

Pilzinfektionen – welche Diagnostik, welche Therapie?

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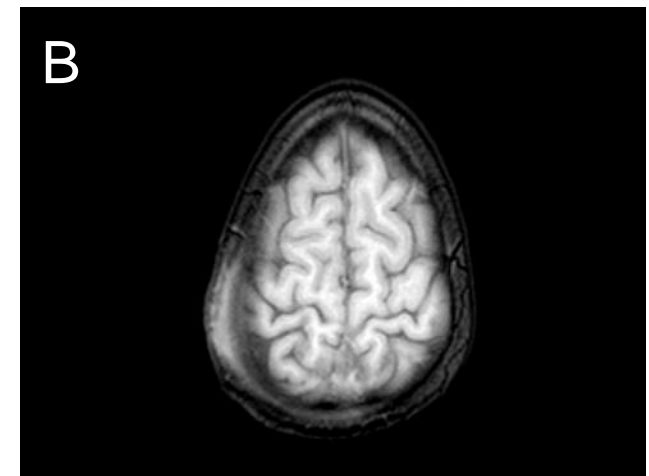


Disclosures

- **Grants**
 - **Gilead, Merck, Sharp & Dohme, Pfizer**
- **Consultant**
 - **Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough, Scynexis**
- **Speakers' bureau**
 - **Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon**

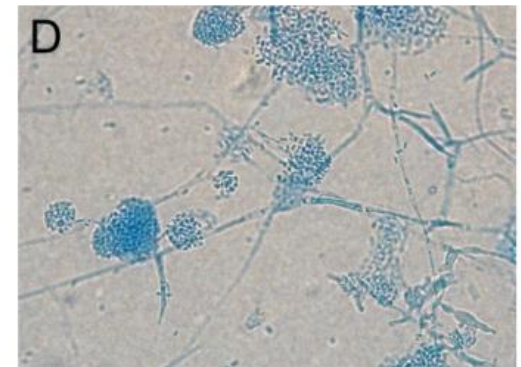
6 yo Neutropenic Girl with Recurrent Acute Lymphoblastic Leukemia

- 6-year old profoundly neutropenic girl with recurrent lymphoblastic leukemia
- accidental fall into her sister, laceration on the scalp requiring surgical suture
- admitted with new fever on the next day
 - persistent fever despite broadspectrum ABX, *development of severe headaches, increasing swelling and liquid discharge from the wound*
 - surgical debridement and biopsies on day 12



6 yo Neutropenic Girl with Recurrent Lymphoblastic Leukemia (2)

- Histology revealed invasive hyphal growth, and cultures white/cream-colored colonies with aerial mycelium identified as *Coprinopsis cinerea* by gene sequence analysis (ITS1/ITS2)
- Antifungal susceptibility by E-Test ($\mu\text{g/ml}$):
 - *Amphotericin B* 0.006
 - Flucytosine >32
 - Caspofungin >32
 - *Voriconazole* 0.125
 - *Posaconazole*: 0.5
- Complete recovery with L-AMB (3 mg/kg/d x6 until neutrophil recovery on HD 18), then POS (100/200 mg QD alternating) + TDM for 66 days



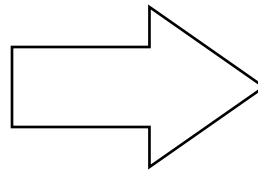
6 yo Neutropenic Girl with Recurrent Lymphoblastic Leukemia (3)

- ***General points to be made :***
 - **Importance of a microbiological diagnosis**
 - **Invasive, potentially life-threatening infection by a rare environmental filamentous basidiomycete of uncertain behavior reported in only few human beings**
 - **Antifungal therapy largely empiric**
 - **MIC- testing not standardized**
 - **no *in vitro* / *in vivo* correlations**
 - **no meaningful clinical data**

Risk Factors and Epidemiology

Immunological Risk Factors for IFDs in Pediatric Patients

**Deficits of
Phagocytic cells**

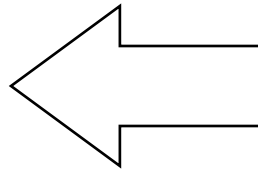


Invasive infections by

- *Candida* spp.
- *Aspergillus* spp.
- rare opport. moulds and yeast

Invasive infections by

- *Cr. neoformans*
- dimorphic moulds



**Deficits of
T-Lymphocytes**

Mucocut. candidiasis

Pediatric Populations at Risk to Develop IFDs

- **AML and ALL if neutropenic and on steroids**
 - **Recurrent leukemias**
 - **Hematopoietic stem cell transplantation**
 - During granulocytopenia until engraftment
 - During augmented immunosuppression for GVHD
 - **Very low and extremely low birth weight infants**
 - **Children with life-threatening problems in the ICU**
- ... chronic granulomatous disease; chronic lung disease/CF; lung and heart/lung, liver, small bowel/pancreas transplantation; metabolic diseases

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A Preterm Infant...



- Preterm infant, GA 26 w, BW 620gr
- Ventilator
- Multiple perinatal problems
- Day 3-7 CONS sepsis
- Day 16 *Pseudomonas* sepsis
- Day 35 suspected necrotizing enterocolitis
- Day 36-39 *Candida albicans* bloodstream infection
 - CSF sterile, WBC-75, Glucose-N, Protein-115
 - Brain US (-)

Congenital Cutaneous Candidiasis: Prompt Systemic Treatment Is Associated With Improved Outcomes in Neonates

Clinical Infectious Diseases

MAJOR ARTICLE

David A. Kaufman,¹ Sarah A. Coggins,² Santina A. Zanelli,¹ and Jörn-Hendrik Weitkamp³

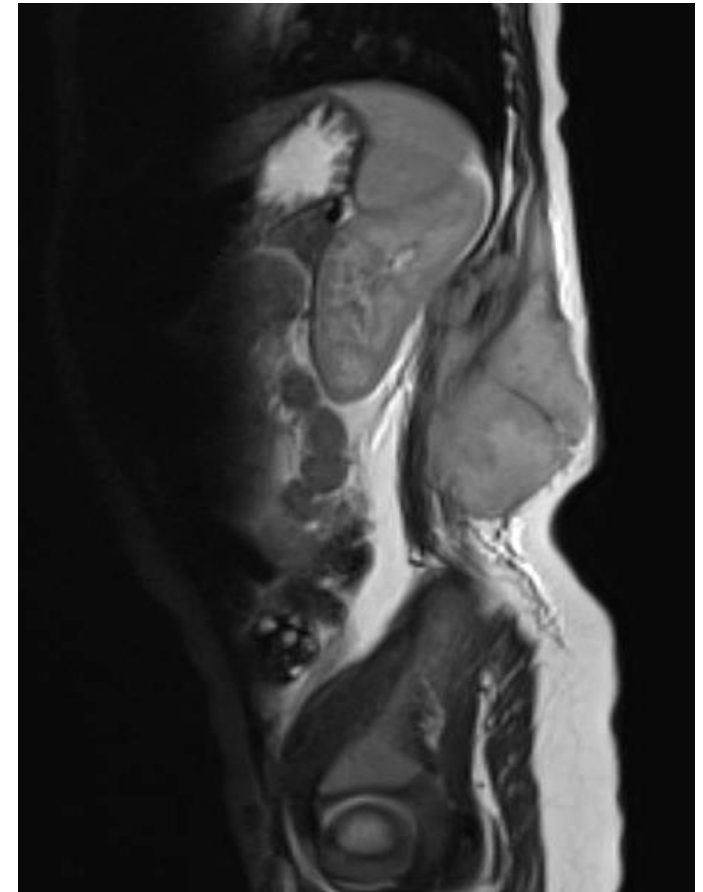


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18 mo Previously Healthy Girl

- New palpable left lumbosacral mass
- Malaise, refusal to walk
- Elevated temperatures
- ...
- MRI shows large paravertebral mass, suggestive of neuroblastoma
- CRP 5.6 mg/dL, laboratory values otherwise 'normal'
-
- *Catecholamines negative*



...18 mo Previously Healthy Girl

- **Surgical biopsy for tissue diagnosis**

- Liquid collection
- Multiple cultures: *A.fumigatus*
- Histopathology: Branching hyphae

...

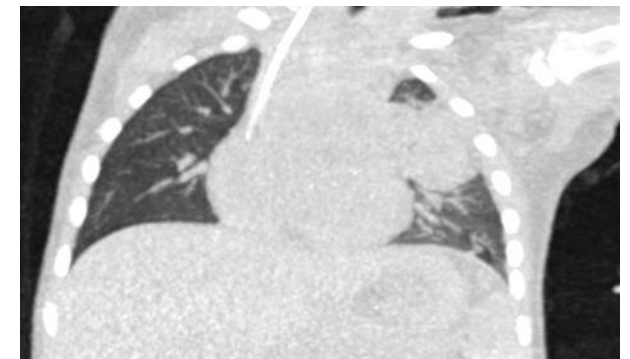
- **CT shows intrapulmonary lesion**

- **BAL performed**

- *A. fumigatus* by culture
- Positive Antigen test

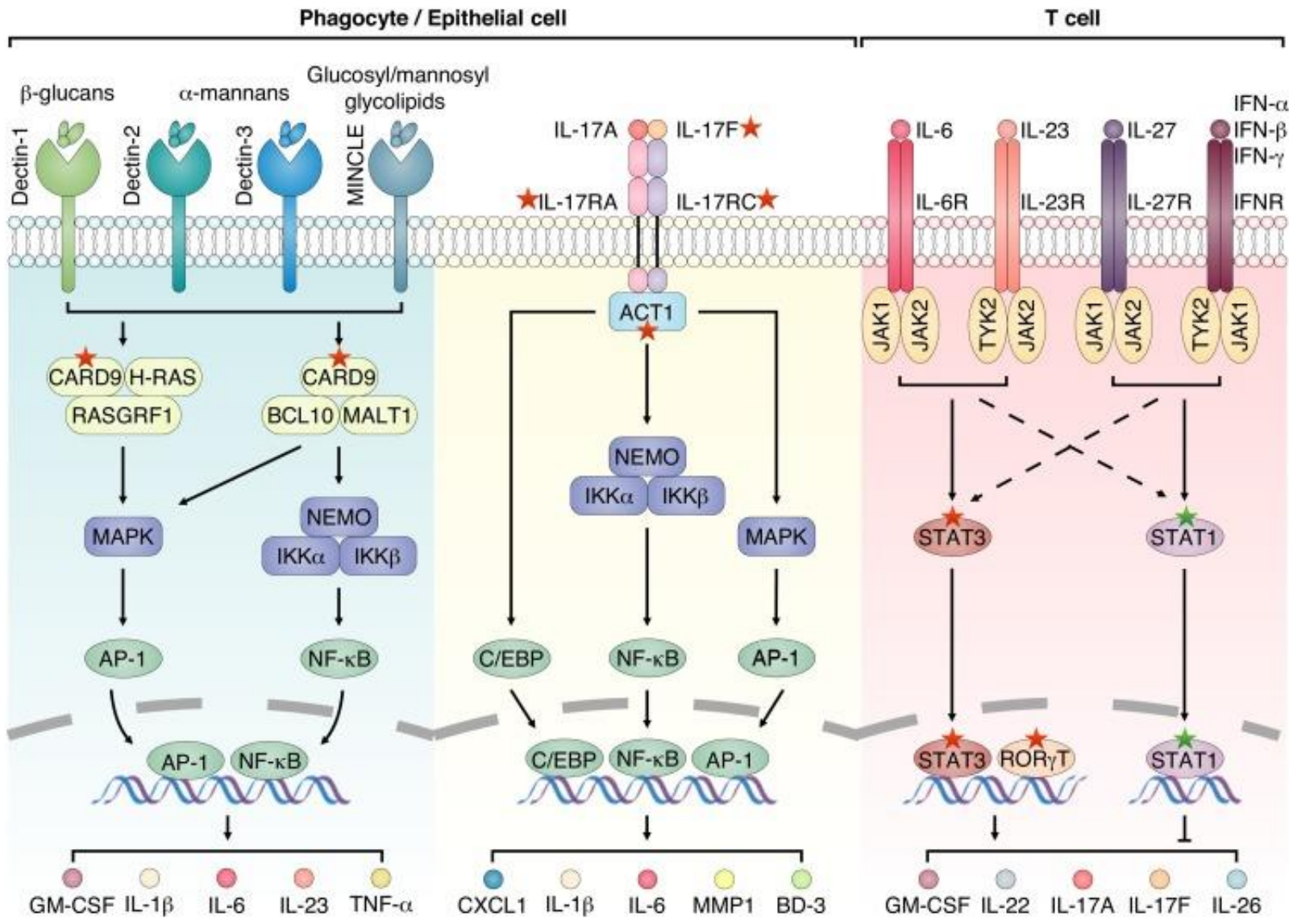
...

... diagnosis of ***Chronic Granulomatous Disease*** by functional tests and sequencing



Invasive fungal diseases (CARD9 immunity)

Chronic mucocutaneous candidiasis (IL-17 immunity)



Current Opinion in Microbiology

CARD9 Deficiency: Clinical Spectrum

➤ Presentation with superficial but also invasive mycoses:

Table 4 Main characteristics of patients and fungal diseases in CARD9 deficiency

Fungal diseases	Number of cases (58)	Median age at onset (years)	Mean age at onset (years)	Range of age at onset (years)	Outcome (alive/dead)
CMC	22 (37.9%)	8.0	12.9	[Birth–42]	17/5 [#]
Superficial dermatophytosis	8 (13.8%)	8.0	17.7	[3–42]	7/1 [#]
Invasive <i>Candida</i> infections	21 (36.2%)	17.5	21.9	[3.5–58*]	17/4
Extensive/deep dermatophytosis	21 (36.2%)	19.0	24.1	[12–52]	16/5 [£]
Phaeohyphomycosis	10 (17.2%)	19.0	24.6	[5–48]	9/1
Invasive extrapulmonary aspergillosis	2 (3.4%)	13.0	13.0	[8–18]	1/1

CARD9-Deficiency: Focus on Superficial / Deep Dermatophytoses



Male	12 (70)
Median age at first symptoms [years]	8 [2-21]
First symptoms	
Severe or recurrent tinea capitis	14
Severe or recurrent tinea corporis	10
Onychomycosis	6
Presentations in adulthood	
Lymph node involvement	10
Central nervous system invasion	1
Local organ invasion (bone, GI)	2
Associated infection: thrush	6
Death	5

STAT 1 GOF Mutation and Fungal Infections

- Chronic mucocutaneous candidiasis (98%)
 - median age first symptoms 1 year
- Superficial dermatophytosis (16%)
- 10% IFI
 - 10 invasive candidiasis
 - 6 *P. jirovecii* pneumonia
 - 5 *Aspergillus* sp. pneumonia
 - 4 cryptococcosis
 - Dimorphic fungal infection: 2
Histoplasma sp. pneumonia, 2
disseminated coccidioidomycosis
 - 1 disseminated mucormycosis
- 12% death (30 ans) (38% severe infections (2 fungal))



Diagnostic Considerations for Invasive Fungal Diseases

Diagnostic Considerations: Standard Procedures

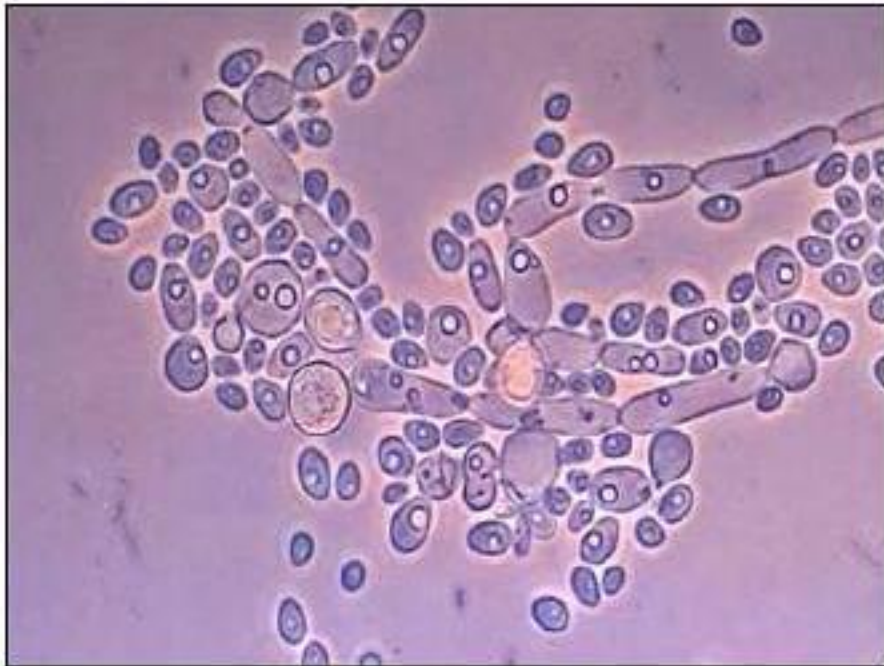
- **Standard diagnostic procedures**
 - **Comprehensive clinical assessment**
 - **Blood cultures for yeast and certain molds**
 - **Cultures, microscopy and, if available, PCR from appropriate liquid and solid diagnostic specimens**
 - **Imaging studies as mandated by clinical findings**

- **Also:** Antigen markers (galactomannan, glucan, glucuronoxymannan) in serum, BAL and CSF for screening and diagnostics

Diagnostic Considerations: 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 these circumstances, however, all efforts should be made to perform the necessary procedures to identify the causative agent and to allow for resistance testing
 - Bronchoscopy and BAL
 - Aspirates / tissue biopsies
- Always an interdisciplinary approach

“Yeast in blood culture”



50/50

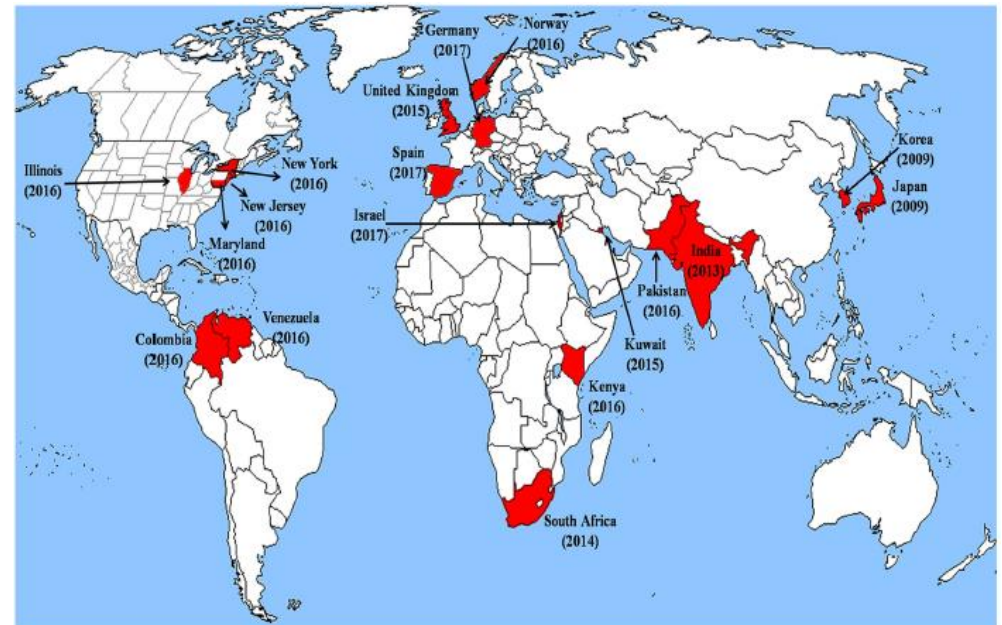
Candida albicans
Non-alb. *Candida* spp
glabrata
parapsilosis
tropicalis

Rare opportunistic yeast

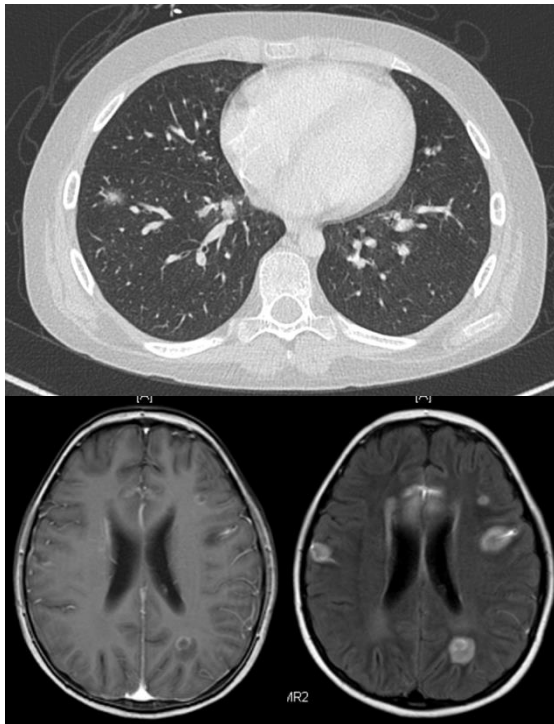
Non-albicans *Candida* Isolates: New Kid on the Block

Since 2009, *Candida auris* has emerged as a global concern due to **multidrug resistance** and **efficient nosocomial spread** in healthcare settings:

- Among clinical isolates, resistance to **FLU**, **AMB** occurs in **> 90**, and **40–50** % of isolates, respectively



“Lesions suggestive of IFD”



≥ 80%

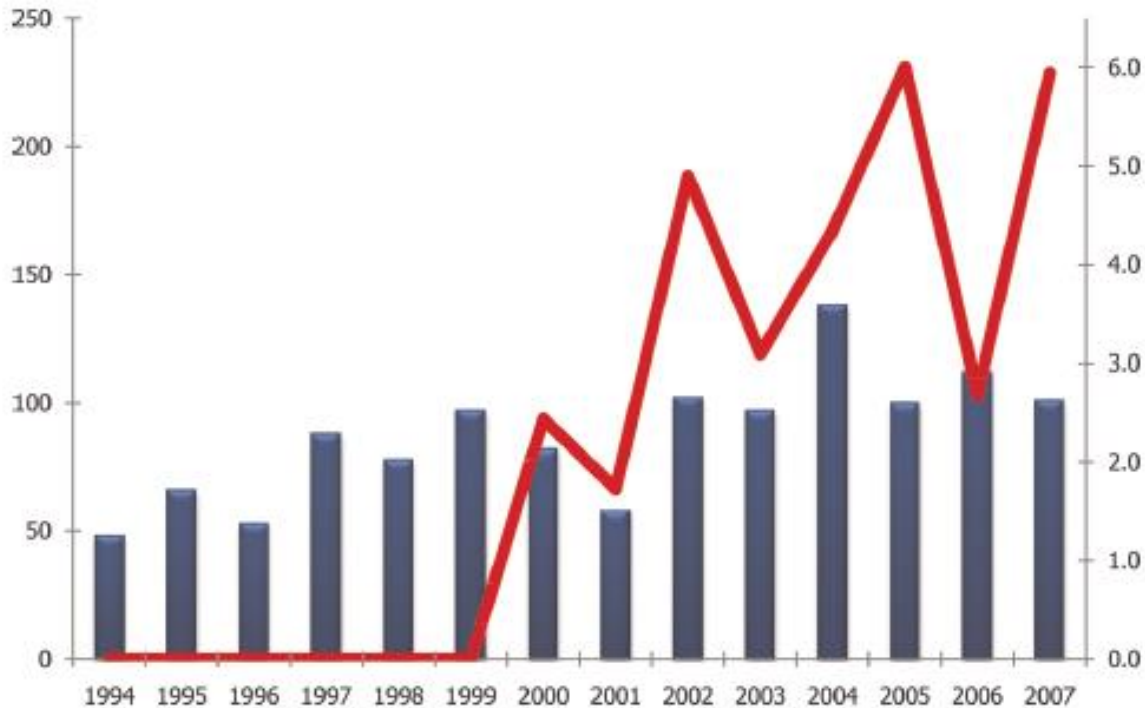
Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus

≤ 20%

Other hyalohyphomycetes
Phaeohyphomycetes
Mucorales

Emergence of Azole Resistance in *Aspergillus fumigatus*

- ITZ-resistant isolates found in 32 / 1,219 patients
 - All cases were observed after 1999



Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander FA D Schauwvlieghe*, Bart J A Rijnders*, Niele Philips, Rosanne Verwĳj, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou, Paul E Verweĳ, Frank L Van de Veerdonk, Diederik Gommers, Peter Spronk, Dennis C J J Bergmans, Astrid Hoedemackers, Eleni-Rosalina Andrinopoulou, Charlotte H S B van den Berg, Nicole P Juffermans, Casper J Hodiament, Alike G Vonk, Pieter Depuydt, Jerina Boelens, Joost Wauters, on behalf of the Dutch-Belgian Mycosis study group

Logistic regression analyses to determine if influenza was independently associated with invasive pulmonary aspergillosis ***in non-immunocompromised (ie, no EORTC/MSG host factor) influenza-pos. pts compared with non-immunocompr. pts with severe community-acquired pneumonia*** who had a negative airway influenza PCR test (control)

- Overall incidence of IPA of 19% (83/432) in the influenza vs. 5% (16/315) in CAP cohort
- Influenza independently associated with IPA (adjusted OR 5.19; $p < 0.001$)
- 51% 90-day mortality in influenza patients with IPA and 28% in those without IPA ($p = 0.001$).



Antifungal Drugs and Management Principles

PK Challenges in Pediatric Patients

- **Distribution: larger Vd**
- **Metabolism/elimination: greater Cl**
- **Oral Bioavailability/Absorption:**
 - may be different
 - development of a palatable oral solution may be a major challenge to providing oral delivery
- ***Particular challenge: NICU and PICU patients***
- ***Also a challenge: transition to adulthood***

Antifungal Agents: Approval in Pediatric Patients

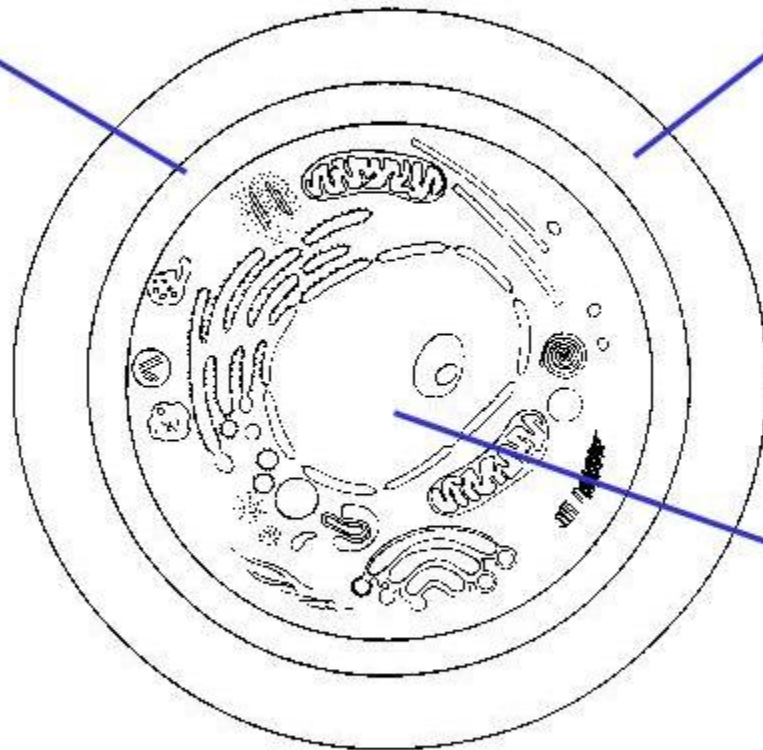
Cell membrane

- Polyenes

- > D-AmB
- > L-AmB
- > ABLC

- Triazoles

- > Fluconazole
- > Itraconazole
- > Voriconazole
- > Posaconazole
- > Isavuconazole



Cell wall

- Echinocandins

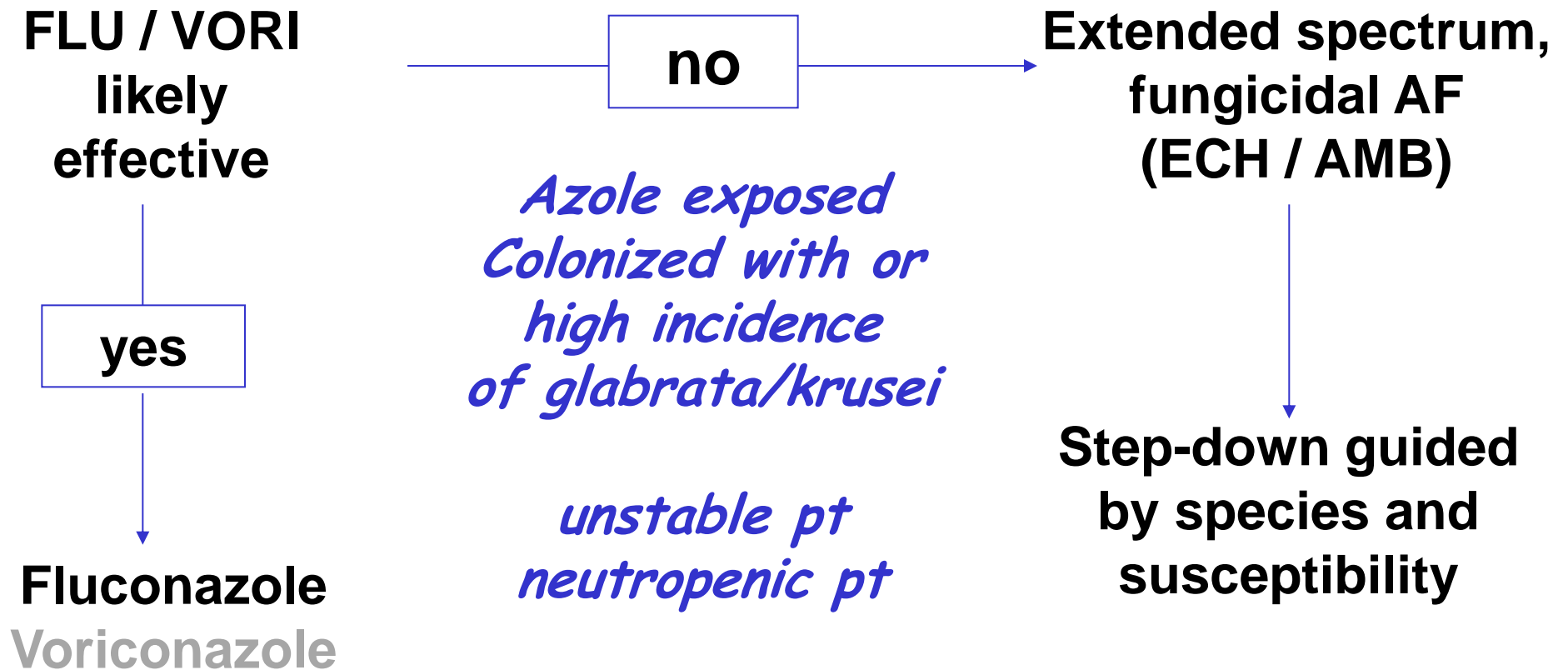
- > Caspofungin
- > Micafungin
- > Anidulafungin

Nucleic acid synthesis

- > Flucytosine

Treatment Algorithms for Invasive Candidiasis

Initial Treatment Algorithm for Invasive Candidiasis



Candidemia and Invasive Candidiasis: Recommended Pediatric Dosages

- Fluconazole 12 mg/kg
- Liposomal amphotericin B 3 mg/kg
- Caspofungin 50 (25) mg/m² (d1:70mg/m²) (max.70mg)
- Micafungin 2-4 (4-10) mg/kg (>40 kg: 100 – 200 mg)
- Other options:
 - Voriconazole (IV) 2-11, 12-14 yrs, <50kg: 2x8 (d1: 2x9)
12-14 yrs >50kg and ≥15: adult dose
 - ABLC 5 mg/kg
 - D-AMB B 0.7-1.0 mg/kg +/- 5-FC 100mg/kg

Inv. Candidiasis: Predictors of Outcome

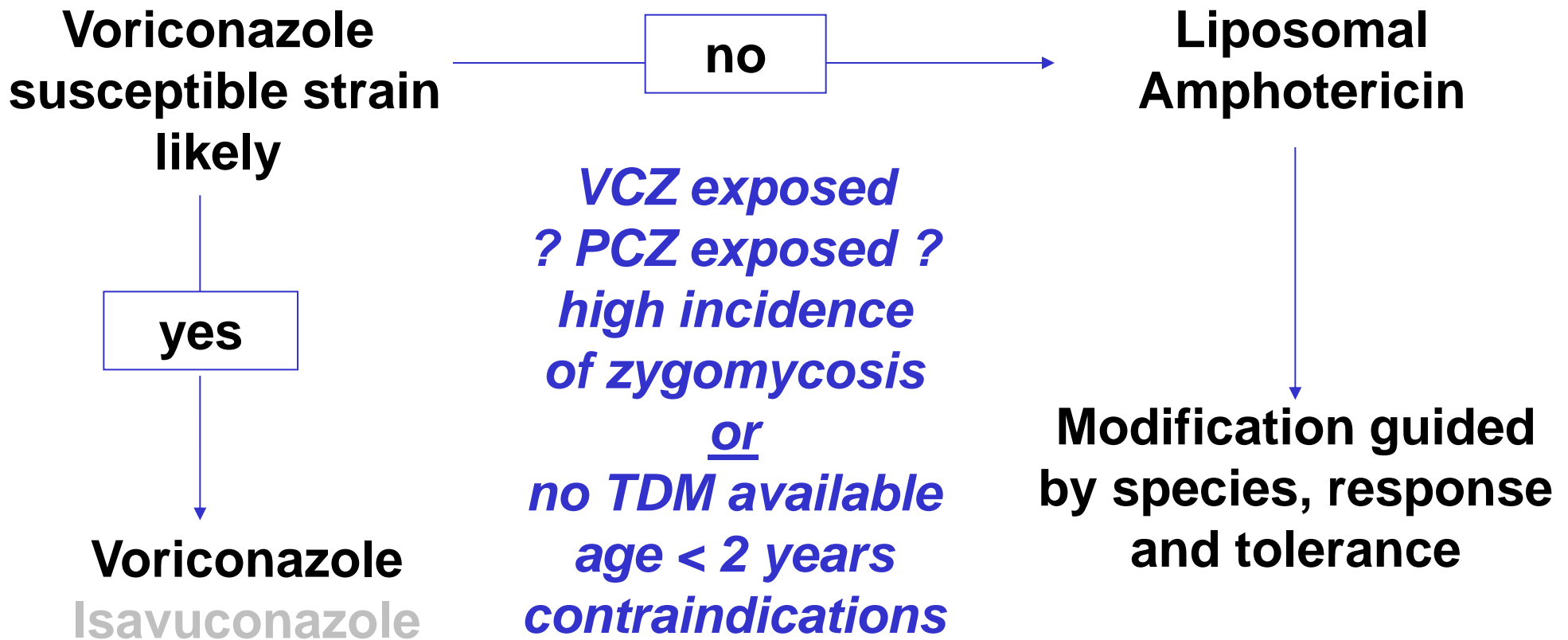
- *Patient-level quantitative review of 7 randomized trials for treatment of IC including a total of 1915 patients*
- *Logistic regression analysis*
 - *Increasing APACHE II score, immunosuppressive therapy*
 - *Predictors of mortality*
 - *removal of a central venous catheter, and*
 - *treatment with an echinocandin*
 - *associated with decreased mortality*

General Management Issues

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

Treatment Algorithms for Invasive Aspergillosis

Initial Treatment Algorithm for Invasive Aspergillosis



Invasive Aspergillosis: Current Dosage Recommendations

- Voriconazole 2-11 and 12-14 yrs <50kg: 2x8 (d1: 2x9)
12-14 yrs >50kg and ≥15: adult dose +TDM
- L-AMB 3 (-5) 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 *
 - IV / PO POS 1x300 mg (d1: 2x300)*
 - IV / PO Isavuconazole 1x200 mg (d1-2: 3x200mg) *

Serum-Galactomannan: Monitoring of Treatment Response

Monitoring Responses to Treatment

- *risk assessment*
- *clinical evaluation*
- *CT monitoring at d 7 and d 14*
- *... biomarkers*

... treatment duration: months - years

Treatment of Rare Molds / Prophylaxis

Non-*Aspergillus* Mold Infections: Treatment Recommendations

- **Mucormycosis:** > LAMB* 5-10 mg/kg and day
 - > ISAVU* 200 mg/day (d1-2: 3x200)
 - > ABLC* 5-7.5 mg/kg and day
 - > POSA 300mg/day (d1: 2x300)
- **Hyalohyphomycetes (*Fusarium*, *Scedosporium* ...):**
 - Triazoles (VORI*, POSA*, ISA) > AMB
- **Phaeohyphomycetes (*Alternaria*, *Bipolaris* ...):**
 - Triazoles (ITRA, VORI, POSA*, ISA) > AMB

ECIL 4 / ESCMID Recommendations: Primary Chemoprophylaxis

- **Allogeneic HSCT**
 - *granulocytopenic phase: until engraftment (B II; B II t)*
 - *GVHD and augmented immunosuppression (A II; A II t)*
- **AML and recurrent acute leukemia (B II; A II t)**
- **High-risk ALL (B II; A II t)**
- *ESCMID:*
 - *VSAA and MDS (A II t)*
 - **Chronic granulomatous disease (A II)**
 - **Lung transplant patients (A III)**
 - *Liver (B-III), heart transplant pts (B-III) with high risk profiles*

Why are Fungi Medically Important ?

Estimated Burden of Fungal Infections, Germany 2015

Table 1 Burden of fungal diseases in Germany according the selected underlying diseases.

	Number of infections per underlying disorder per year					Total burden	Rate/100K ²
	Unknown	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Fungal skin diseases	6 721 000	n.a. ¹	n.a.	n.a.	n.a.	6 721 000	8347
Oral candidosis	n.a.	15 600	n.a.	97 965	n.a.	113 565	141
Oesophageal candidosis ³	3685	100 ⁴	n.a.	n.a.	n.a.	3785	4.7
Candidaemia	n.a.	n.a.	n.a.	n.a.	3712	3712	4.6
<i>Candida</i> peritonitis	n.a.	n.a.	n.a.	n.a.	3700	3700	4.6
Recurrent vaginal candidosis (4 × year ⁻¹ or more)	2 470 200	n.a.	n.a.	n.a.	n.a.	2 470 200	3068 ⁵
Allergic bronchopulmonary aspergillosis	n.a.	n.a.	123 960	n.a.	n.a.	123 960	154
Severe asthma with fungal sensitisation	n.a.	n.a.	163 131	n.a.	n.a.	163 131	203
Chronic pulmonary aspergillosis	n.a.	n.a.	2320	n.a.	n.a.	2320	2.9
Invasive aspergillosis	n.a.	n.a.	n.a.	2569	1711	4280	5.1
Mucormycosis	19	n.a.	n.a.	n.a.	n.a.	19	0.02
Cryptococcal meningitis	42	15	n.a.	n.a.	n.a.	57	0.07
<i>Pneumocystis</i> pneumonia	n.a.	860	n.a.	153	n.a.	1013	1.3
Histoplasmosis	5	10	n.a.	n.a.	n.a.	15	0.02
Fungal keratitis	32	n.a.	n.a.	n.a.	n.a.	32	0.04
Total burden estimated						9 610 789	

¹n.a. = not applicable or unknown.

²Rate/100K = rate per 100 000 individuals from total population in Germany.

³According ICD10 code 37.8 (mostly EC).

⁴New AIDS-defining disease per year with about 280 AIDS per year in Germany (~20% have oesophageal candidosis) Source: www.gbe-bund.de.

⁵According to survey by Foxman *et al.* 2012, 9% of woman in Germany have VVC, we have used a 6% rate to account for some misdiagnosis. Rate per 100 000 is for all females.