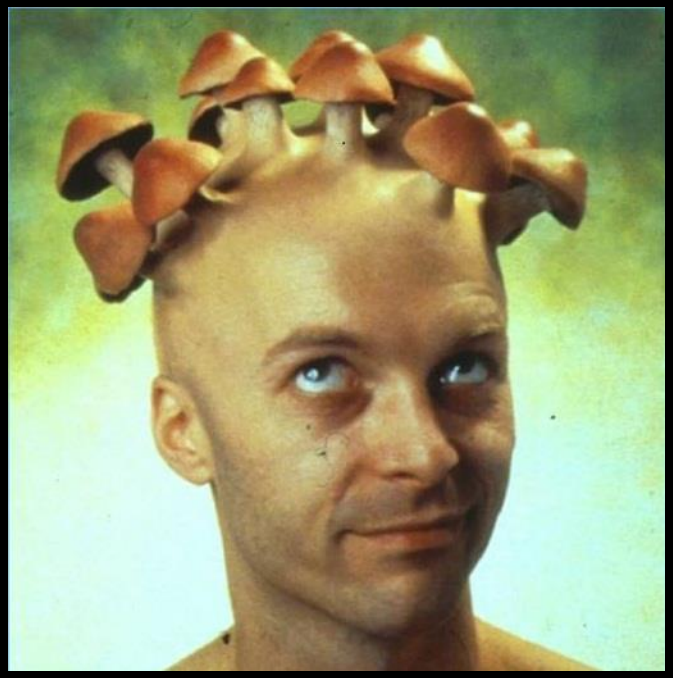
Invasive Fungal Infection in critically ill patients



Ata Mahmoodpoor.MD.FCCM
Assistant professor , TBZMed

The rate of sepsis due to fungal organisms in the USA increased by 207% during the past 30 years, which was the largest increase observed due to any group of organisms.

Despite the remarkable progress in diagnostic modalities, difficulty in prompt diagnosis and the complexity of the clinical characteristics of at-risk patients make the management of IFIs a great challenge.

The shift of species

The most commonly recognised causes of IFIs traditionally are Candida albicans, Cryptococcus neoformans and Aspergillus fumigatus.

With the widespread use of antifungal prophylaxis, the epidemiology of IFIs has shifted towards non-albicans Candida,non-fumigatus Aspergillus, opportunistic yeast-like fungi(e.g. Trichosporon and Rhodotorula spp.),zygomycetes and hyaline moulds(e.g. Fusarium and Scedosporium spp.)

Critically ill patients with hematologic malignancies are at high risk for Candida and Aspergilous species.

Clinicians have often considered fungal infections a problem of neutropenic patients, but today, at least half of all nosocomial fungal infections occur in critically ill surgical patients.

Table 1 General differences between immuno-compromised and critically ill populations.

Mechanism	Immuno-compromised	Critically ill
Underlying problems	Single/simple	Multiple
Immune system problem	Defined	Non-specific
Relevance of underlying problem	Direct	Indirect
Risk assessment of likelihood of fungal infection	Easy	Difficult
Physiological derangement	Minimal	Extensive
Organ systems	Reasonable condition	Often damage, always vulnerable
Attributable mortality	Direct relationship	Indirect and difficult to assess
Treatment toxicity	Unlikely	Probable

Table 1. Identified Risk Factors for the Development of Fungal Infections

Neutropenia related to chemotherapy for cancer, connective tissue disease, or HIV
Immunosuppression secondary to corticosteroid use
Acute renal failure
Central venous catheter use for hemodialysis, total parenteral nutrition, etc.
Hyperglycemia
Surgery, especially gastrointestinal surgery and acute pancreatitis
Candida colonization, more than two body sites, or a colonization index >0.5
Broad-spectrum antibiotic use, both extended spectrum and duration of use
Mechanical ventilation >10 days
High severity of illness
Prolonged ICU length of stay (risk increases depending on ICU; range, 3–9 days)

Candidiasis

Epidemiology

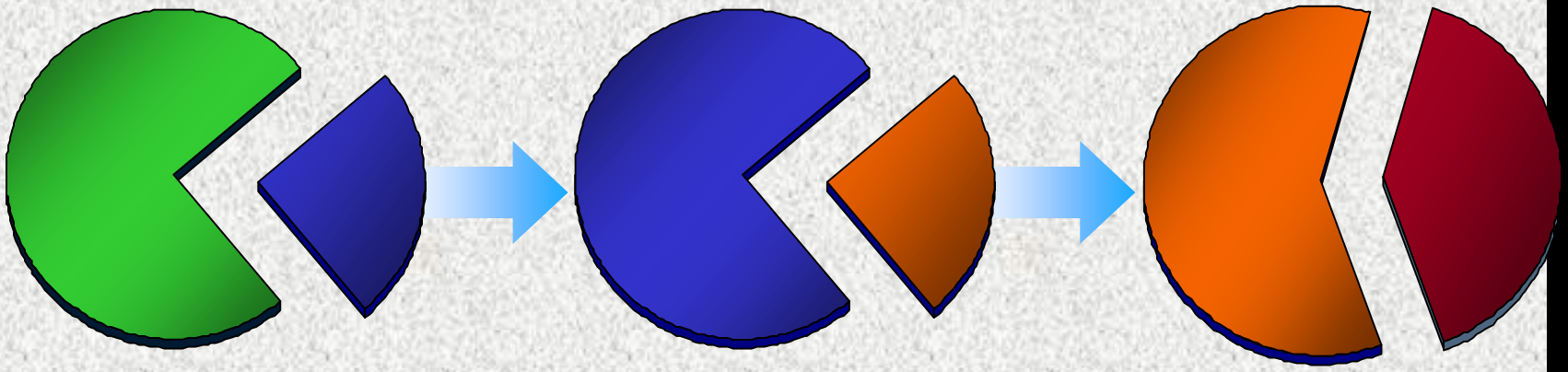
- The most predominant causes of IFIs.
- More than 95% of Candida-associated BSIs are caused By five major species:
- C.albicans
- C.glabrata
- C.parapsilosis
- C.tropicalis
- C.krusei
- The remaining include Candida lusitaniae, guilliermondii and rugosa.

At risk patients

- Previous surgery(relative risk,7.3)
- acute renal failure(relative risk,4.2)
- Receipt of parenteral nutrition(relative risk,3.6)
- Patients with surgery, a triple-lumen catheter(relative risk,5.4)
- Immunosuppresion specially solid organ transplant recipients
- Candida colonization
- Duration of antibiotic use or anti-anaerobic therapy
- GI performance
- Duration of ICU stay(Colonization dramaticaly at day 7 and peaks around day 21).

Some believe that ICU patients are at risk with more than 3 risk factors.

Risk for Invasive Candidiasis Is a Continuum



High-risk patients

- Surgery
- Leukopenia
- Burns
- Premature infants

Exposures

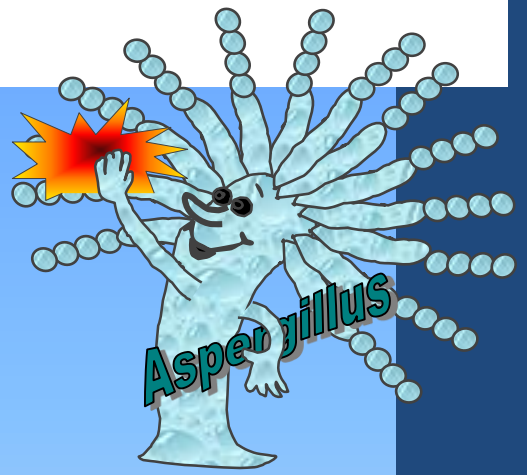
- ICU ≥7 days
- CVCs
- Antibiotics
- TPN
- Colonization

If candidemia develops…

- ~40% die
- ~60% survive

Invasive Aspergillosis

INCIDENCE OF INVASIVE ASPERGILLOSIS



24%

1%

4%

8%

12%

7%

31%

Variation due to:

- Inconsistent definitions
- Diagnostic tools applied
- Timing diagnostic procedures
- Invasive procedures
- Autopsy rate

- Aspergillosis incidence ranges from 2.7 to 58 cases per 1000 admissions, with a mortality of 75-95%.
- Aspergillus rarely cause infection in surgically critical ill patients .
- Most infections are exogenously, via inhalation.
- Lung is the most common site, others include cutaneous, CNS and cardiac vasculature.
- Highest incidences in AML
- Is higher in allogenic HSCT recipient than autologus HSCT recipient.

Risk Factors

- Hemato-oncological patients
  - Allogeneic SCT, graft-vs.-host disease
  - Persistant neutropenia
- Solid organ transplant patients,
  lung/heart,lung>>liver>renal
- Immunosuppressive therapy
- Chronic granulomatous disease
- Severe combined immunodeficiency
- HIV
- Neutrophil dysfunction(espicially> 3 weeks)
- Mismatched transplant recipients

Conclusion

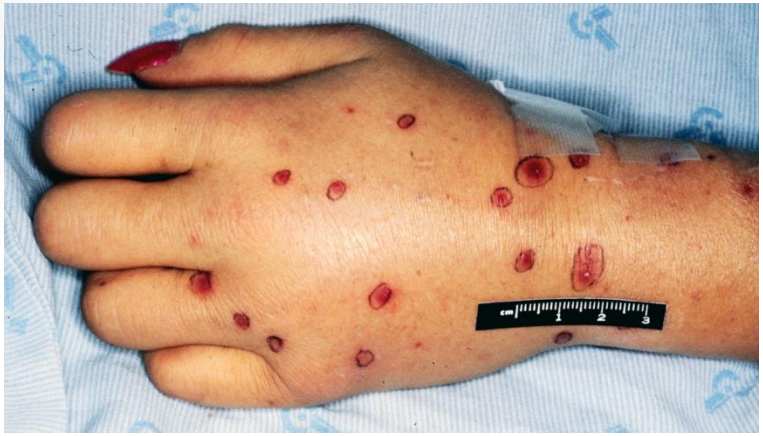
- Invasive Aspergillosis in ICU patient is a Fact …
- Incidence …
  - 0.33 – 5.8%
  - Depending on patient mix: MICU > SICU
  - Underestimated?
- Delayed diagnosis
  - Diagnosis post mortem
- Grim prognosis
  - Mortality exceeding 77%
  - Observed mortality >> predicted mortality

Diagnosis

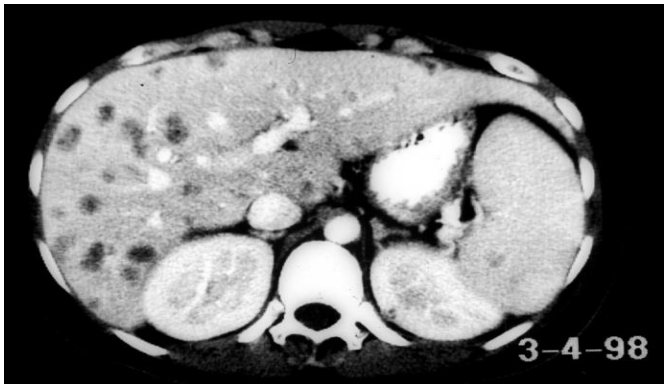
"Of course I'll need to run some tests; but offhand I'd say it's some sort of fungus infection."

Candidiasis Spectrum of Infection

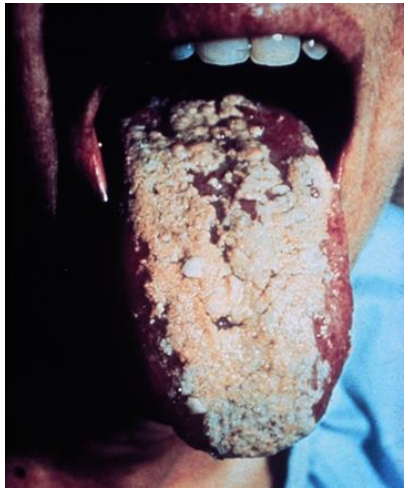
A. Cu



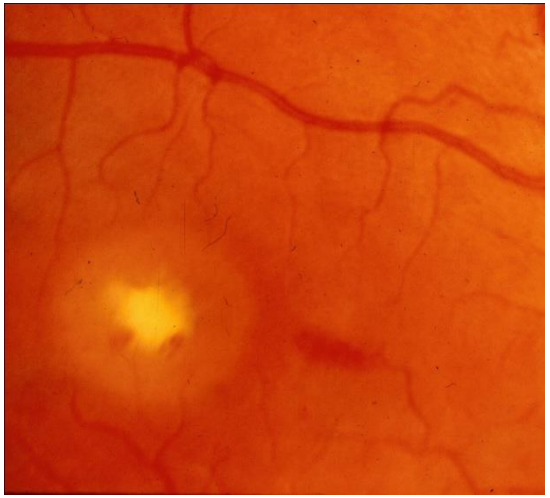
C. Disseminated



B. Mucosal

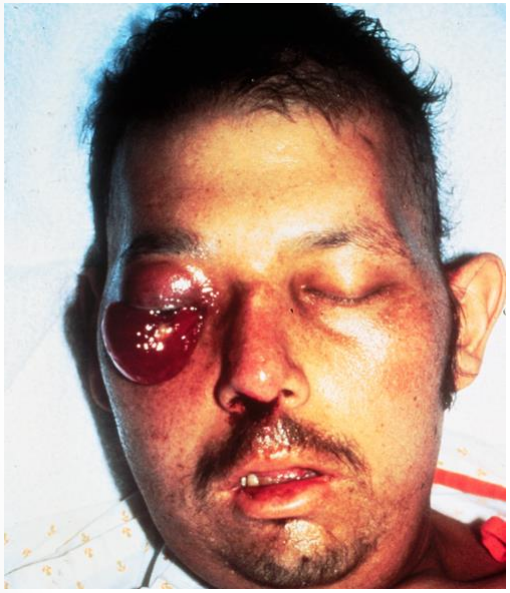


D. Chorioretinitis

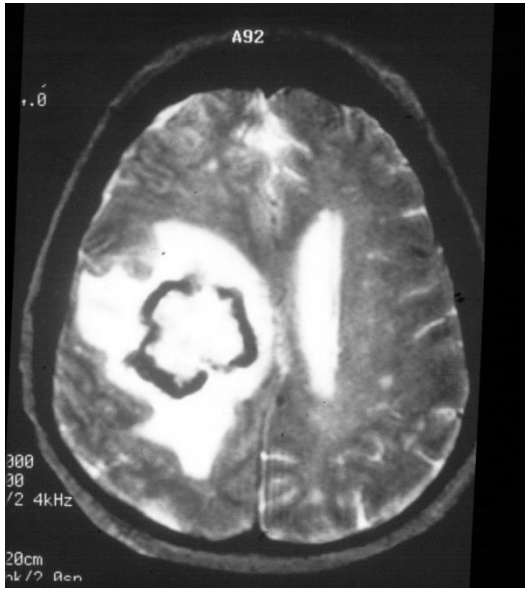


Invasive Aspergillosis

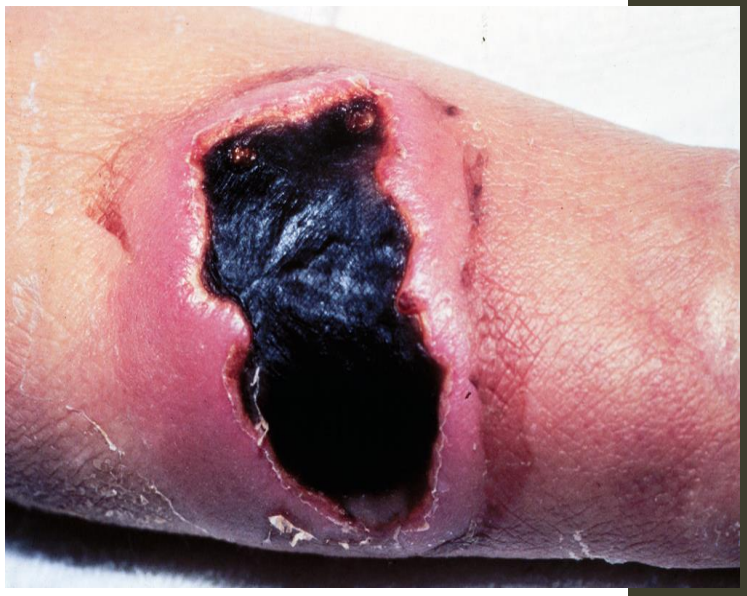
Other Clinical Presentations



A. Sino-orbital disease

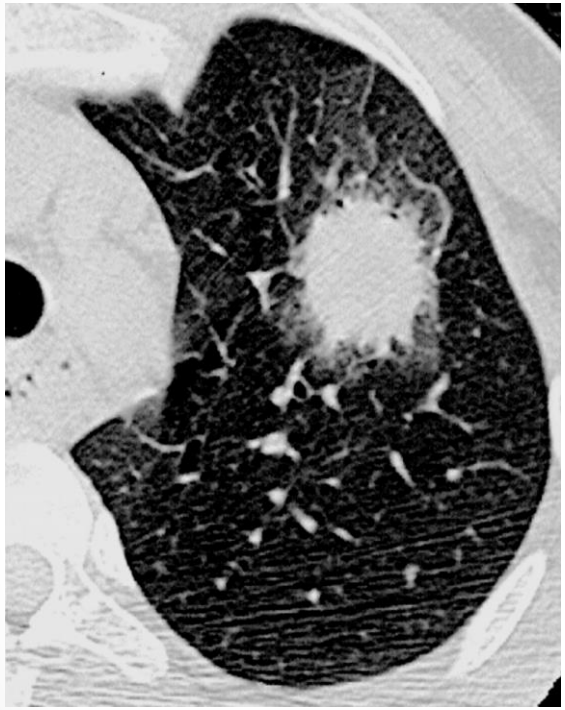


B. Cerebritis

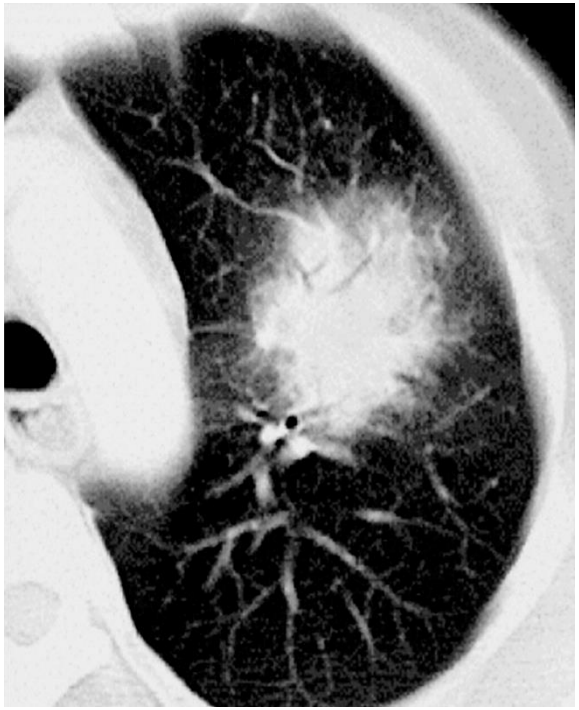


C. Cutaneous infection

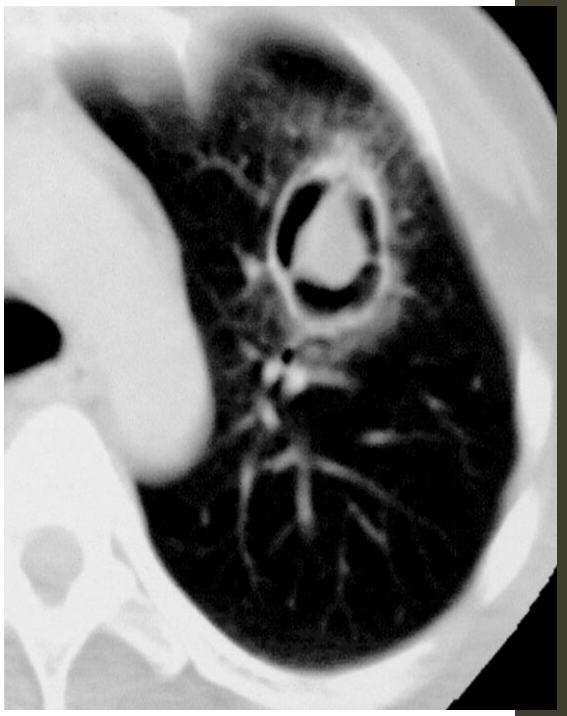
Evolution of Invasive Aspergillosis



Halo sign (day 0)



Non-specific (day 4)



Air crescent (day 7)
neutrophil recovery

Galactomannan antigen test

- FDA approved for I.A, Non-invasive, easy to use
- Good sensitivity, specificity, PPV and NPVThe sensitivity in nonneutropenic patients may be lower, possibly because of a lower residual fungal burden or anti-Aspergillus antibodies.

False positive results in

- patients receiving antibiotics (pip-taz or amox-clav)
- children colonization with Bifidobacterium
- patients with circulating aspergillus antibodies
- patients receiving antifungal agents active against aspergillus
- Dietary GM (cereals, pasta),
- plasmalyte is used in bronchioalveolar lavage fluids
- patients with other invasive mycoses (including Penicillium, histoplasmosis, and blastomycosis.)

Cut-off (0.5, 0.7, 1.0, 1.5) ?

Used for terapeutic monitoring ??

Detection of glucan

- Glucan is a good indiator of systemic fungal infection, if detectable in blood rather normally sterile body fluids. But is not specific for Aspergillus species
- False positive results: glucan contaminated blood collection tubes,gauze, depth-type membrane filters for blood processing,and invitro tests using various antibiotics (e.g.,some cephalosporins, carbapenems, and ampicillin-sulbactam), Gram positive infections, biofilms on vascular catheters, hemodialysis, or the administration of intravenous immunoglobulins.

The G Test seemed to be negative in pulmonary cryptococcosis.

PCT in surgical ICU

- A low PCT value(less than2.0ng/mL) in a surgical patient with clinical signs of sepsis and risk factors for fungal infections is more likely to be related to candidemia than to bacteremia.

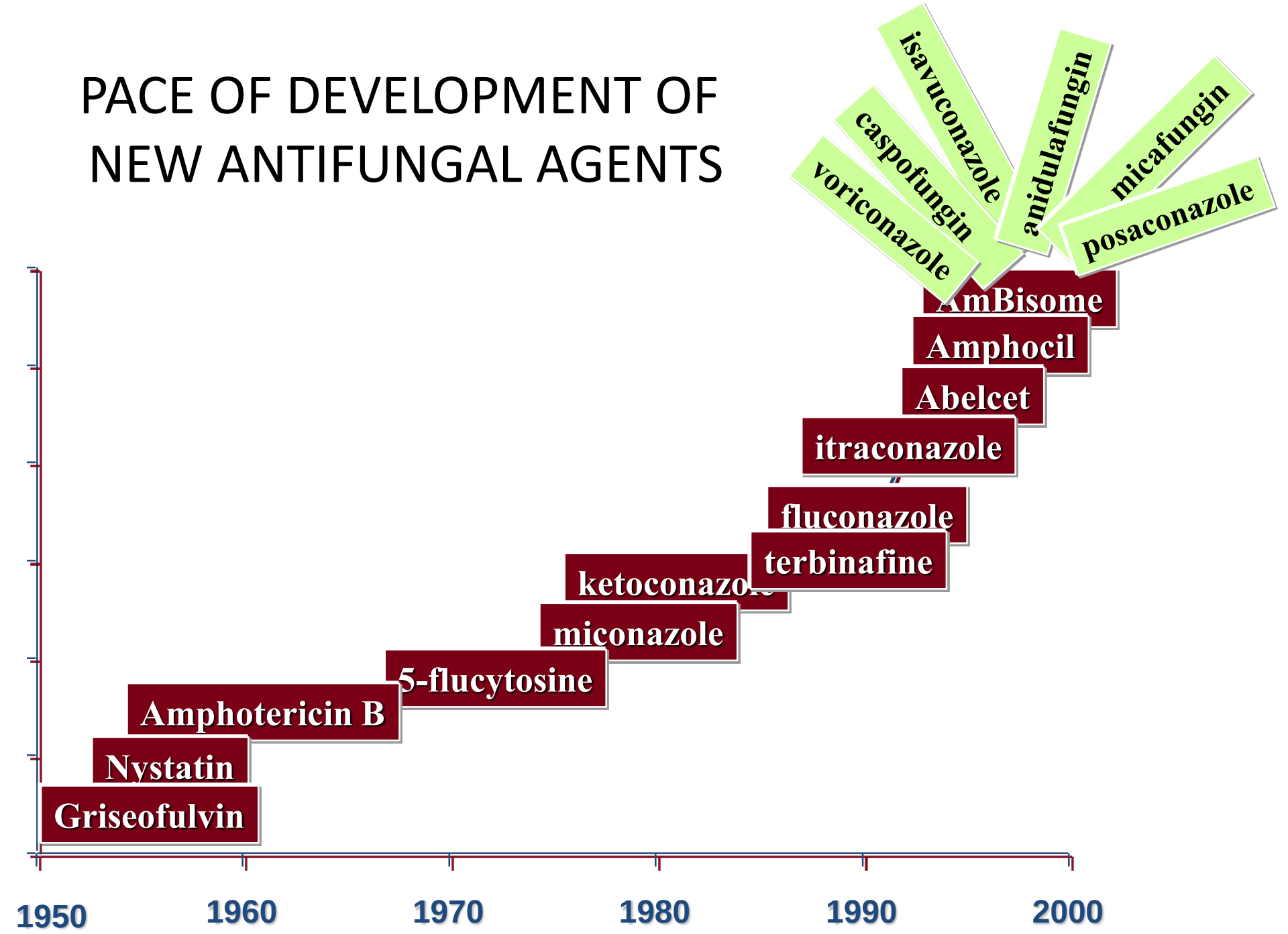
- **Clinical signs and symptoms**: non specific
- **High resolution CT scan**(Early stage:Halo sign), late sign:air crescent sign).

  Bulls eye :specific for organ candidiasis.
- **Histology**:require invasive procedures, identification of microorganism alone is not possible and culture is required.
- **Culture**:low sensitivity in Asp.Rapid identification is possible by CHROM-agar,any + resp results require diagnostic workup. cultures become positive at a late stage and delayed therapy is associated with a poor outcome

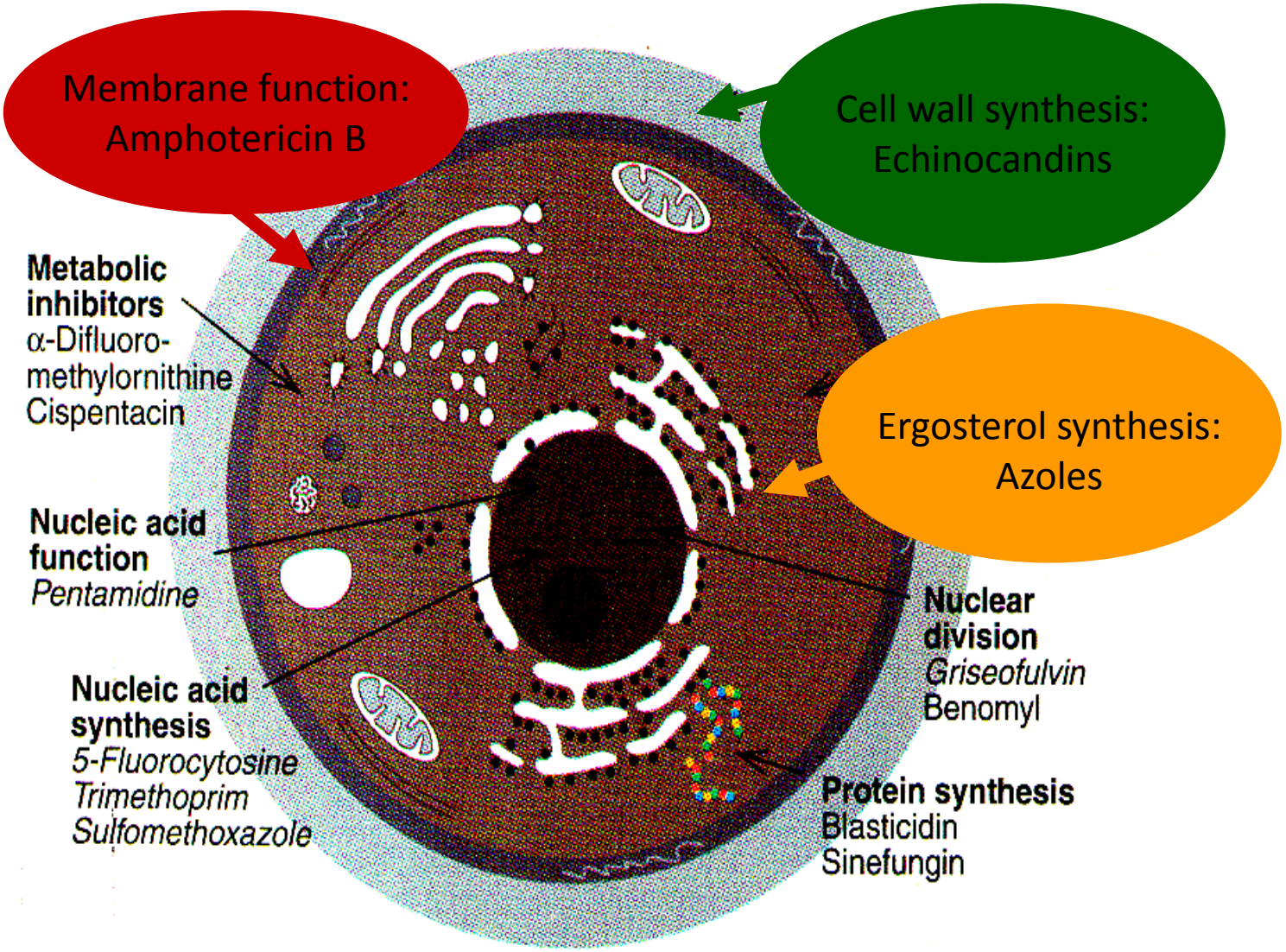
- Microscopy: low sensitivity,alone dose not allow identification
- PCR: early indicator, variable performance due to nonstandardization of assays.
- Antigen detection:Early indicator, limited performanse in I.C compared to I.A.Repeat increase sens and specifity
- Antibody detection: suboptimal performance in neutropenics, combination of antibody and antigen detection useful in I.C in critically ill patients

Antifungal drugs

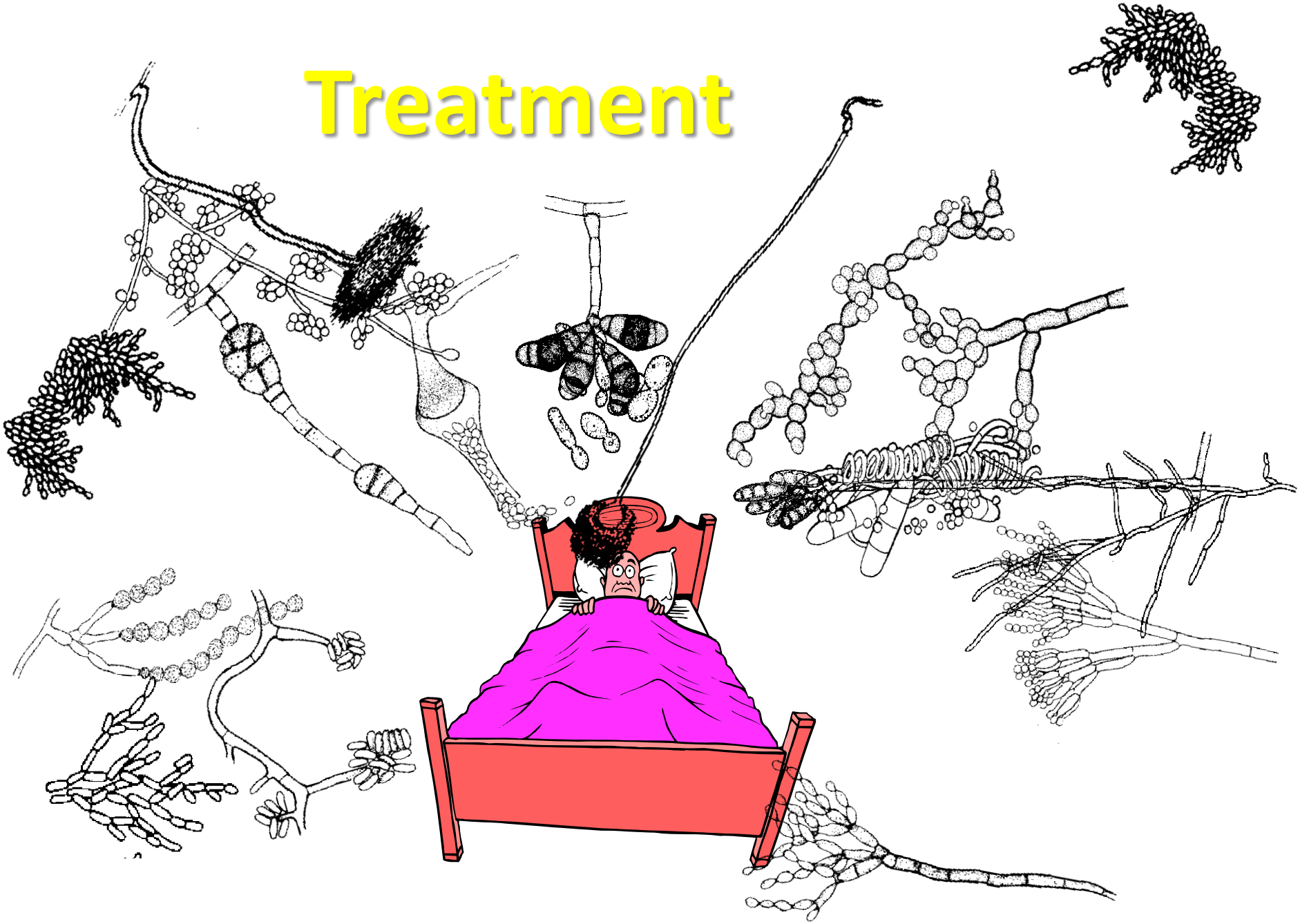
PACE OF DEVELOPMENT OF NEW ANTIFUNGAL AGENTS



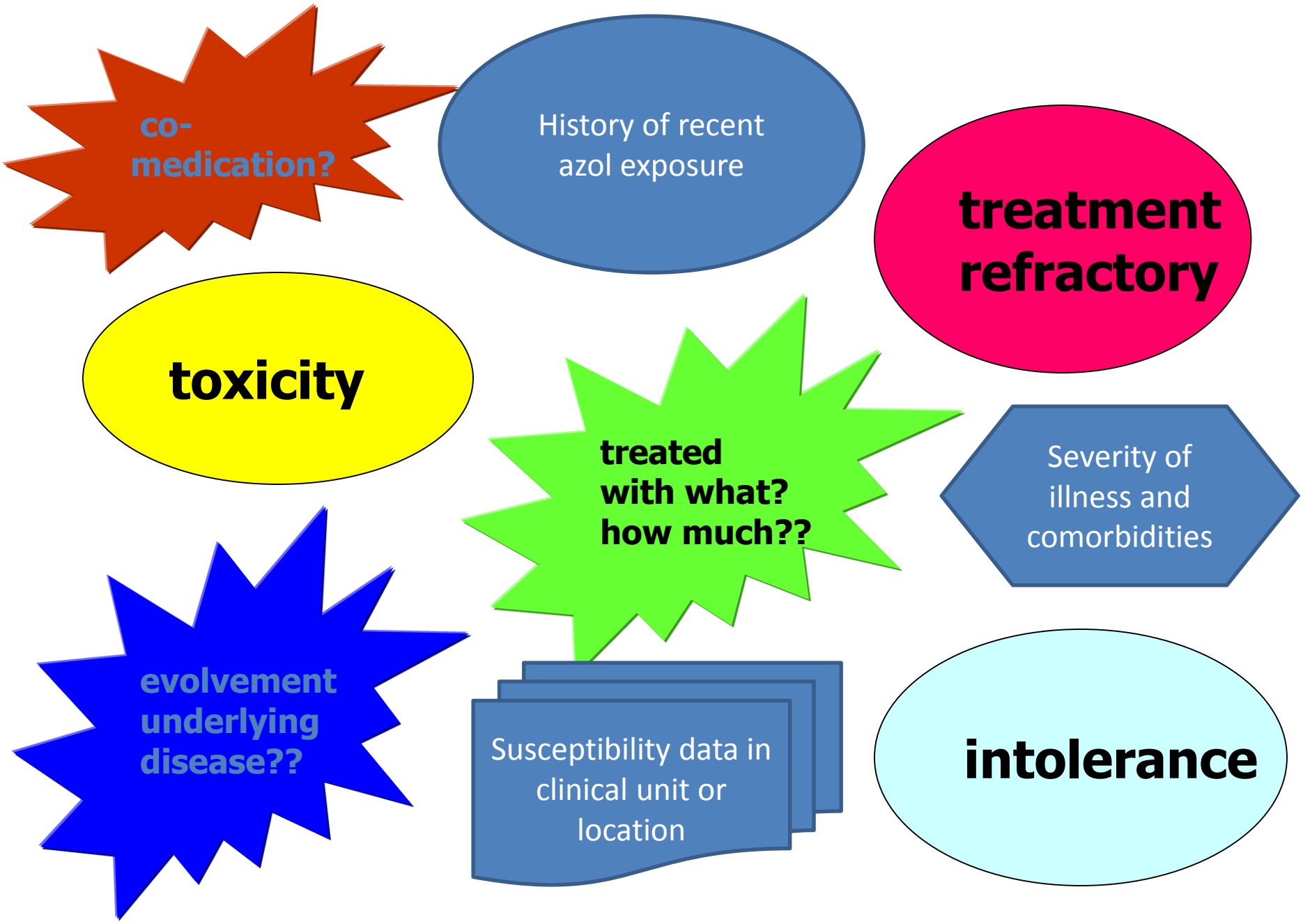
The (small) world of antifungals



Treatment



HOW TO PROCEED?


co-medication?
History of recent azol exposure
treatment refractory
toxicity
treated with what? how much??
Severity of illness and comorbidities
evolvement underlying disease??
Susceptibility data in clinical unit or location
intolerance

EORTC Definitions of IFI

These criteria are made for clinical trials and should not be used for clinical decision making

HOST FACTORS	CLINICAL FACTORS	MYCOLOGY
Neutropenia >96h ARNF GvHD >3 w corticosteroids prior mycosis AIDS Immunosuppressives	Halo sign Air-crescent sign Radiological evidence Unexplained papular or nodular skin lesions Chorioretinitis Endophthalmitis	Culture of mould from tissue, aspirate, BAL or sputum Fungus seen in tissue or sterile body fluid Aspergillus antigen in BAL, CSF or >2 blood

HOST FACTORS + CLINICAL FACTORS **OR** MYCOLOGY — POSSIBLE

HOST FACTORS + CLINICAL FACTORS + MYCOLOGY — PROBABLE

HOST FACTORS + CLINICAL FACTORS + MYCOLOGY + TISSUE — PROVEN

Treatment of Suspected Invasive Candidiasis (Definitions)

- **Prophylactic therapy:** protective or preventive therapy given to everyone in a given class (ex. BMT patients who are at very high risk for IC).
- **Preemptive therapy:** therapy given to deter or prevent anticipated infection; patients at risk are monitored closely and therapy is initiated with **early evidence suggesting infection** (ex. positive Candida cultures at non-sterile sites, clinical suspicion) with the goal of preventing disease.
- **Empirical therapy**: therapy guided by practical experience and observation, but **with nonspecific evidence** in a given patient (ex. therapy is started because a cancer patient has remained febrile after several days of broad-spectrum antibiotics).
- **Directed therapy:** is based on a clinical or laboratory finding indicating that an infection is present (ex. positive blood culture for Candida species).

Can we wait for the blood culture results in candidemia?

- Delay in empiric Rx of candidemia till after blood cultures turn positive resulted in higher mortality.
- Start of anti-fungal Rx >12 hrs of drawing a blood culture that turns positive had AOR= 2.09 for mortality, $p=0.018$.

- In a high-risk critically ill surgical patient with

a long length of stay, multiple sites of fungal colonization, and a suspected infectious disease unresponsive to broad-spectrum antibiotics, the time for prophylaxis is long past.

- This patient is a candidate for empirical or preemptive therapy.

Summary (Empiric Therapy)

- If *Candida* infection is suspected, treatment will need to be initiated empirically without delay on the basis of individual patient factors before a definitive diagnosis is made.
- Choice of agent will rely on local resistance patterns, microbiology data, prior azole therapy, recent GI surgery, neutropenia, hemodynamic stability, & other host factors.
- Azoles are effective unless high rates of resistance, or neutropenia in which case **echinocandins** or **triazoles** should be used.

- Patients with candidemia and a central line generally should have central lines removed as soon as possible.
- Although there is some controversy,catheter removal may not change mortality but blood cultures clear more quickly.

  In patients with limited venous access such as those dependent on total parenteral nutrition for life,successful treatment with the catheter in situ has been reported.

Summary

- In certain high-risk critically ill surgical patients
  patients with gastrointestinal surgery
  central venous catheters
  multiple antibiotics
  multiple sites of fungal colonization

a high index of suspicion should be developed for the assessment of the need for **early presumptive therapy**.

Summary (Candida Prophylaxis)

- Prophylaxis is effective in the highest risk patients.
- Prophylaxis reduces the incidence of IC.

A positive impact on mortality has not been shown except in severely immunocompromised hosts (neutropenia, BMT, or solid organ transplantation)

Table 4
Summary of recommendations for targeted treatment for invasive candidiasis (n = 19).

Guideline Title	Initial drugs for *Candida* spp. mentioned					Alternative drugs for *Candida* spp. mentioned					Dosage mentioned	Duration mentioned	Drugs for ≥2 *Candida* Subspecies mentioned
	ECH	FLU	L-AMB	D-AMB	VOR	FLU	L-AMB	VOR	D-AMB	ITR			
IDSA guidelines-2016	✓					✓	✓	✓			✓	✓	✓
MEDICAL: Consensus proposal-2016	✓						✓						
2016 IFI Taiwan guidelines-2016	✓	✓		✓			✓	✓				✓	✓
French IAI guidelines-2015[a]	✓	✓											✓
Middle East guidelines-2014	✓					✓	✓	✓	✓			✓	
Australian guidelines-2014	✓					✓	✓	✓	✓			✓	
Iranian IC guidelines-2014	✓					✓					✓	✓	✓
JMF guidelines-2014	✓	✓	✓					✓		✓	✓	✓	✓
EPICO 2.0 project-2014[a]	✓											✓	
Chinese burn IFI guidelines-2013											✓		✓
Italian IAI guidelines-2013[a]	✓		✓			✓		✓				✓	
ITALIC-2013	✓					✓	✓	✓				✓	
JSMM Guidelines-2013	✓	✓					✓	✓	✓	✓	✓	✓	✓
ESCMID guidelines-2012	✓					✓	✓	✓			✓	✓	
Brazilian guidelines-2012	✓					✓	✓				✓	✓	
ATS guidelines-2011	✓	✓	✓	✓	✓						✓	✓	✓
German guidelines-2011	✓	✓					✓	✓			✓	✓	
Spanish guideline for IC-2011	✓						✓				✓	✓	✓
Canadian guidelines-2010	✓						✓		✓		✓	✓	

ECH, Echinocandin; FLU, Fluconazole; L-AMB, Liposomal amphotericin B; D-AMB, Amphotericin B deoxycholate; VOR, Voriconazole; ITR, itraconazole.
[a] Guidelines for intra-abdominal candidiasis.

What Is the Treatment for Candidemia in Nonneutropenic Patients?

- An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (strong recommendation; high-quality evidence).
- 2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill (strong recommendation; high-quality evidence).
- 3. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant Candida isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin (strong recommendation; low-quality evidence).

- 4. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy (strong recommendation; moderate-quality evidence).
- 5. For infection due to C. glabrata, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates (strong recommendation; low-quality evidence).
- 6. Lipid formulation AmB (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents (strong recommendation; high-quality evidence).

- 7. Among patients with suspected azole- and echinocandinresistant Candida infections, lipid formulation AmB (3–5 mg/kg daily) is recommended (strong recommendation; lowquality evidence).
- 8. Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared (strong recommendation; low-quality evidence).
- 9. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida species from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; moderate-quality evidence).

Does the Isolation of Candida Species From the Respiratory Tract Require Antifungal Therapy?

- Growth of Candida from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy (strong recommendation; moderate-quality evidence).

Should Prophylaxis Be Used to Prevent Invasive Candidiasis in the ICU Setting?

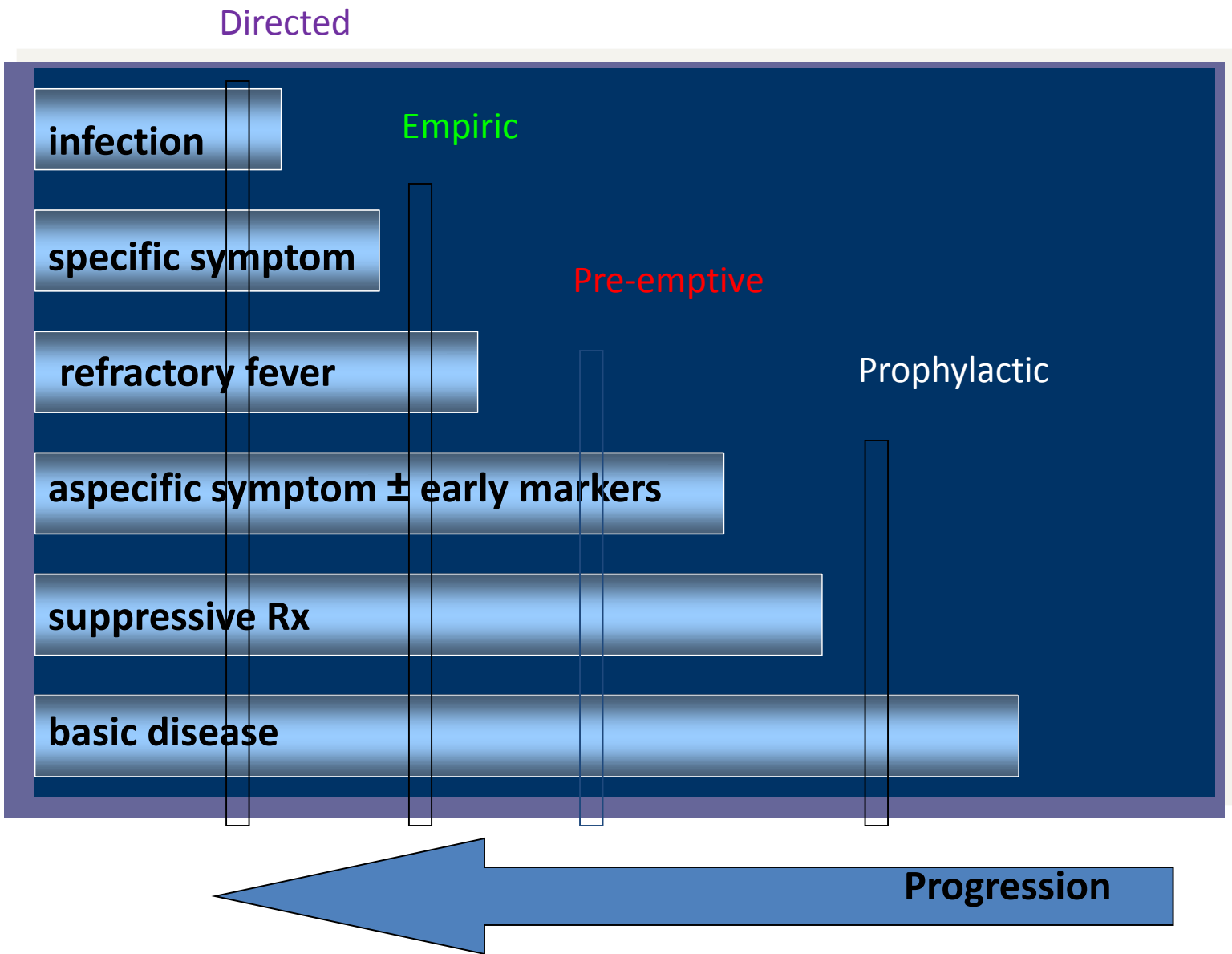
- Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (weak recommendation; moderate-quality evidence).
- An alternative is to give an echinocandin (caspofungin: 70-mg loading dose, then 50 mg daily; anidulafungin: 200-mg loading dose and then 100 mg daily; or micafungin: 100 mg daily) (weak recommendation; low-quality evidence).
- Daily bathing of ICU patients with chlorhexidine, which has been shown to decrease the incidence of bloodstream infections including candidemia, could be considered (weak recommendation; moderate-quality evidence).

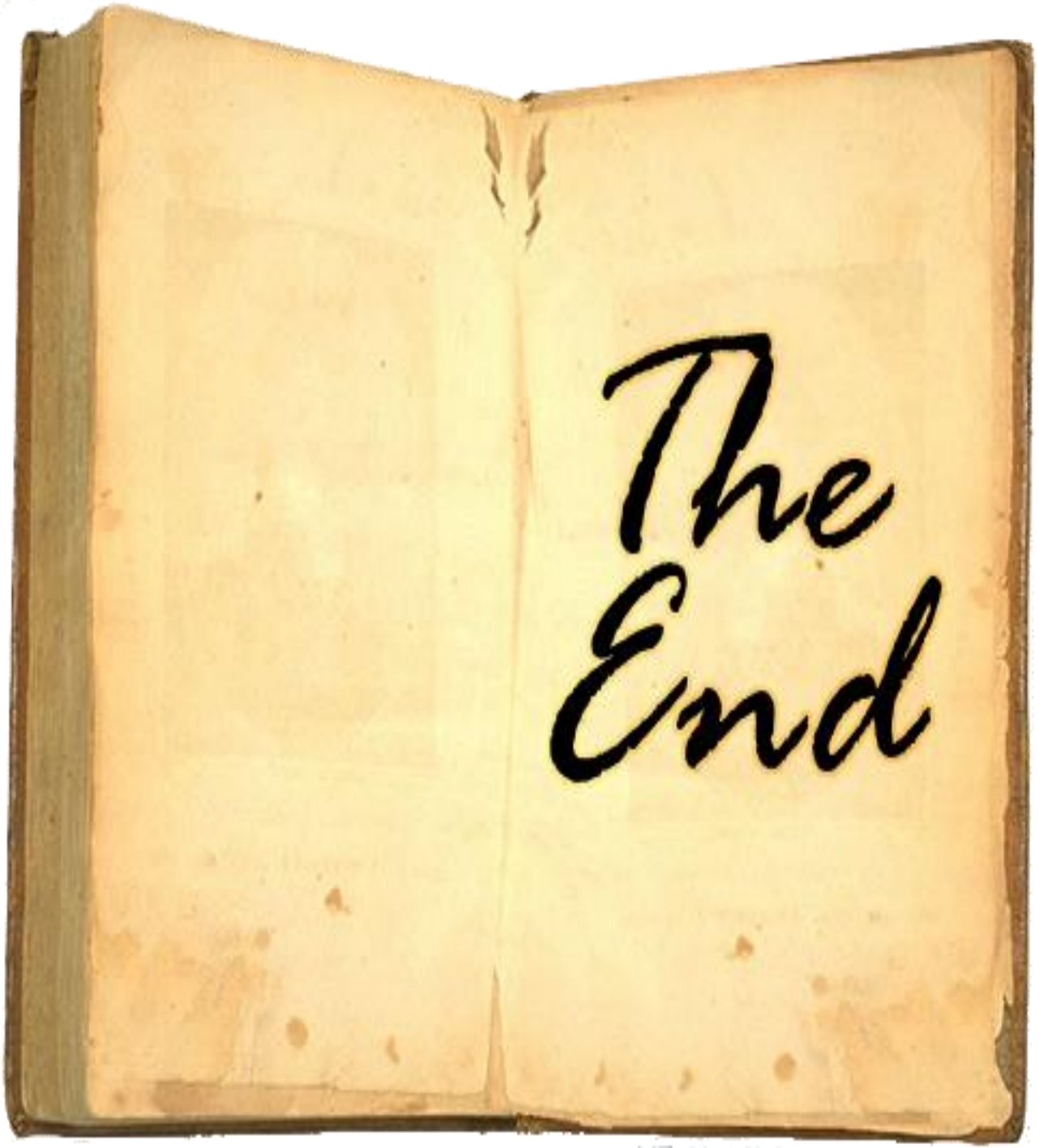
- There is no general consensus about how candiduria should be managed.
- Asymptomatic candiduria rarely requires therapy. Candiduria should be treated in symptomatic patients,neutropenic patients, patients with renal allografts, and patients with urologic manipulation.
- All urologic devices should be removed when possible. However,removal of the catheter may result in clearance in as many as 40% of patients.
- Bladder irrigation may achieve clearance of funguria but is rarely indicated certainly never when there is a concern about disseminated disease.

Treatment indication according to risk groups for invasive fungal infections

Low risk	● No primary antifungal prophylaxis ● Empirical antimycotic therapy rarely necessary ● Treat proven / probable infections
Intermediate – low – risk	● No primary antifungal prophylaxis (in most circumstances) ● Empirical antimycotic therapy usually indicated
Intermediate – high – risk	● Antifungal prophylaxis recommended ● Empirical antimycotic therapy recommended
High risk	

Timing of Intervention




The
End