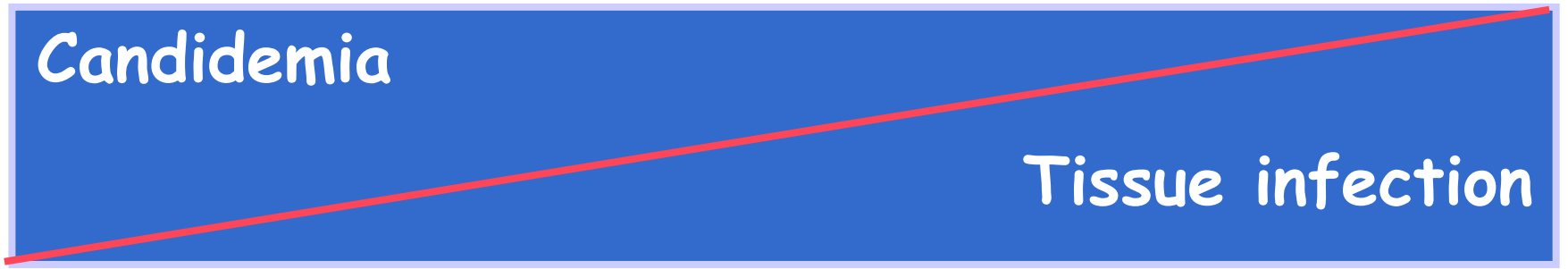
Invasive *Candida* Infections

Inv. candidiasis: Spectrum of the disease



catheter-associated candidemia	acute dissemin. candidiasis	candidiasis of deep compartments	chronic dissem. candidiasis

"Yeast in blood culture"

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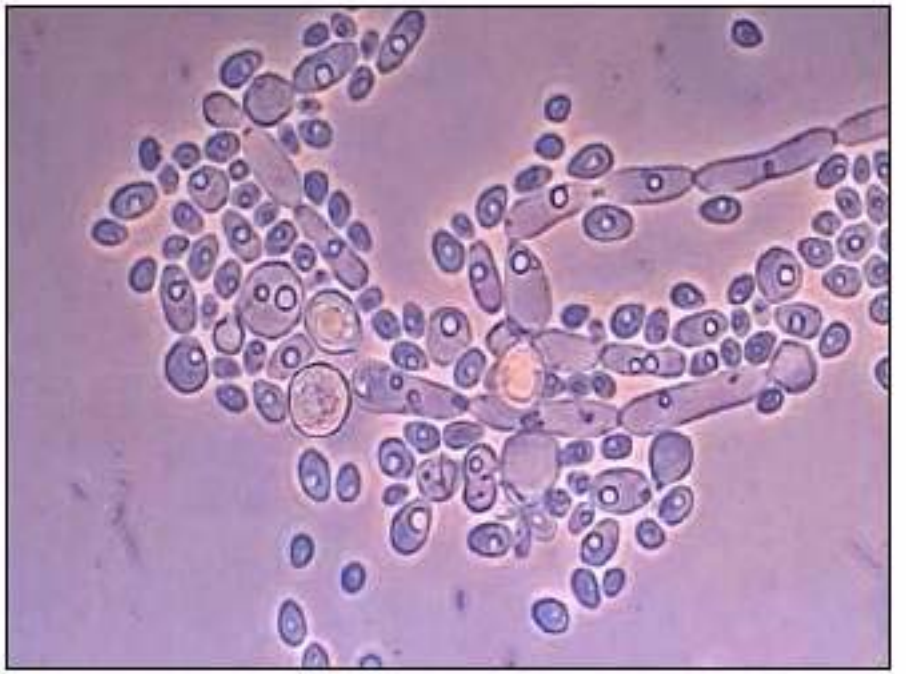


50/50

- *Candida* albicans
- Non-alb. *Candida* spp
  - *glabrata*
  - *parapsilosis*
  - *tropicalis*

Rare opportunistic yeast

Susceptibility of *Candida* species

	AMB	5-FC	FCZ	VCZ	ECH
C. albicans	S	S	S	S	S
C. glabrata	S-I	S	Sdd-R	S-I	S
C. parapsilosis	S	S	S	S	S(-I)
C. tropicalis	S	S	S	S	S
C. krusei	S-I	I-R	R	S-I	S
C. lusitaniae	S-R	S	S	S	S
C. guilliermondii	S	S	S	S	R

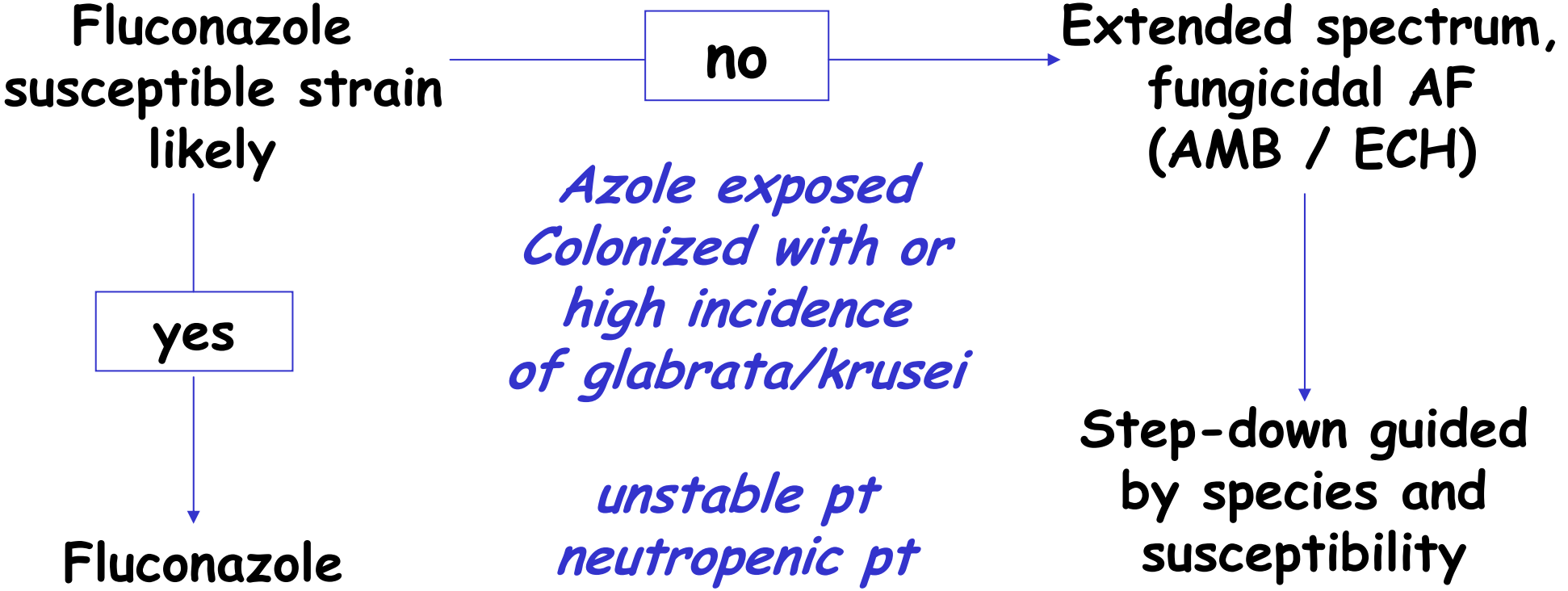
Espinel-Ingroff 98; Rex 00; Cuenca-Estrella 06

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]

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

Initial Treatment Algorithm



modified from Kullberg 05

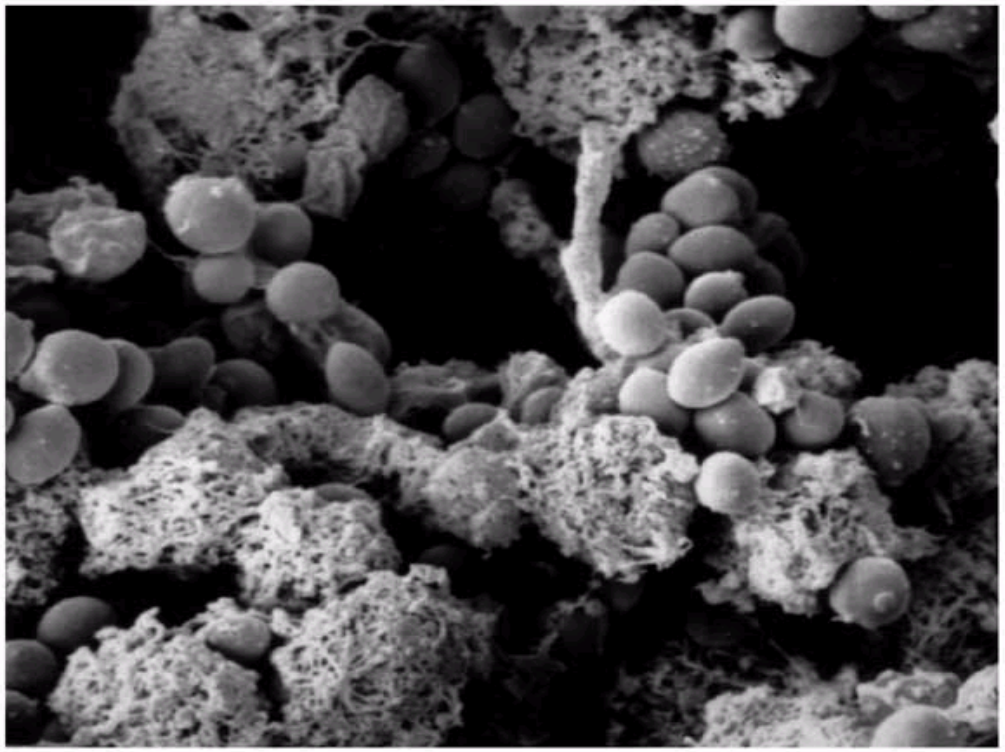
Invasive candidiasis: Initial therapy

- Fluconazole 8-12 mg/kg
- Liposomal amphotericin B 3 mg/kg
- Caspofungin 50 mg/m² (d1:70mg/m²) (max.70mg)
- Micafungin 2 mg/kg (>40 kg: 100mg)

- ***Other options***:
  - Voriconazole ≥13: 2x3mg/kg (d1: 2x6); <13: 2x7mg/kg
  - ABLC 5 mg/kg
  - D-AMB B 0.7-1.0 mg/kg +/- 5-FC 100mg/kg

Chiou et al. 07

Central catheter management



Maki EID 01

Consensus: *Removal*

- Non-granulocytopenic
  - more rapid clearance,
  - reduced mortality
- Granulocytopenic
  - less evidence,
  - gut vs. catheter

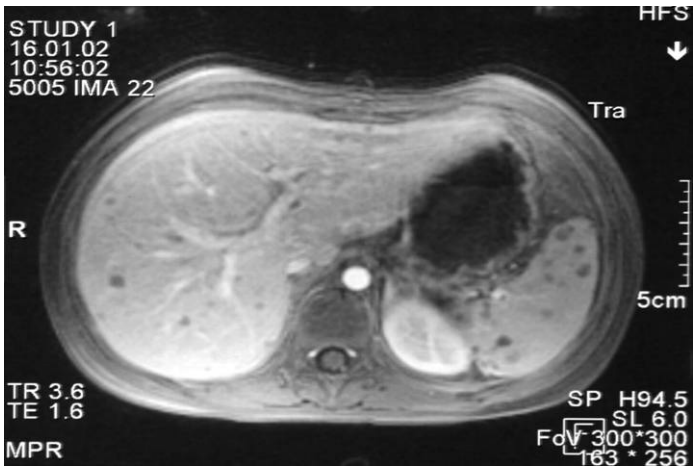
- ! Always: *C.parapsilosis*

Pappas CID 04

General management issues

- Therapy for 14 days after last pos. BC and resolution of all clinical symptoms
- Change from AMB/CAS to FLU
- CSF's in granulocytopenic patients
- Reduction/ disc. of *steroids* in immunosuppressed pts

Recommended follow-up



Non-neutropenic patients:

Fundoscopy to r/o endophthalmitis (neg. BCs)

Neutropenic patients:

Fundoscopy

+/- ultrasound to r/o

CDC (neg. BCs and ANC >500)

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Invasive *Aspergillus* Infections

Inv. Aspergillosis: Spectrum

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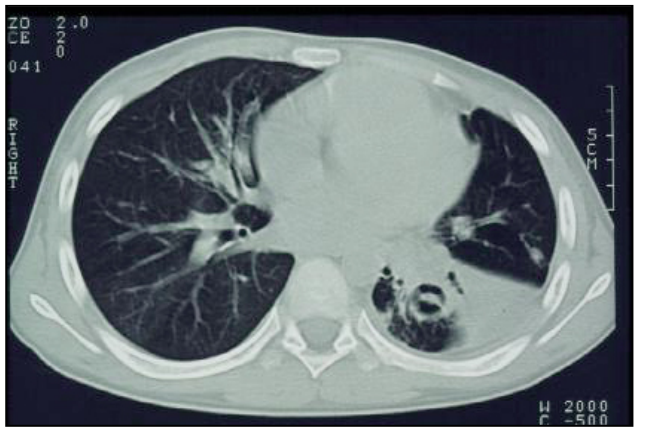
- **Invasive pulmonary aspergillosis**
- Paranasal sinus
- Primary cutaneous
- Primary gastrointestinal
- Disseminated aspergillosis
  - CNS
  - Other sites

'Invasive pulmonary aspergillosis'



≥ 80%

- *Aspergillus fumigatus*
- *Aspergillus flavus*
- *Aspergillus niger*
- *Aspergillus terreus*

≤ 20%

- Other hyalohyphomycetes
- Phaeohyphomycetes
- Zygomycetes

Susceptibility of filamentous fungi

	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 02; Johnson & Kauffman 03; Lass-Floerl ICAAC 07

Invasive aspergillosis: Clinical trial data

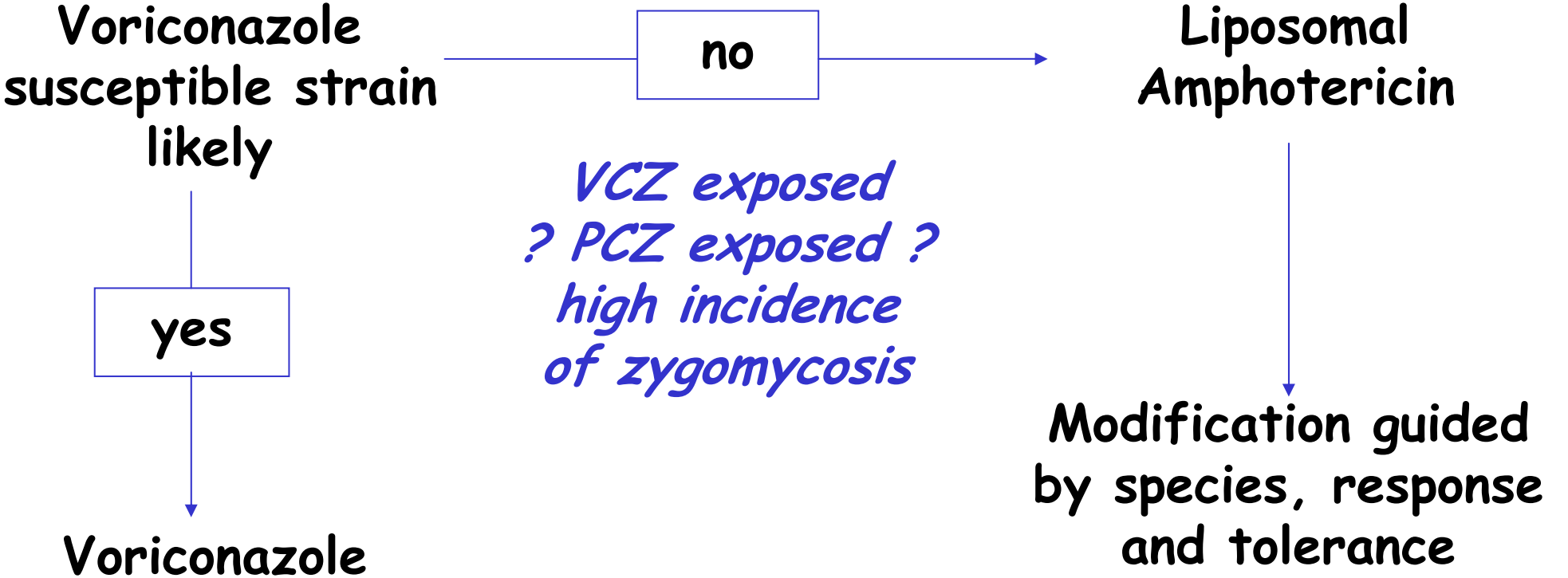
Treatment	CR/PR at 3 mo	Surv. at 3 mo
Voriconazole 12/8 mg/kg	52.8 %	70.8 %
D-AMB 1.0 mg/kg + OLAT	31.6 % *	57.9 % *

	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 %

- No controlled data on outcome following first-line therapy with CAS and other triazoles

Herbrecht 02; Cornely 05

Initial Treatment



Invasive aspergillosis: Initial therapy

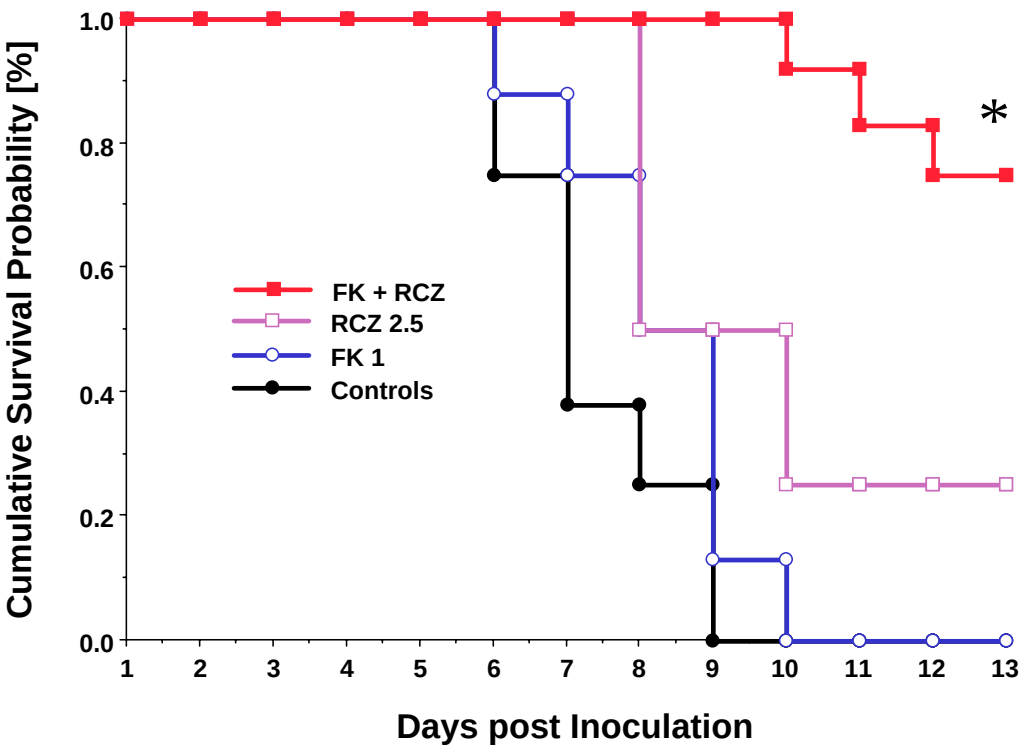
- IV VCZ 2x4 mg/kg, <13 a: 2x7 mg/kg
- L-AMB 3 mg/kg

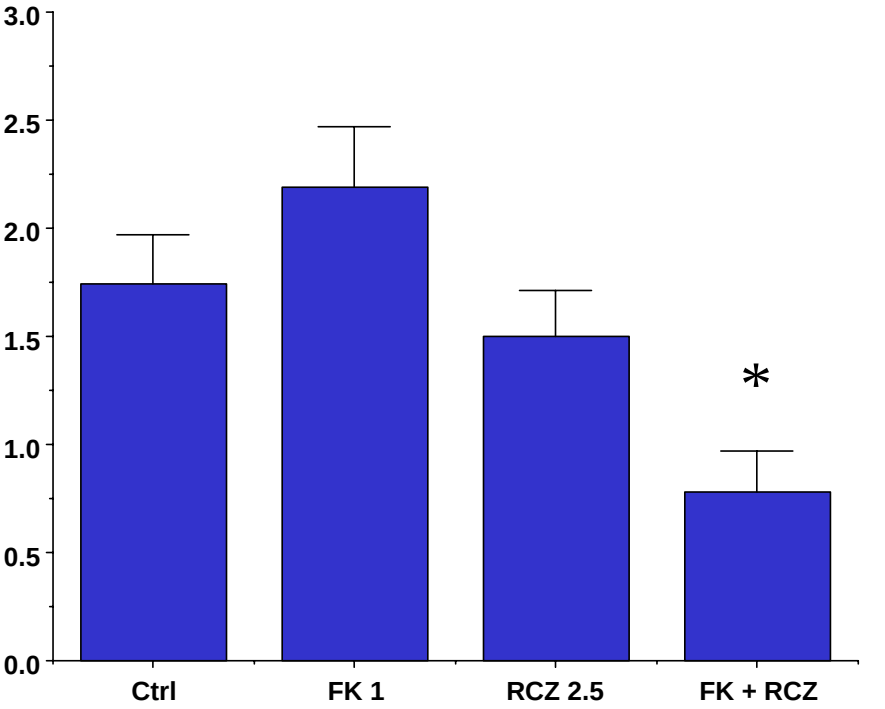
- 'Second line':
  - ABLC 5 mg/kg / L-AMB 3-5 mg/kg
  - CAS 50 mg/m² (d1:70 mg/m²) (max. 70 mg)
  - IV / PO ITZ 200 mg (d1/2: 2x200)/ 2.5mg/kg BID *
  - PO POS 2x400 / 4x200 mg/d *

- *A.terreus:* VCZ
- *CNS infections:* VCZ > L-AmB ≥5mg/kg
- *Severe infections:* L-AmB+CAS / VCZ+CAS

Stevens 00; Herbrecht 03; Groll 03:Raad 04; Steinbach 04; Cornely 05

Antimicrobial interactions: Animal data (FK+RCZ)





Petraitis et al. JID 03

Dosage escalation: Clinical evidence for LAMB

- No benefit but increased toxicity of a 14-days loading dose (10mg/kg) in primary treatment of IA with LAMB

- Dose escalation of *triazoles* may be associated with increased likelyhood of AEs (VCZ; ITC) or decreased gastrointestinal absorption (PCZ)

- Dose escalation of *echinocandins* not yet investigated beyond esophageal candidiasis

Cornely CID 07; Denning 02; Courtney 03

General management issues

- *Adjunctive surgery:* skin and soft tissue infections; impeding arrosion of pulmonary arteries; operable CNS- or lung lesions

- CSF's in neutropenic /
- reduction / disc. of steroids immunosuppressed pts

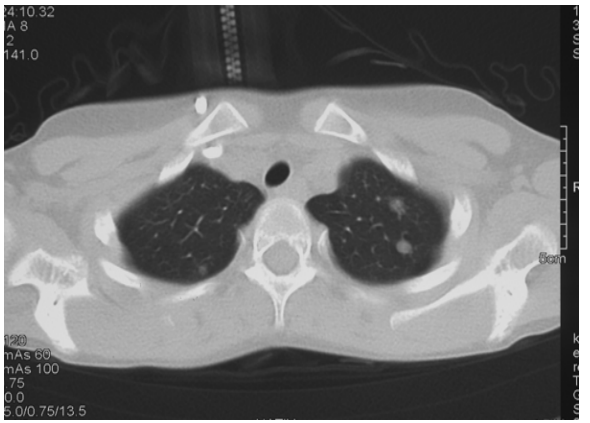
- Consolidation with PO VCZ (A-I) / ITZ* or POS* following stabilization

Stevens 00; RAAD 04; Groll 02

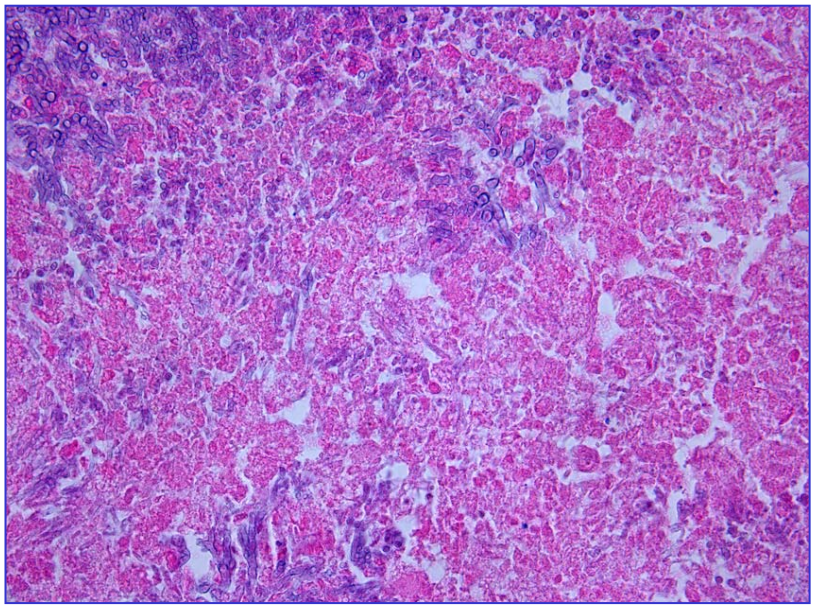
Treatment duration

+ 13:

+ 330:



+338: Thoracoscopic lung biopsy



- CX negative
- PCR: *A. fumigatus*

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Empirical Antifungal Therapy

Empirical therapy for F+N: Rationale / Indications

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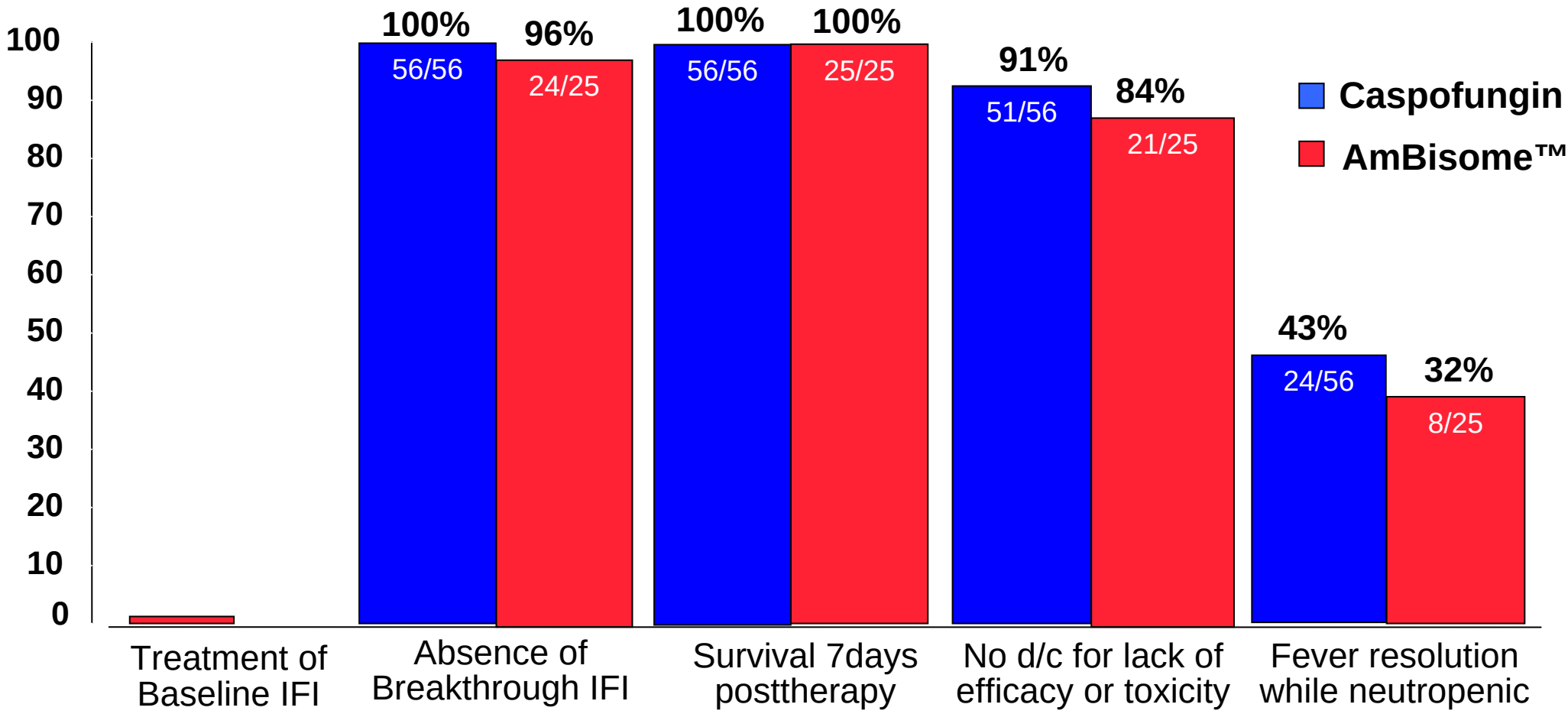
- Targeted prevention in high risk situations
- Early treatment of still occult infections

- Longstanding 'standard of care' in pts with
  - ANC ≤500/µl ≥ 10 days
  - Persistent fever >3 days
  - Recurrent fever despite ABX

- Several alternative interventions
- Approved in children: L-AmB and CAS

Protocol 044, CAS vs. LAMB: Response, indiv.Endpoints (MITT)



04/09

Maertens et al. ICAAC 07

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Conclusions

Conclusions

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- Management of invasive fungal infections increasingly complex
- Consideration of
  - Results of pivotal clinical trials
  - Patient-specific information
  - Safety and drug interactions
  - Species-dependent susceptibility
- Best pharmacology-based initial therapy unclear for most indications
- New antifungals offer hope for improved outcomes