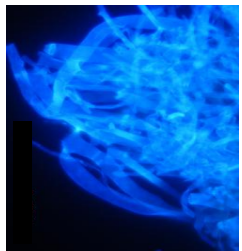
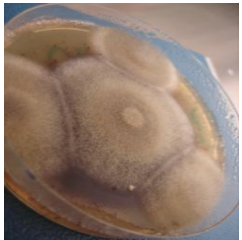
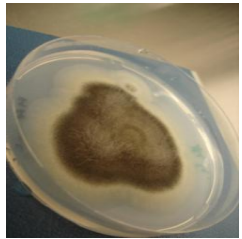
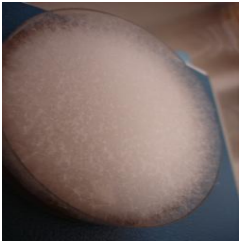
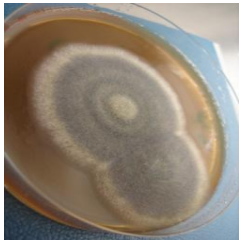


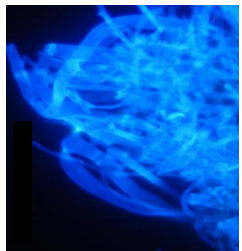
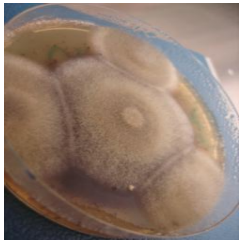
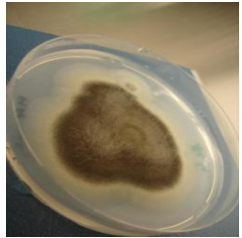
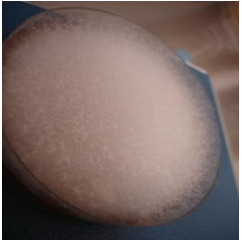
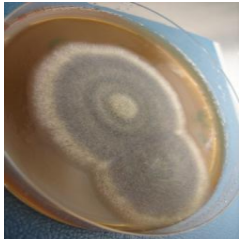
Invasive Pilzinfektionen: Von der Epidemiologie zur Therapie

Infektionskolloquium CIDiC
Tübingen
13.07.2016

Cornelia Lass-Flörl

Division of Hygiene and Medical Microbiology
Innsbruck Medical University





Roadmap

Epidemiology
Pathomechanism
Diagnosis
Treatment

Trends in fungal diseases

Increasing cases of invasive fungal infections (immunocompromised pts)

Clinical signs are non specific: a continuum of presentations

Poor diagnostic tools

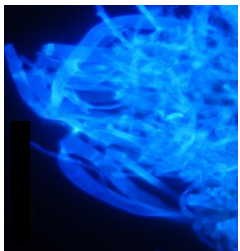
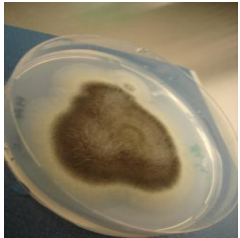
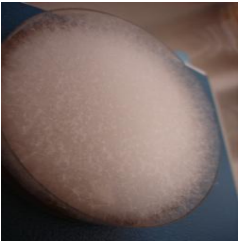
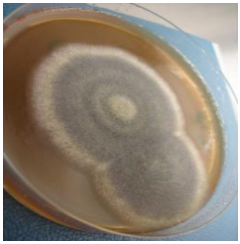
Replacement of sensitive species by resistant ones

Increasing use of prophylaxis and empirical therapy

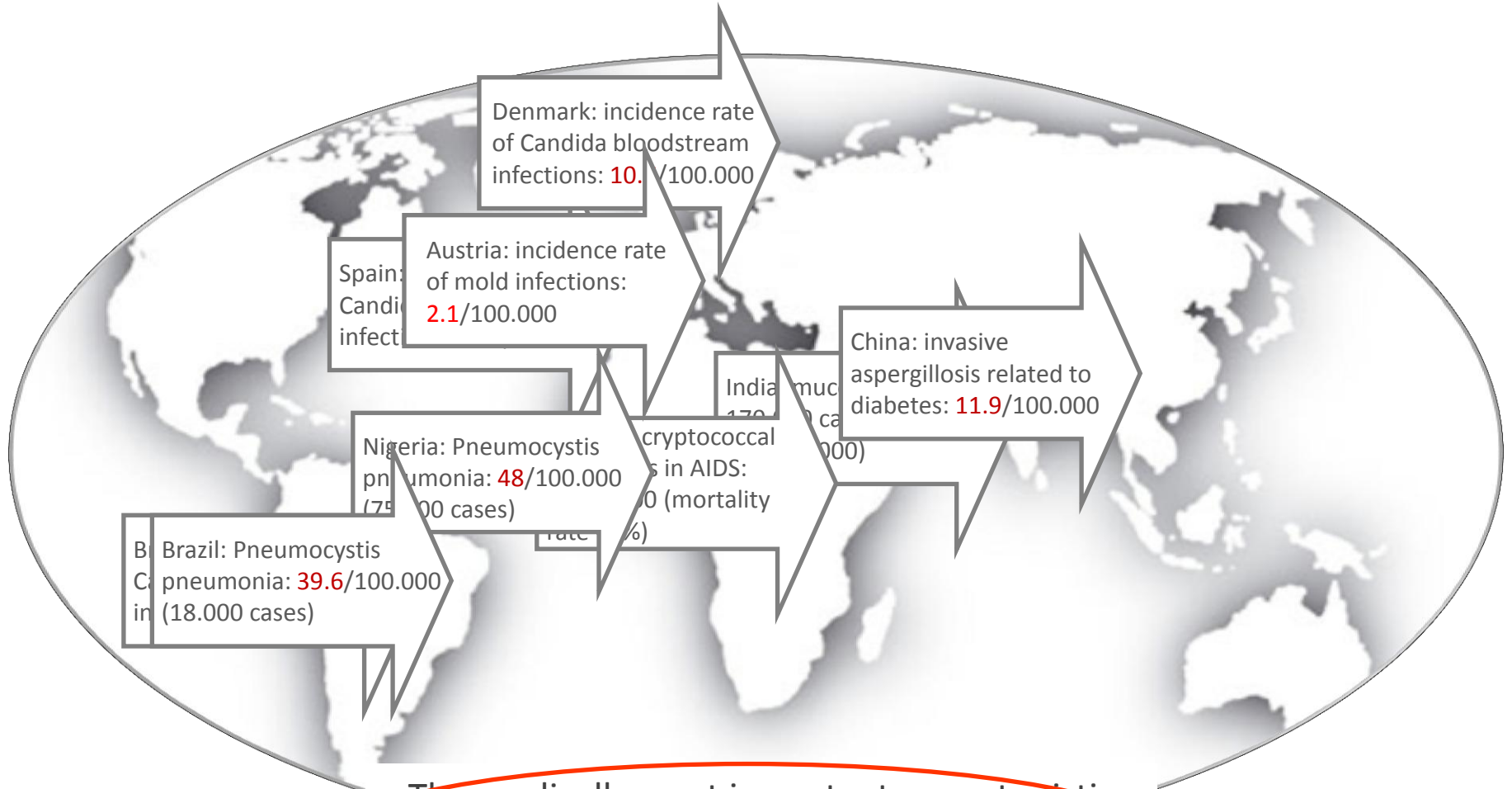
Increasing drug and hospitalization costs

New hosts – ageing population

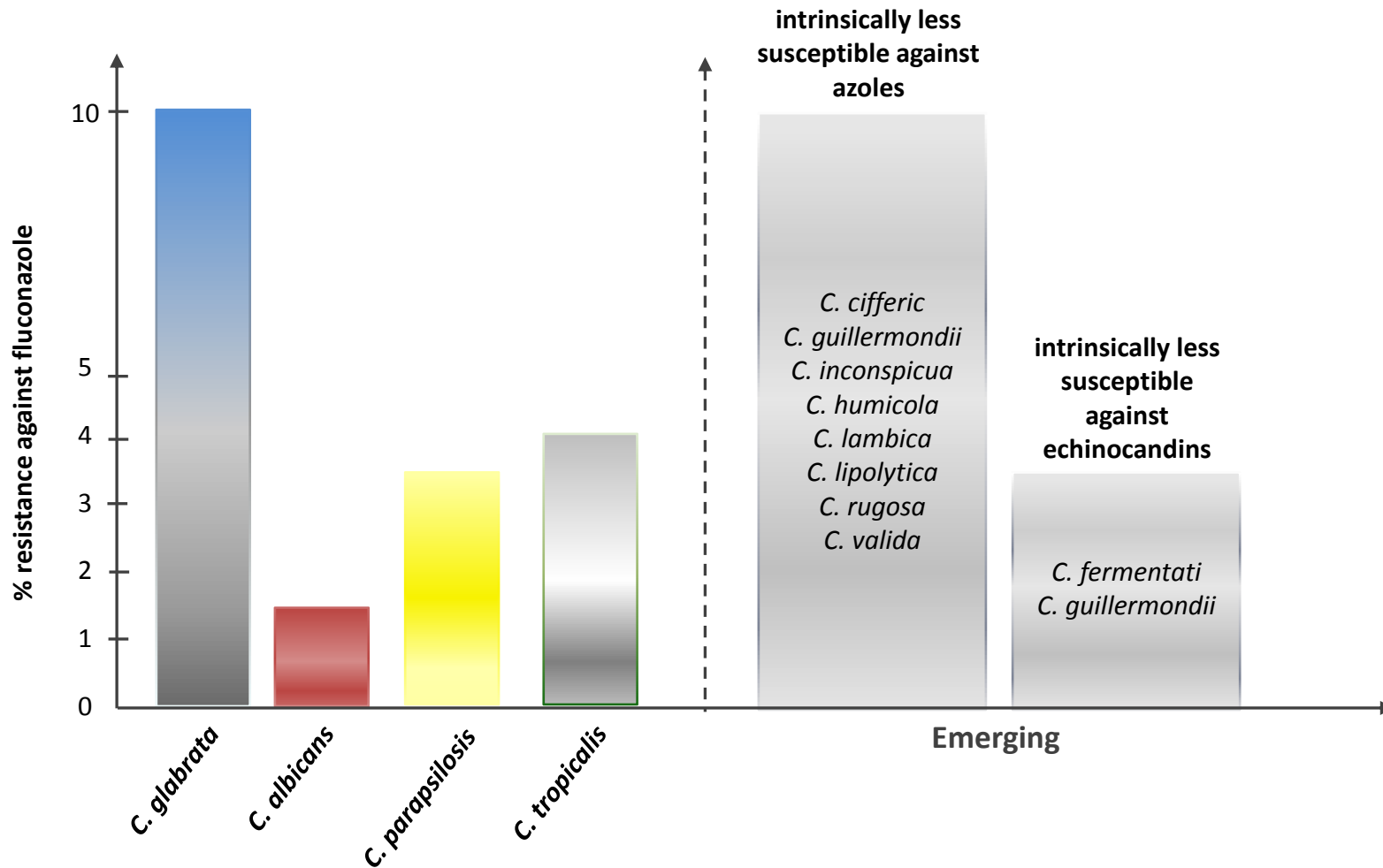
No regular surveillance – incidence varies on underlying diseases



Multi-country burden of fungal diseases



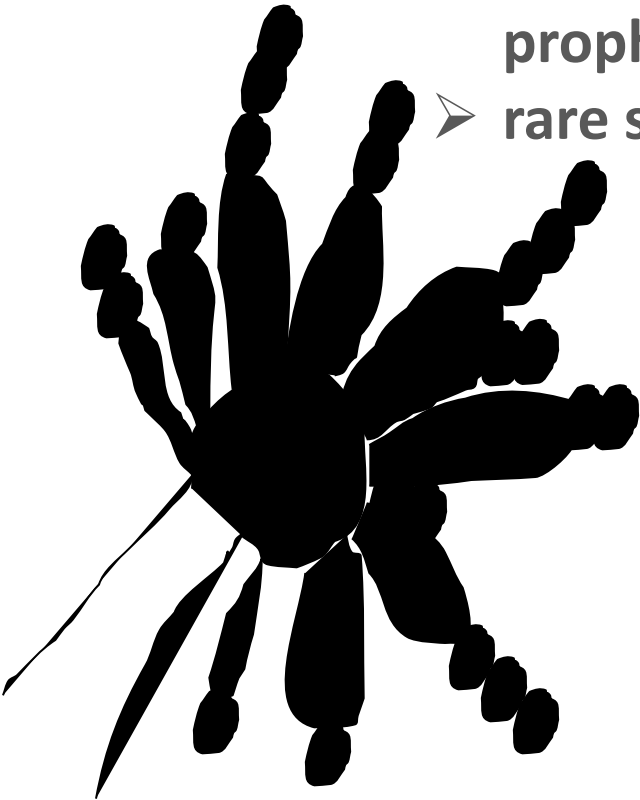
The medically most important opportunistic mycoses in Europe are caused by *Aspergillus spp.* and *Candida spp.*



- Resistance to voriconazole uncommon (< 0.5 % resistant) with exception of *C. glabrata* (10.5 %)
- **Echinocandin-resistant *C. glabrata* were found to be fluconazole resistant (38 %)**

Invasive aspergillosis

- *Aspergillus* sp. is major mold pathogen¹
- importance of early diagnosis²
- shift to other patients³ (ICU and COPD)
- emerging of azole resistance in *Aspergillus* sp.⁴
- decrease of infections due to early diagnosis and prophylaxis⁵
- rare species: hot spot - distributions (eg *A. terreus*)⁶



(1) Baddley et al, BMC Infectious Diseases 2013; 13:29

(2) Taccone et al, Critical Care 2015; 19:7

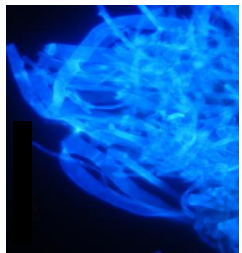
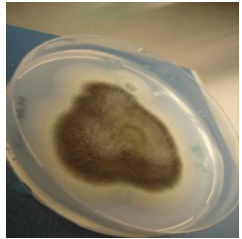
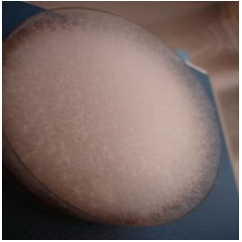
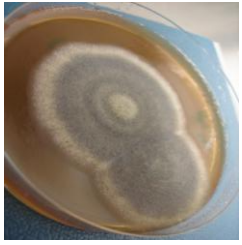
(3) Muñoz Pet al, Mycoses 2015;58 Suppl 2:1

(4) Verweij et al, Drug Resist Rev 2009;12:141

(5) Nachbaur et al, Eur J Haematol 2015;94:258

(6) TerrNet - A Global *Aspergillus terreus* Surveillance Study, ISHAM&ECMM, 2016

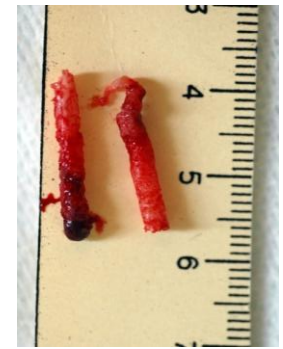
Occurrence of resistance depends



- ✓ within the clinical setting
- ✓ type of fungal disease
- ✓ class of antifungal agent
- ✓ treatment duration
- ✓ varies between center to centre.

Spectrum of opportunistic fungal pathogens is increasing!



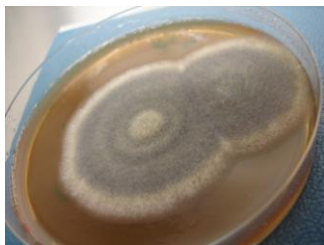


Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: real-life data from a single centre institutional retrospective observational study

Auberger J, Lass-Flörl C, Aigner M, Clausen J, Gastl G and Nachbaur D
J Antimicrob Chemother, 2012

Primary antifungal prophylaxis with micafungin in patients with haematological malignancies: real-life data from a retrospective single-centre observational study

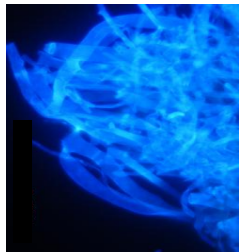
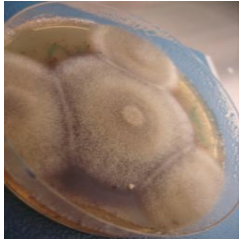
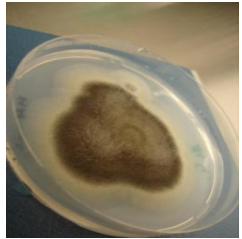
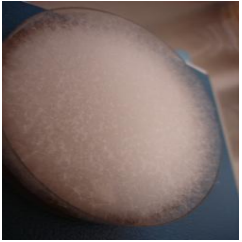
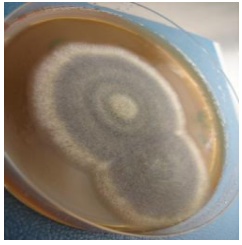
Nachbaur D, Lackner M, Auberger J, Lass-Flörl C
Eur J Haematology, 2014



Mortality in invasive fungal infections is high!

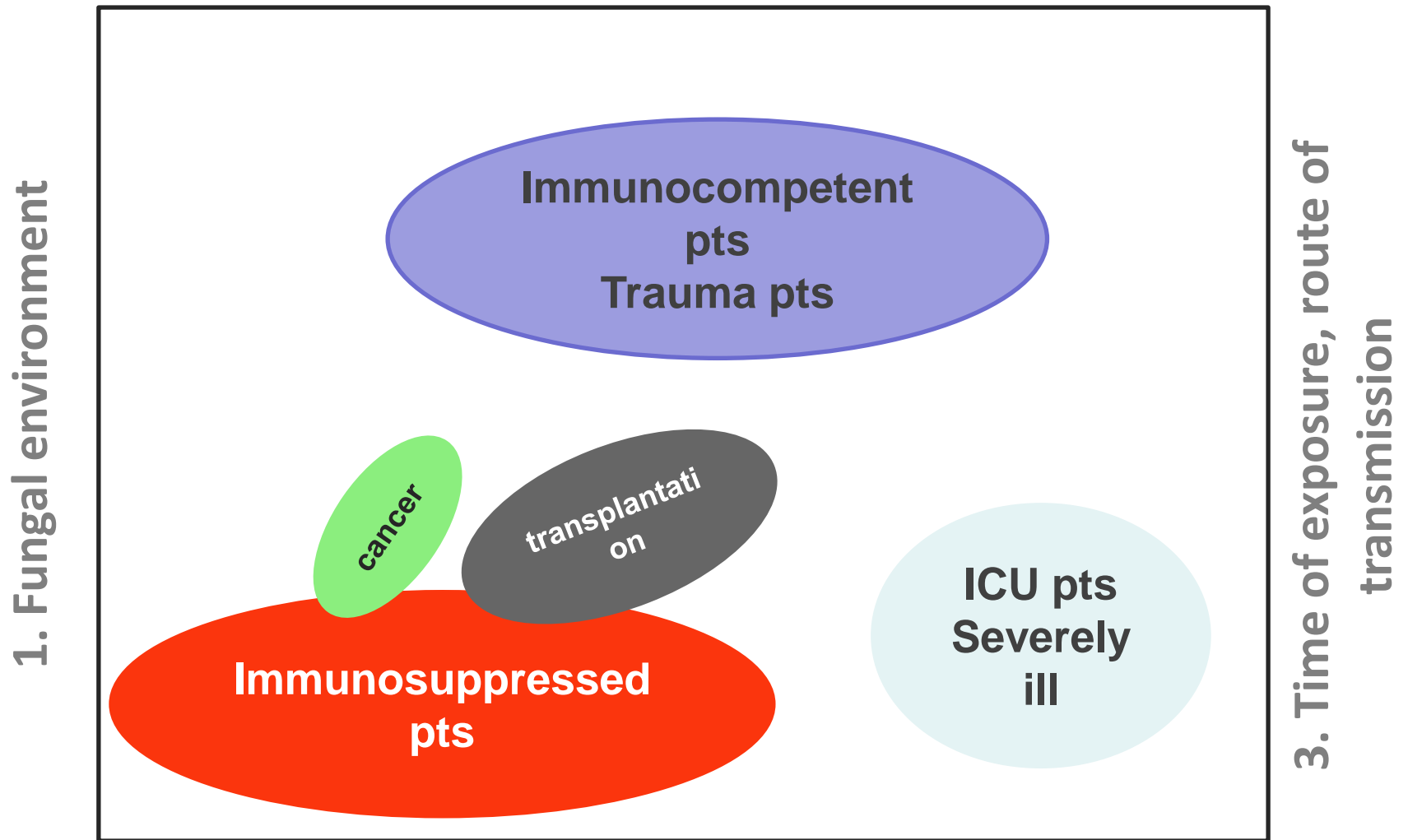
Pathogens	Mortality
Candida spp	40%
Aspergillus spp (2001/2009)	62%/31%
Andere invasive Pilze (Fusarium spp., Zygomyceten)	~80%
Scedosporium spp	100%

Pappas PG, et al. Clin Infect Dis. 2003
 Wisplinghoff H, et al. Clin Infect Dis. 2004
 Perfect J, et al. Clin Infect Dis. 2001
 Marr KA, et al. Clin Infect Dis. 2009



Epidemiology
Pathomechanism
Diagnosis
Treatment

2. Innate and adaptive immunity



4. Selective antifungal pressure

1. Humans: new at risk populations



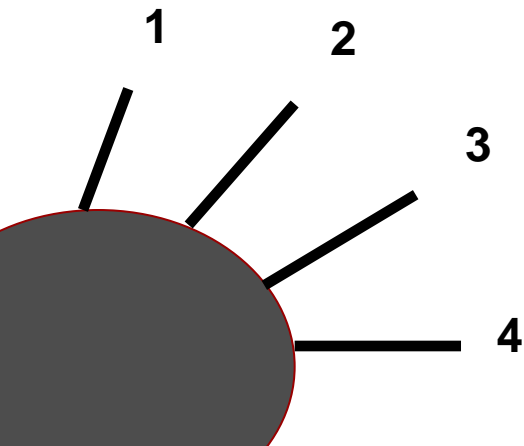
2. Humans and their environment

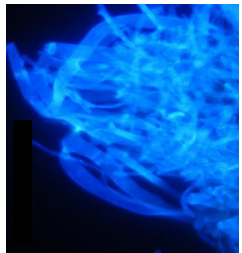
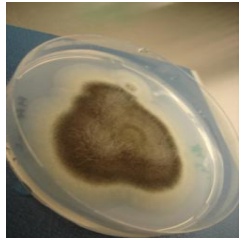
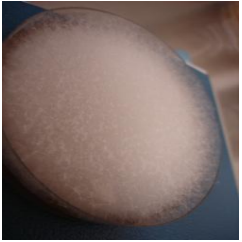
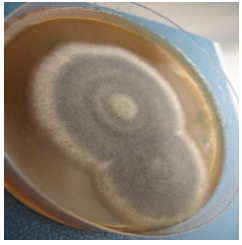


3. Novel treatment strategies



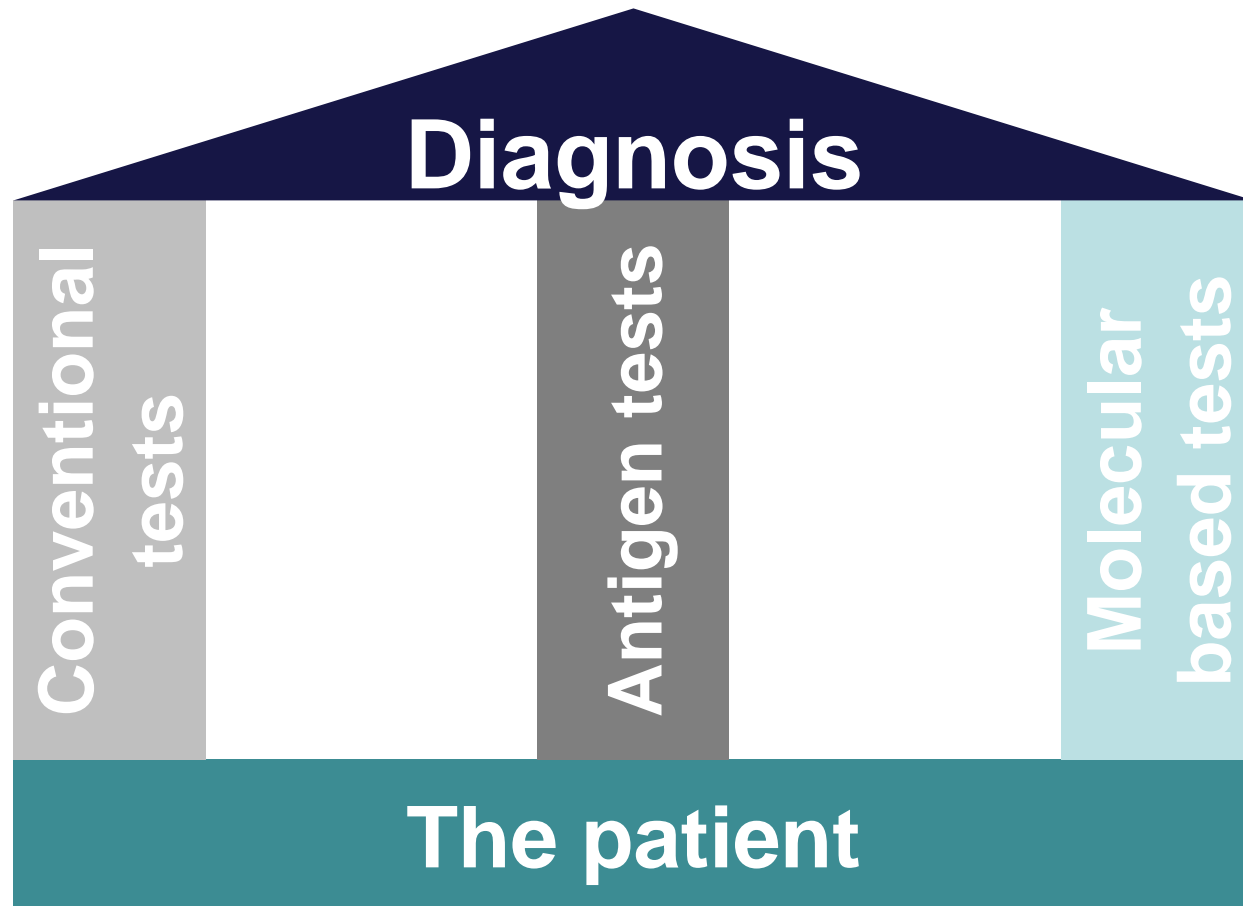
4. Aging population





Epidemiology
Pathomechanism
Diagnosis
Treatment

Define your individual needs of the three cornerstones.....



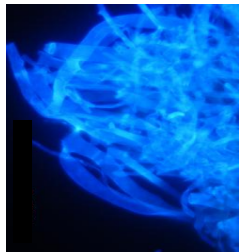
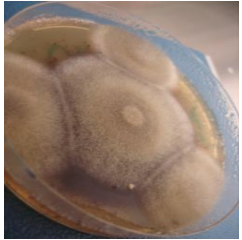
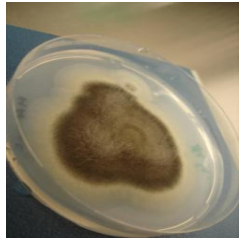
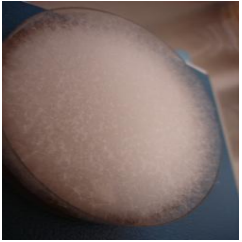
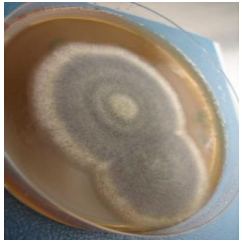
Which test when? Which test is bests?



Diagnosis of Mycotic Infections

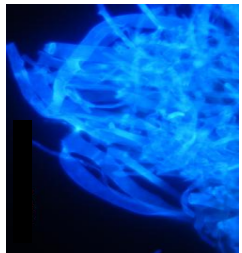
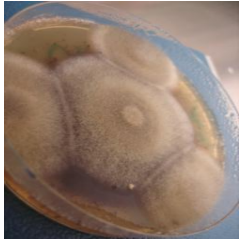
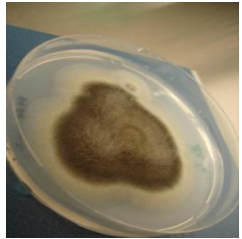
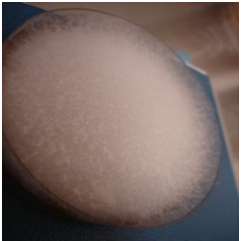
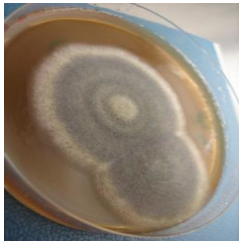
Diagnosis and identification require microscopic viewing of stained specimens, culturing in selective and enriched media and specific biochemical and serological tests





Epidemiology
Pathomechanism
Diagnosis
Treatment

Which drug when to use?



Fungus (spectrum)

Previous therapy

Risk factors

Local epidemiology

Severity of clinical presentation

Underlying diseases

Safety

PK/PD

The echinocandin classes

- Caspofungin: 70 mg load then 50 mg/d
- Anidulafungin: 200 mg load then 100 mg/d (IC);
- Micafungin: 50 mg/d . Not approved yet for IC; dose likely 100/d

- The three sisters. All are IV only
 - Caspofungin
 - Anidulafungin
 - Micafungin
- Mostly similar
 - Safety: Consistently very clean
 - Non-renal clearance (no adjust in renal fail)
 - Hepatic failure:
 - C: 35 mg/d for moderate, no data for severe
 - Drug interactions: More with caspofungin
 - P450 inducers: No effect (A, M), some ↓ (C)
 - Cyclosporine: No effect (A, M), caution (C)
 - Tacrolimus: No effect (A, M), some ↑ (C)

The azoles

- From broad to small spectrum azoles
- Loading dosis
- Cover Candida and/or molds
- Drug-drug interactions

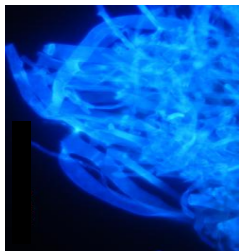
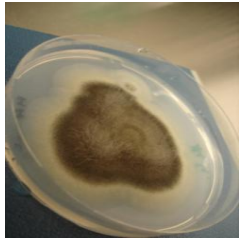
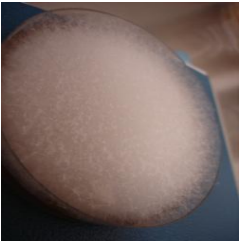
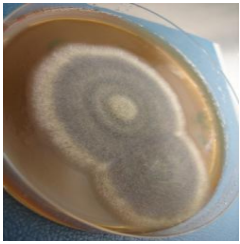
- Fluconazole
 - Small spectrum
 - IV and PO: forms are interchangeable
- Voriconazole
 - Aspegillus
 - IV uses cyclodextrin carrier that is cleared by kidneys. Avoid in renal failure
- Posaconazole (oral, iv)
 - Prophylaxis
 - Broadest azole
- Isavuconazole (oral, iv)
 - Aspergillus & Mucorales
- Safety issues: Are quite good
 - Hepatic injury is main risk
- Drug interactions
 - Have typical range of P450/cytochrome azole problems

The amphotericines

**Some patients
tolerate one but
not another**

- Amphotericin B deoxycholate
 - Fungizone™
- Liposomal amphotericin B
 - AmBisome™
- Amphotericin B lipid complex
 - ABLC, Abelcet™
- Amphotericin B colloidal dispersion
 - ABCD, Amphocil™, Amphotec™
- The names matter
 - Side-effects & dosages are different
 - “Lipid ampho B” does not describe anything at all!
 - Broadest antifungal activity

Four unresolved problems



We lack robust, rapid, simple, and cheap tools for sensitive diagnosis - to allow adequate antifungal treatment.

We need safer and more effective antifungal drugs.

What is best prophylaxis?

Currently there are no approved human vaccines for any invasive fungal pathogen.



Thank you very much for your attention!