WHICH ANTIFUNGAL AGENT IS THE CHOICE FOR SUSPECTED FUNGAL INFECTIONS?

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International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

Infection Rates and Types of Organisms in Culture-Positive Infected Patients According to Geographical Region

	No. (%)[a]							
	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	26 (12.7)	6 (11.1)	75 (15.7)
Aspergillus	70 (1.4)	44 (1.6)	1 (0.3)	5 (0.7)	12 (2.6)	3 (1.5)	0	5 (1)
Other	50 (1)	22 (0.8)	5 (1.4)	7 (1)	10 (2.2)	2 (1)	0	4 (0.8)

Candidiasis

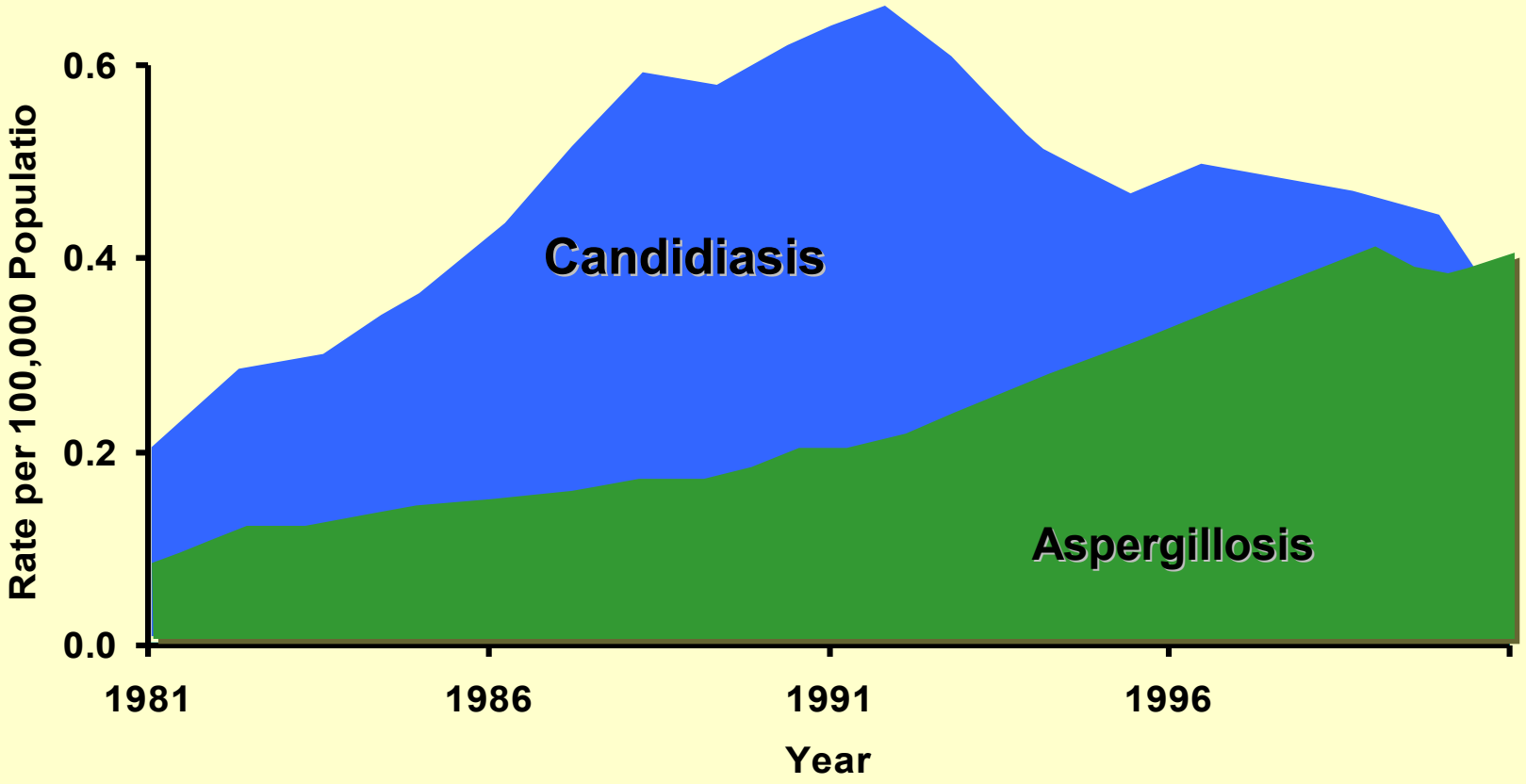
88 % in all fungi infections

Aspergillosis

7 % in all fungi infections

Adapted from International study of the prevalence and outcomes of infection in intensive care units. Vincent JL; Rello J; Marshall J; Silva E; Anzueto A; Martin CD; Moreno R; Lipman J; Gomersall C; Sakr Y; et al.; EPIC II Group of Investigators; JAMA: Journal of the American Medical Association, 2009 Dec 2; 302 (21): 2323-9.

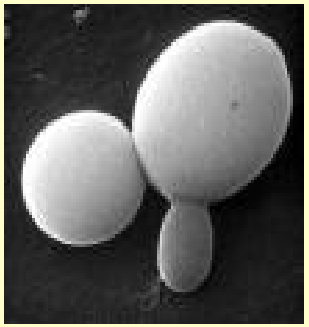
Incidence of Fatal Invasive Mycosis



Mc Neil et al 2001 *Clin Infect Dis* 33;641

Focus on Candidiasis

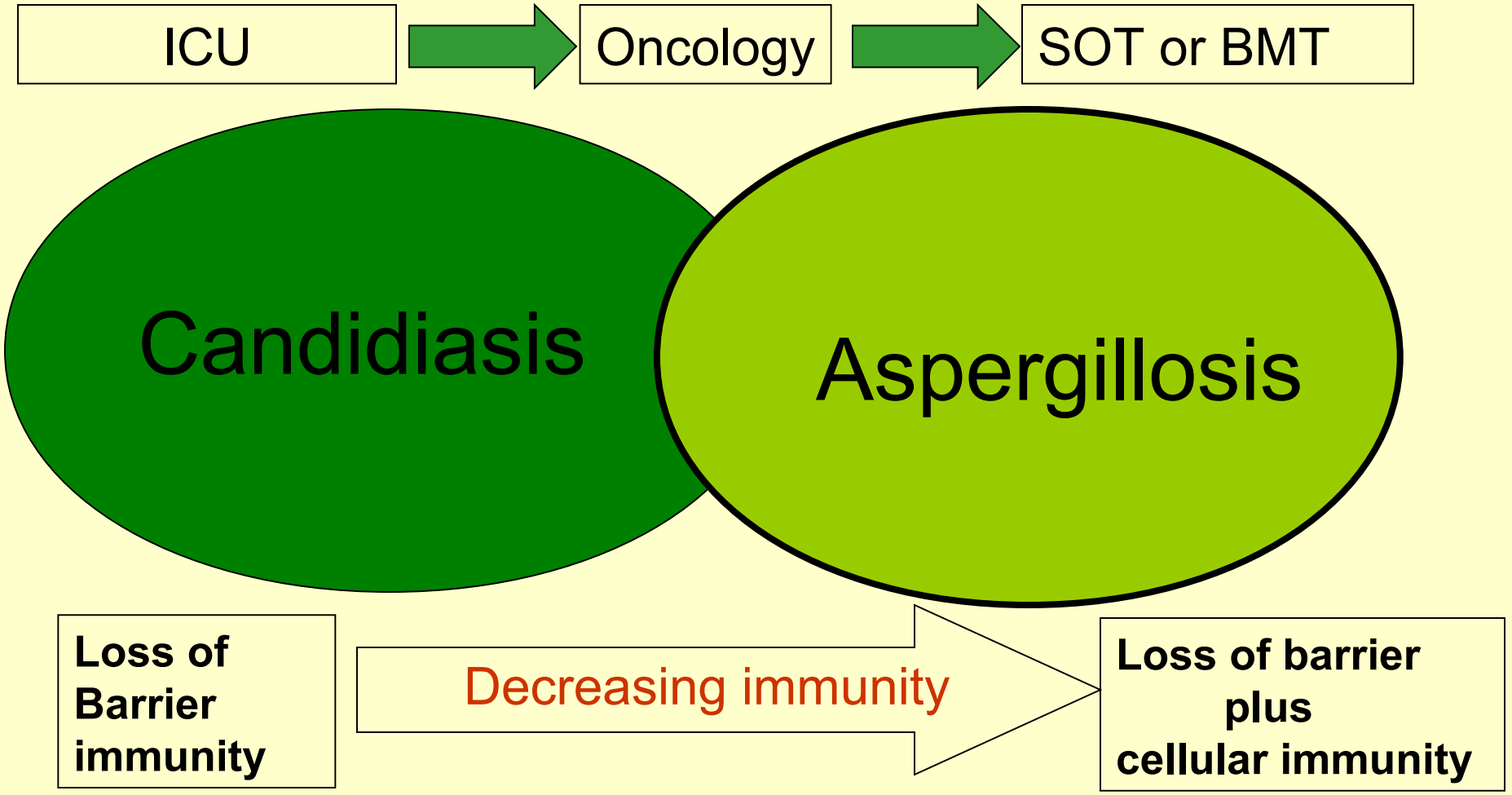
- Invasive *Candida* infections:
  - 4th most common nasocomial bloodstream infection with mortality approaching 40%



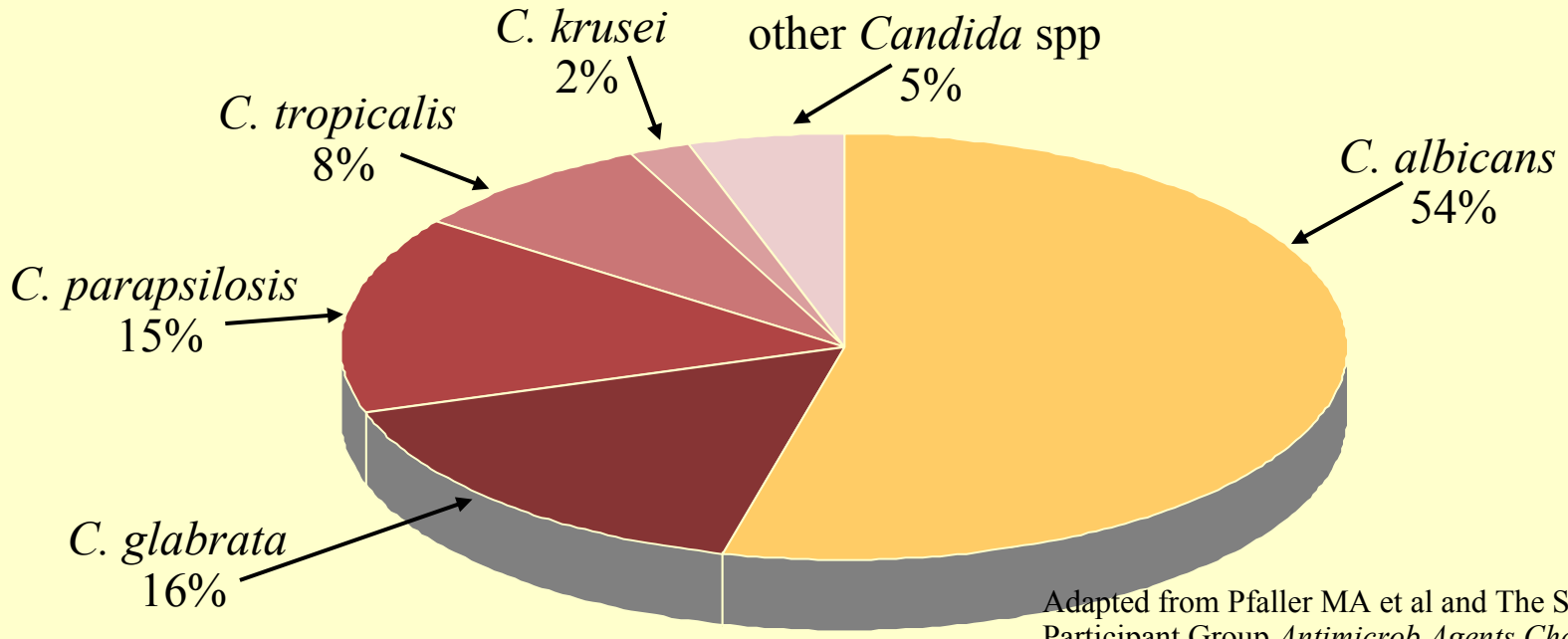
Pathogen	**No. of Isolates**	**Incidence (%)**
Coagulase-negative staphylococci	3908	31.9
Staphylococcus aureus	1928	15.7
Enterococci	1354	11.1
***Candida* species**	**963**	**7.6**

Adapted from International study of the prevalence and outcomes of infection in intensive care units. Vincent JL; Rello J; Marshall J; Silva E; Anzueto A; Martin CD; Moreno R; Lipman J; Gomersall C; Sakr Y; et al.; EPIC II Group of Investigators; JAMA: Journal of the American Medical Association, 2009 Dec 2; 302 (21): 2323-9.

Invasive Mycosis



In an international surveillance study 1997-1998:



Adapted from Pfaller MA et al and The SENTRY Participant Group *Antimicrob Agents Chemother* 2000;44:747–751.

Since then increase in *Candida* spp. with higher incidence of fluconazole resistance.

Snydman DR. 2003. Chest 123(Suppl 5):500S-503S). Garbino J. et al. 2002. Medicine;81:425-433.

Invasive Candidiasis in the ICU

Common in the ICU

(~10 % admissions)

High morbidity

(increased LOS ~22 days)

& **Mortality** (~ 30-40%)

Eur J Clin Microbiol Infect Dis. 2004:23; 739-744.

Major Risk Factors: Candidiasis

Major surgery (abdominal) within one week

Continuous Renal Replacement Therapy

Diabetes

Prior antibiotic use,

Sepsis,

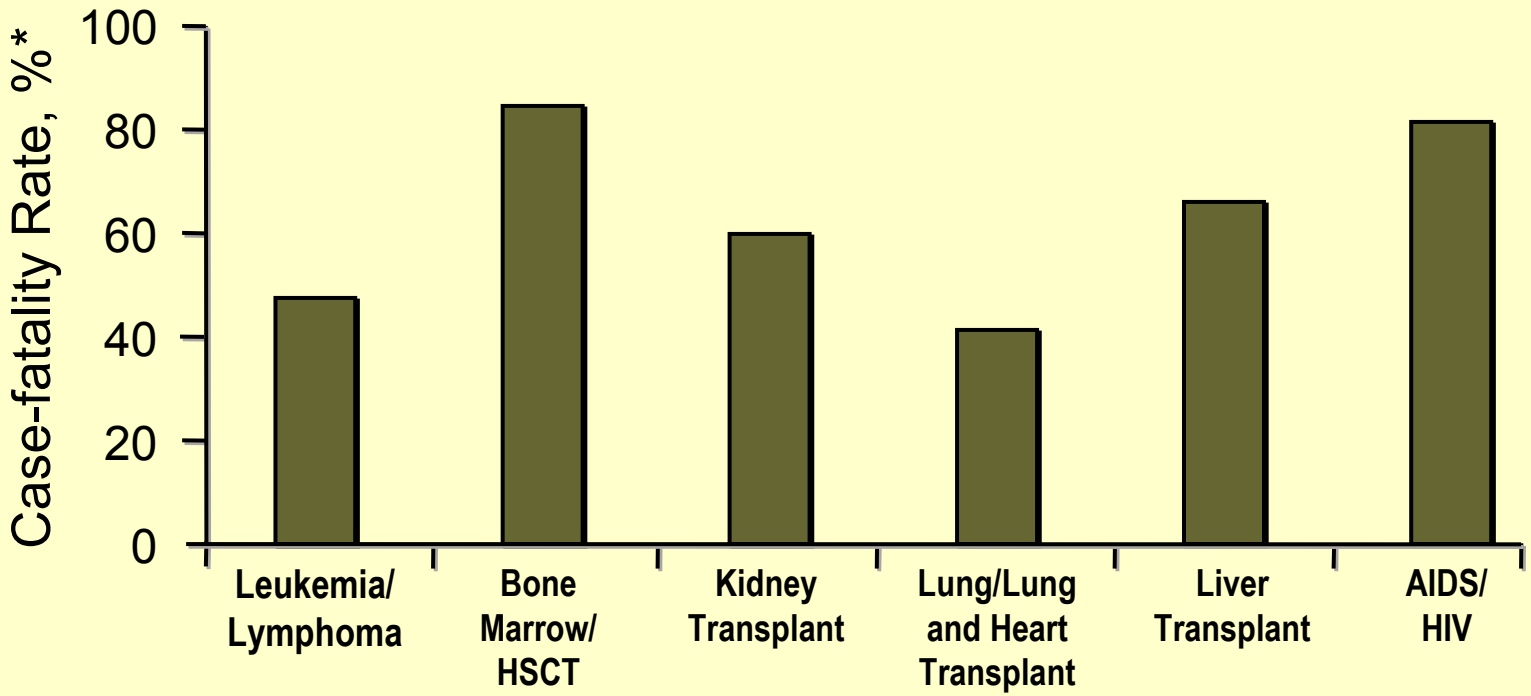
High AACHE II scores

Steroids, Immunosuppression.

Intensive care unit length of stay: the rate of infections rising rapidly after 7-10 days

Dimopoulos G, et al. Candidemia in immunocompromised and immunocompetent critically ill patients: a prospective comparative study. Eur J Clin Microbiol Infect Dis. 2007

Aspergillosis Is Associated With a High Rate of Mortality in Many Patient Populations



Lin SJ, et al. *Clin Infect Dis.* 2001;32:358-366.

Diagnosis: Invasive Candidiasis

Clinical

- Fever and progressive sepsis.
- Invasive candidiasis (IC) related cutaneous lesions.
  - Macronodular rash frequently confused with drug allergies.
- Ophthalmic lesions (Candida endophthalmitis).
  - A fundoscopic evaluation for *Candida* endophthalmitis

Laboratory

- Microbiology : Blood culture positive ~70%
- Molecular : early identification (RT-PCR)
- Serological : early diagnosis (β-D-glucan assay, Mannan Ag & Ab)
- Histopatholgic methods.

Barnes RA. Early diagnosis of fungal infection in immunocompromised patients. J Antimicrob Chemother 2008;61(Suppl 1):i3-6.

McMullan R, Metwally L, Coyle PV, et al. A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. Clin Infect Dis 2008;46:890-6.

Can we wait for the blood culture results in candidemia?

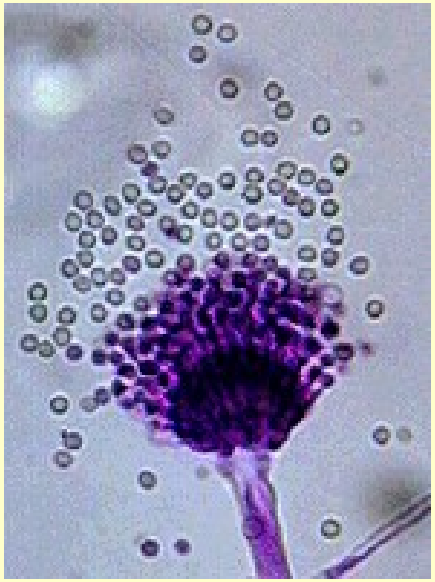
- Retrospective cohort analysis 1/2001-12/2004: N=157 patients with candidemia.
- Delay in empiric treatment of candidemia till after blood cultures turn positive resulted in **higher mortality**.
- Start of anti-fungal treatment >12 hrs of drawing a blood culture that turns positive had OR= 2.09 for mortality, p=0.018.

Morrel M et al. 2005. Antimicrob Agents Chemother. 49(9):3640-5

Aspergillosis

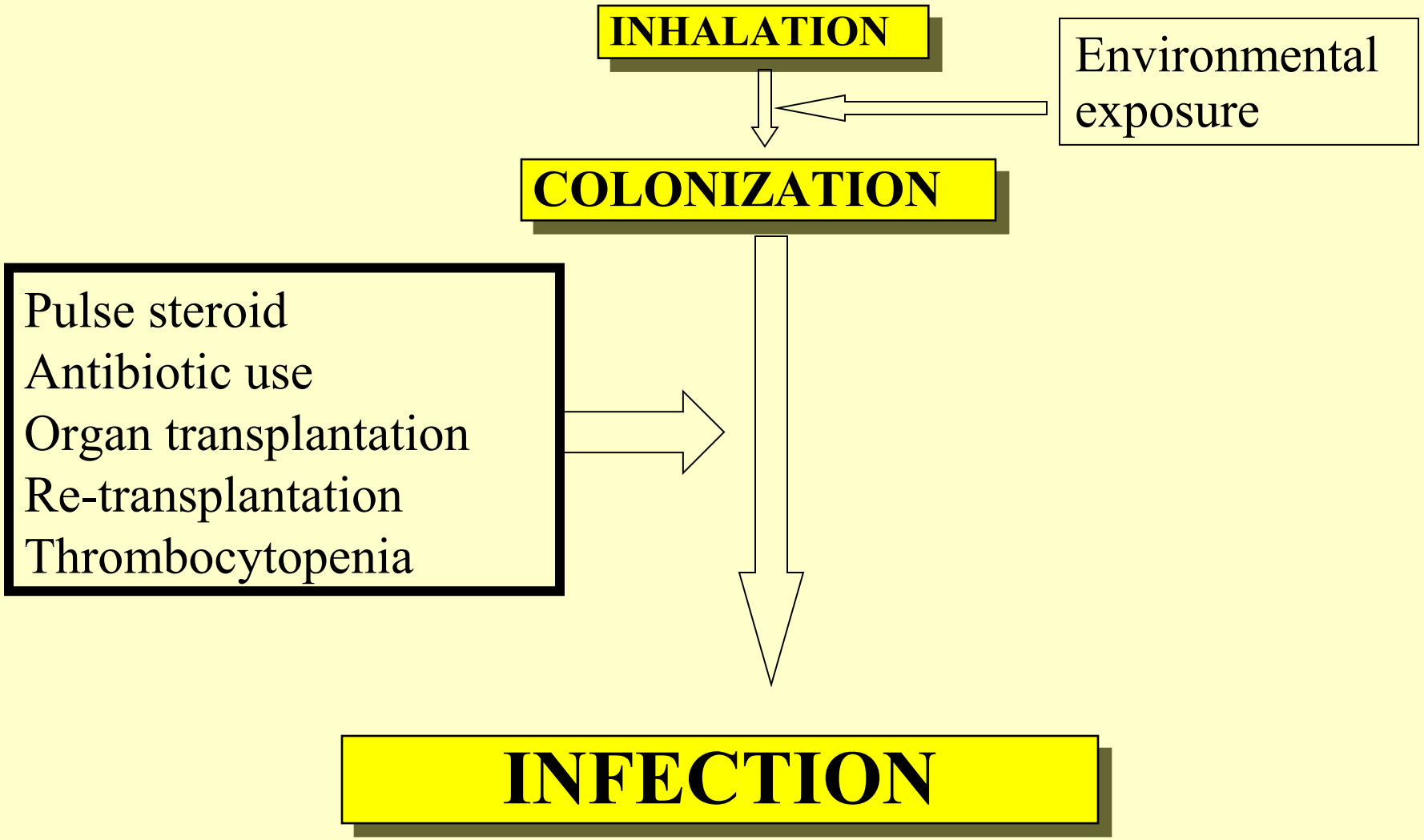
Aspergillus species are found in :

- Soil
- Air; spores may be inhaled
- Water / storage tanks in hospitals etc
- Food
- Compost and decaying vegetation
- Fire proofing materials
- Bedding, pillows
- Ventilation and air conditioning systems
- Computer fans



Aspergillus spores

Development of Aspergillosis



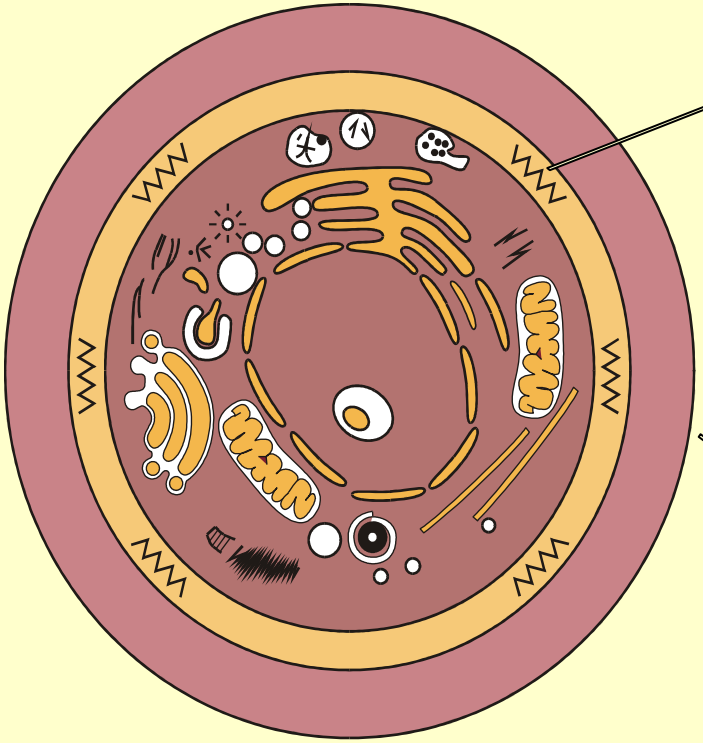
Invasive aspergillosis in solid-organ transplantation: diagnosis

- Radiology: chest X-ray and CT: no halo sign
- Microbiology
  - Respiratory secretions: BAL/biopsy
    - Direct microscopy
    - culture
  - Serological surveillance
    - ELISA for galactomannan
- PCR

Ergin et al. Transplant International 2003; 16: 280-286

Strategies for dealing with systemic fungal infections

Site of Action of Selected Anti-fungal Agents



Cell membrane

Polyene: AmB (ergosterol binding and create pore)

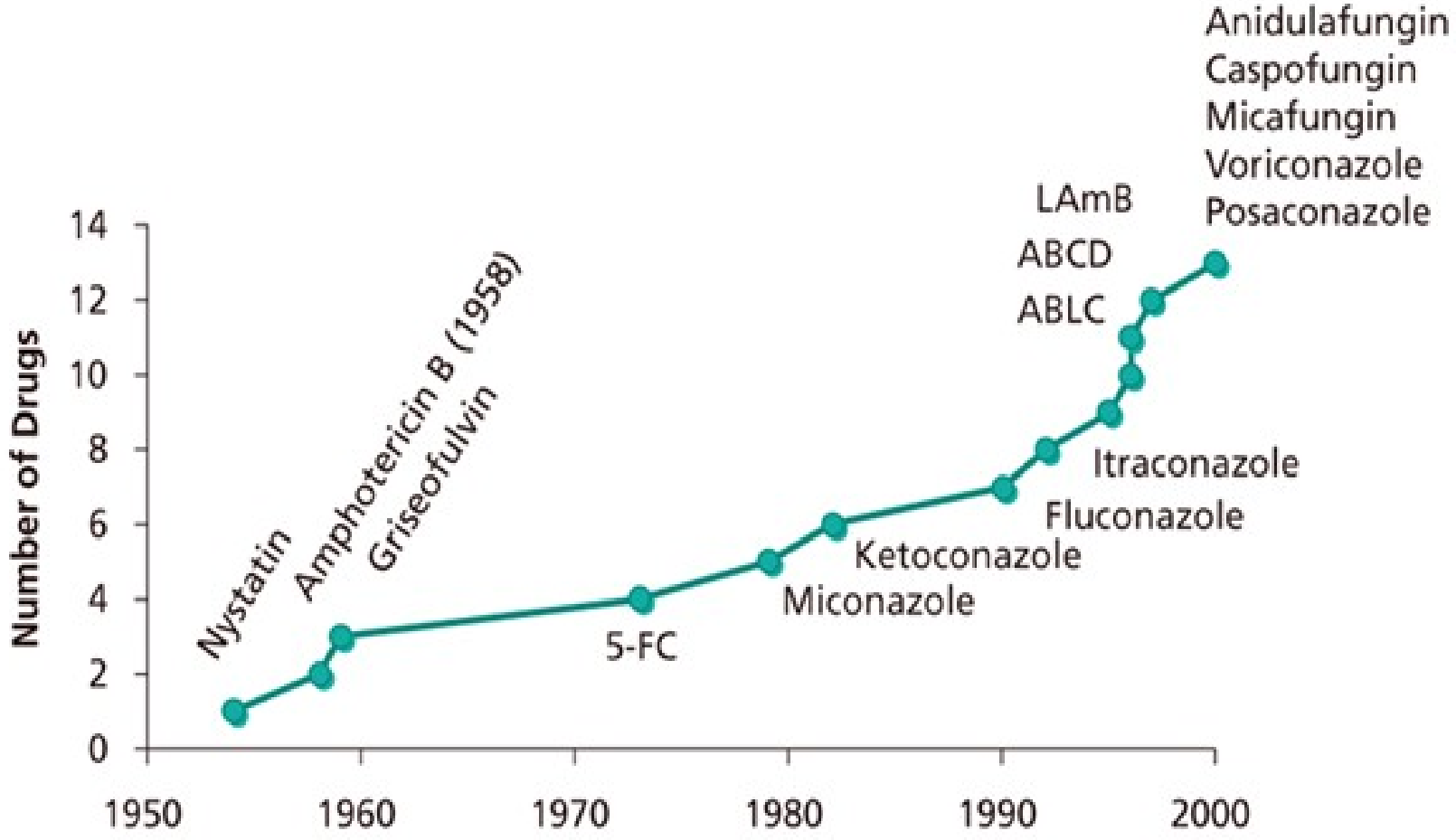
Azoles: Fluconazole (ergosterol synth. inh.)

Cell wall

Echinocandins: Caspofungin (Glucan synthesis inhibitors)

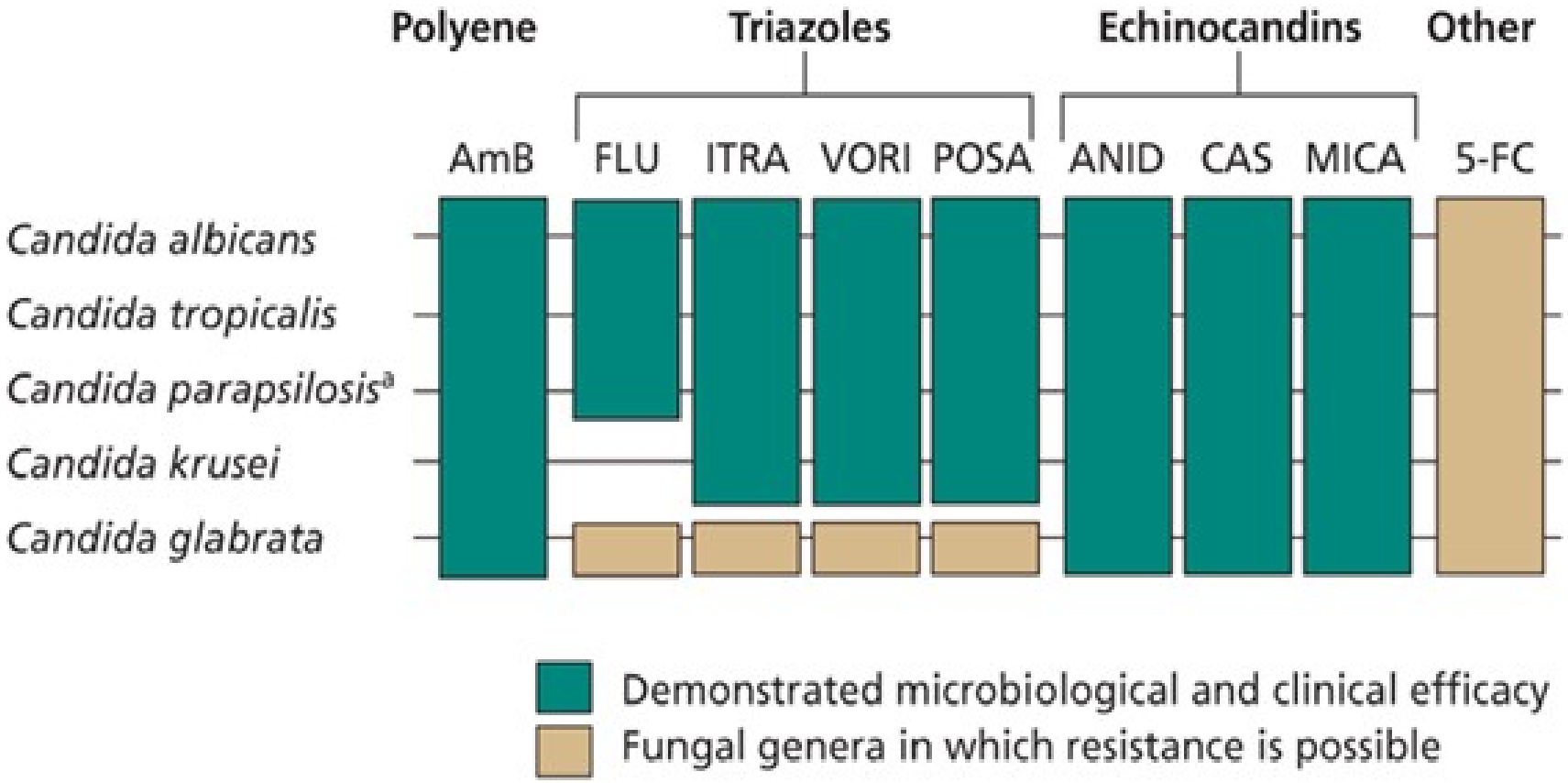
Adapted from Andriole VT *J Antimicrob Chemother* 1999;44:151–162; Graybill JR et al *Antimicrob Agents Chemother* 1997;41:1775–1777; Groll AH, Walsh TJ *Expert Opin Invest Drugs* 2001;10(8):1545–1558.

Antifungal Treatment Development



Deoxycholate amphotericin B (D-AMB); lipid formulations of AMB (LFAB) – amphotericin B lipid complex (ABLC), liposomal AMB (L-AMB), amphotericin B colloidal dispersion (ABCD)

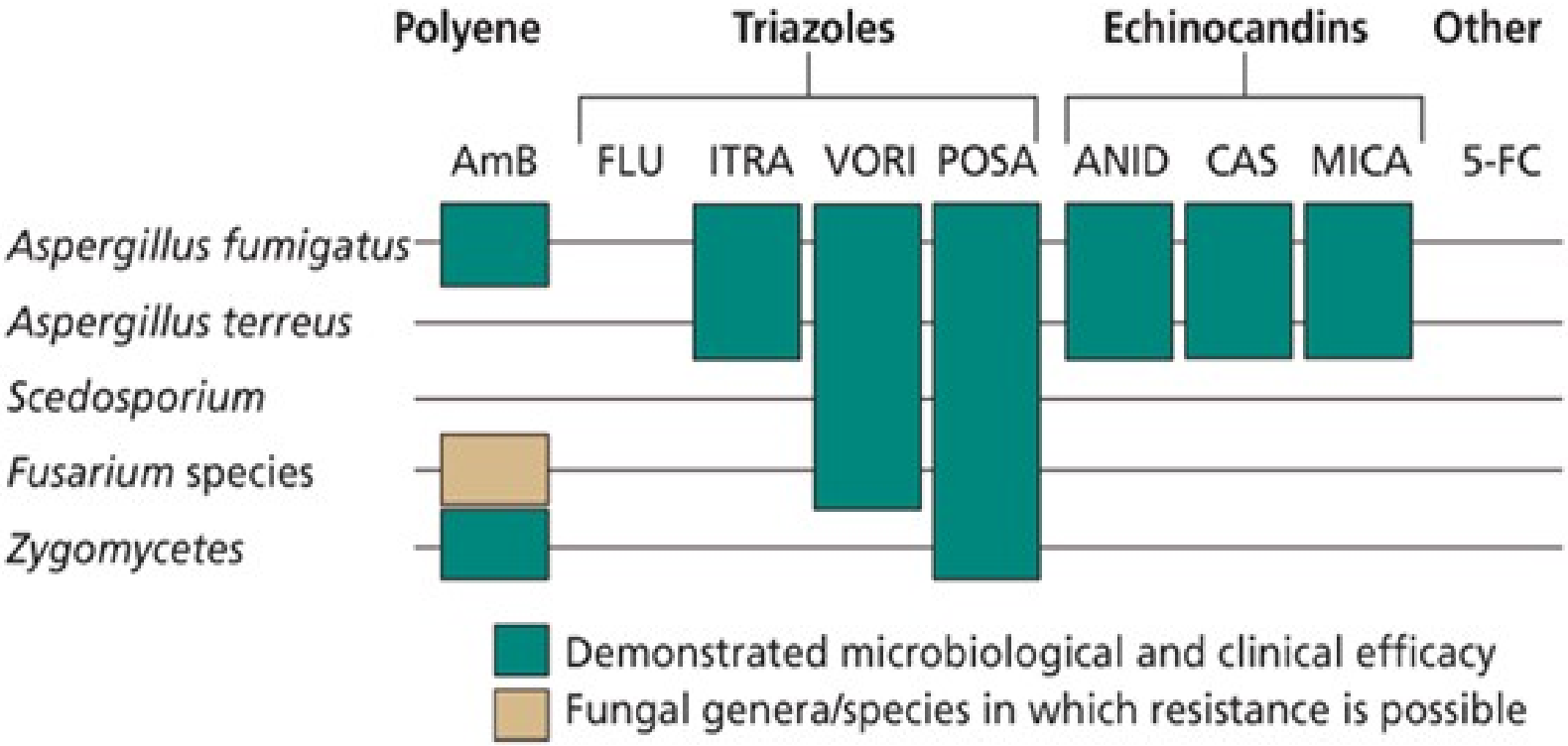
Spectrum of Action of Systemic Antifungal Agents: Candida[1]

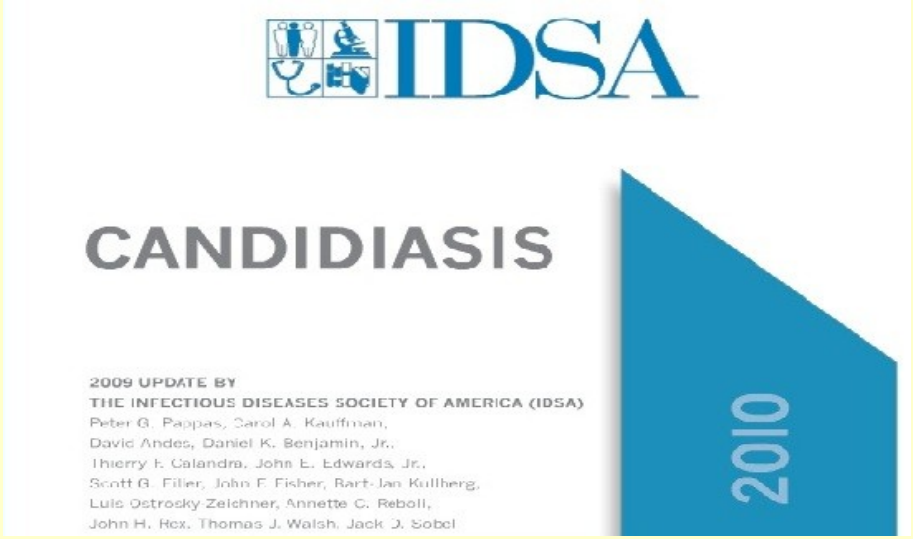


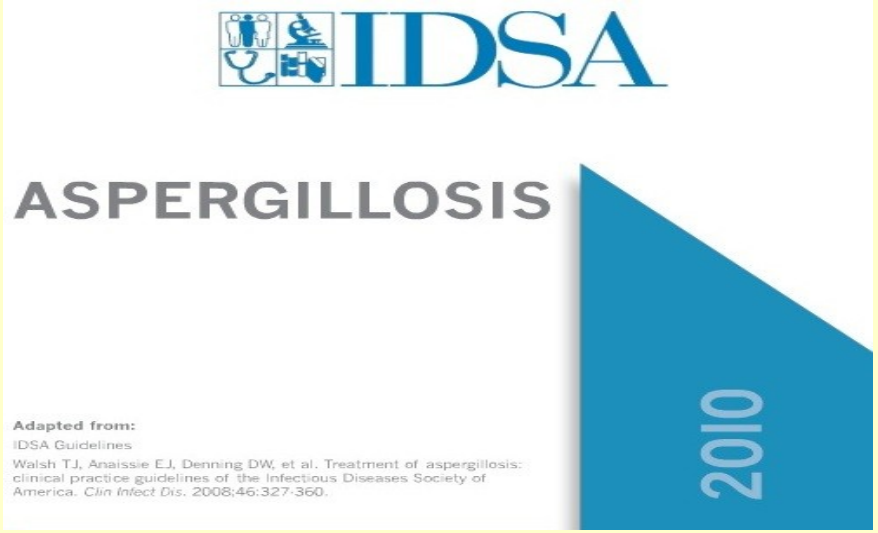
- Most commonly occurring species of Candida is *C. albicans*, followed by *C. glabrata*, and then *C. parapsilosis/tropicalis*

[a] *C. parapsilosis* is associated with higher echinocandin MICs that vary among agents[2,3]

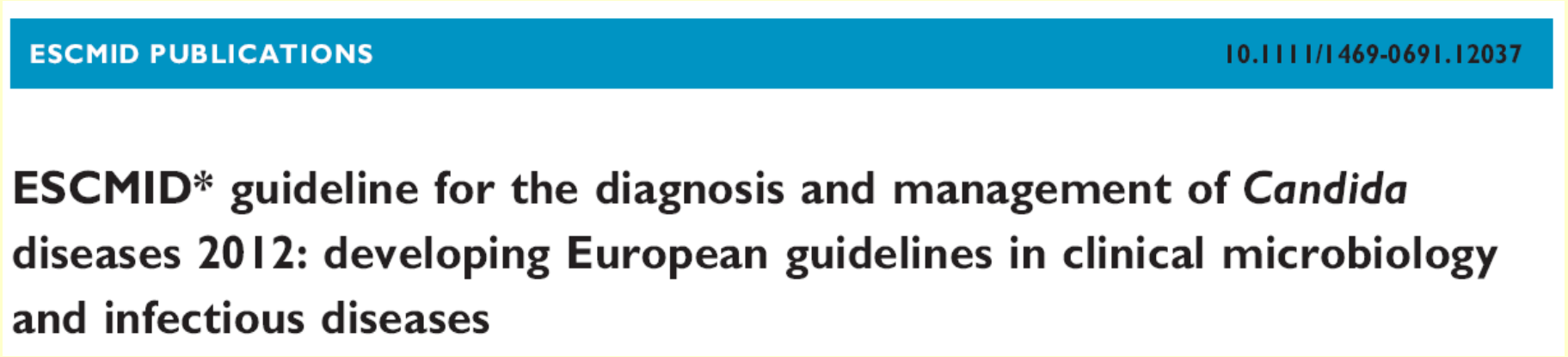
Spectrum of Action of Systemic Antifungal Agents: Molds[1]







The Infectious Diseases Society of America (IDSA)



European Society of Clinical Microbiology and Infectious Diseases

Strength of the recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly designed randomized controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

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ELSEVIER

Journal of Critical Care

Clinical Potpourri

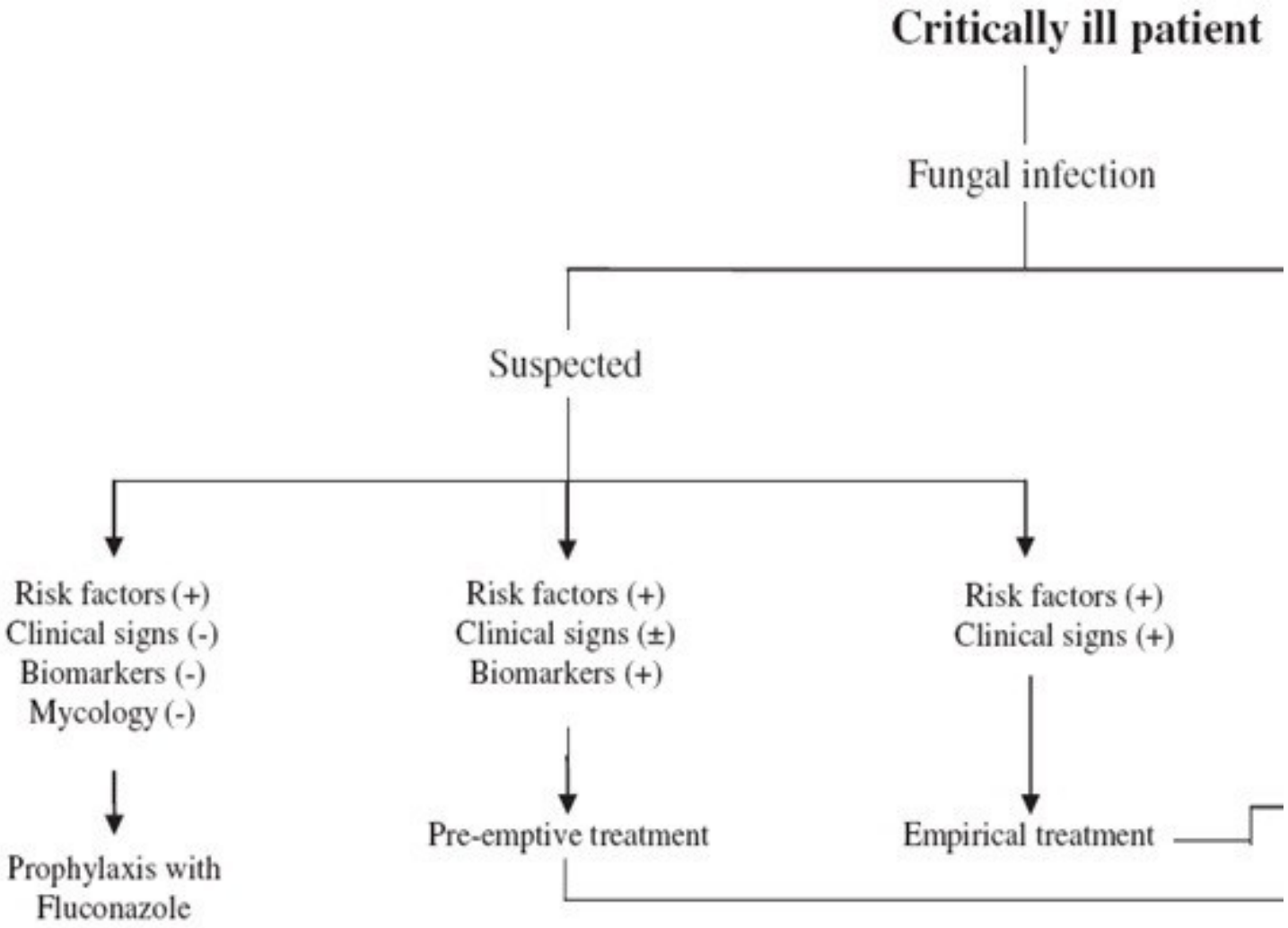
How to select an antifungal agent in critically ill patients☆

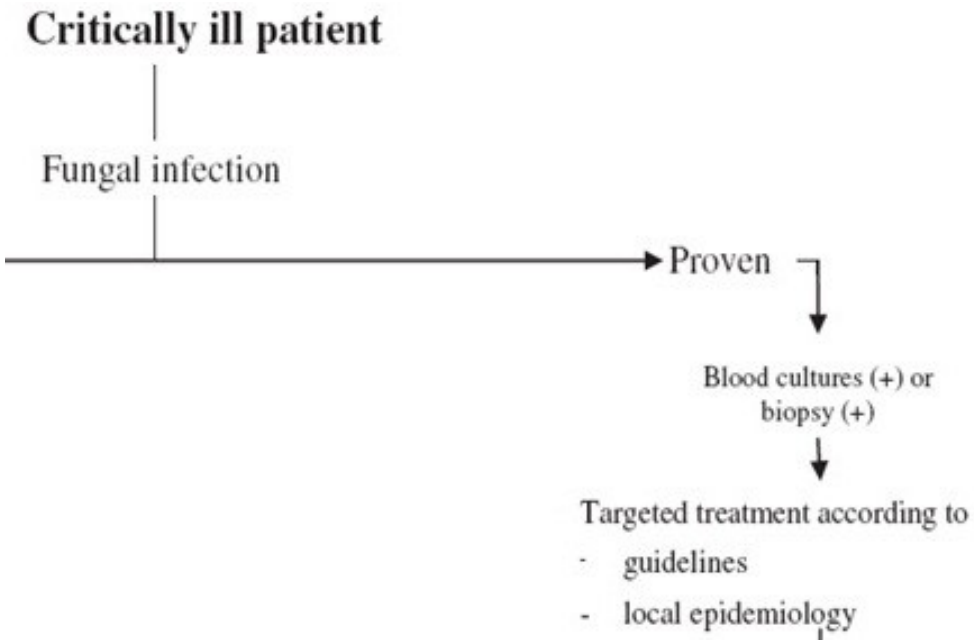
George Dimopoulos MD, PhD[a], Anastasia Antonopoulou MD[a], Apostolos Armaganidis MD[a], Jean-Louis Vincent, MD, PhD[b,*]

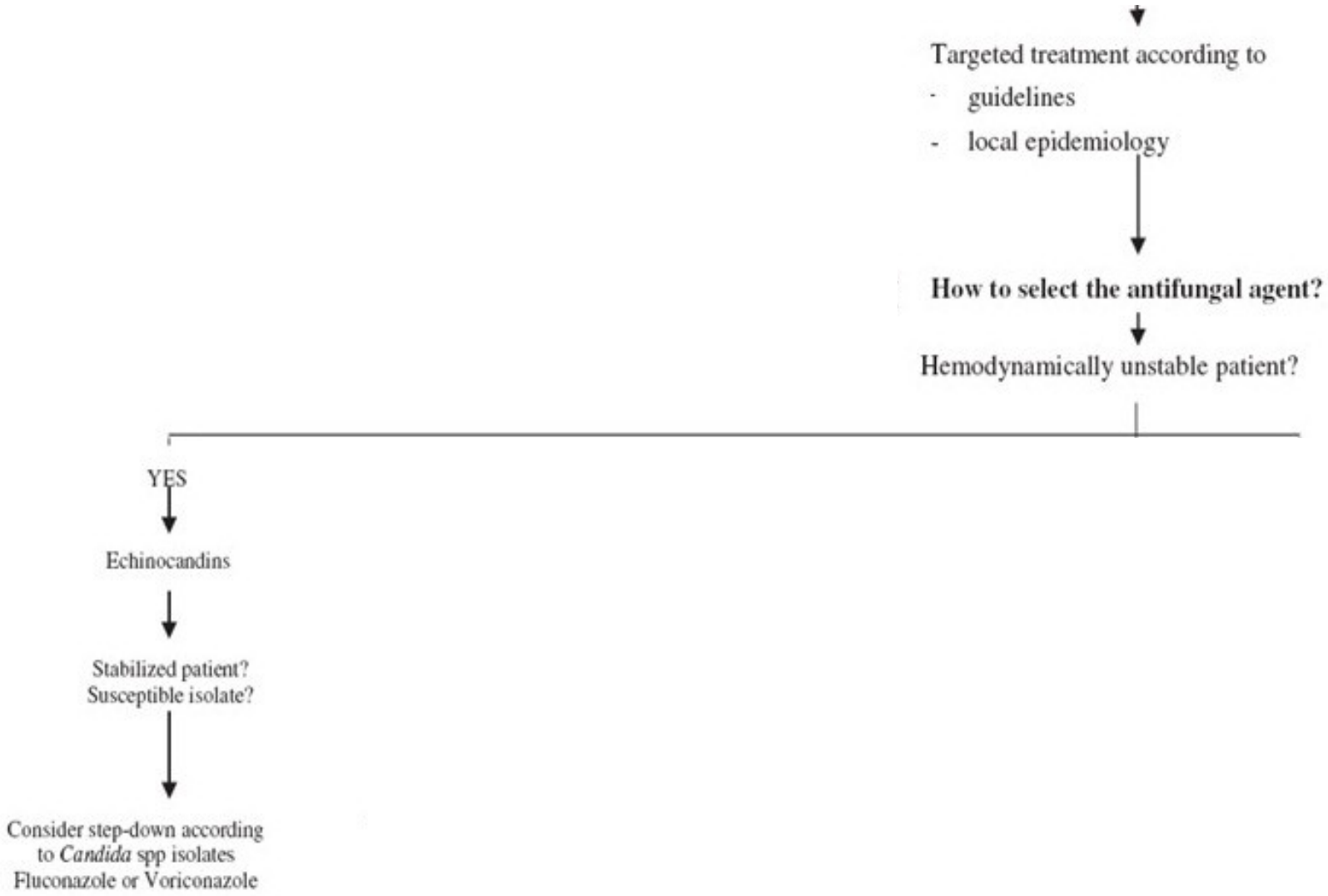
The choice of antifungal agent in critically ill patients will depend on the aim of therapy (prophylaxis, pre-emptive, empiric, definitive), as well as on local epidemiology and specific properties of the drug (antifungal spectrum, efficacy, toxicity, pharmacokinetic/pharmacodynamic properties, cost).

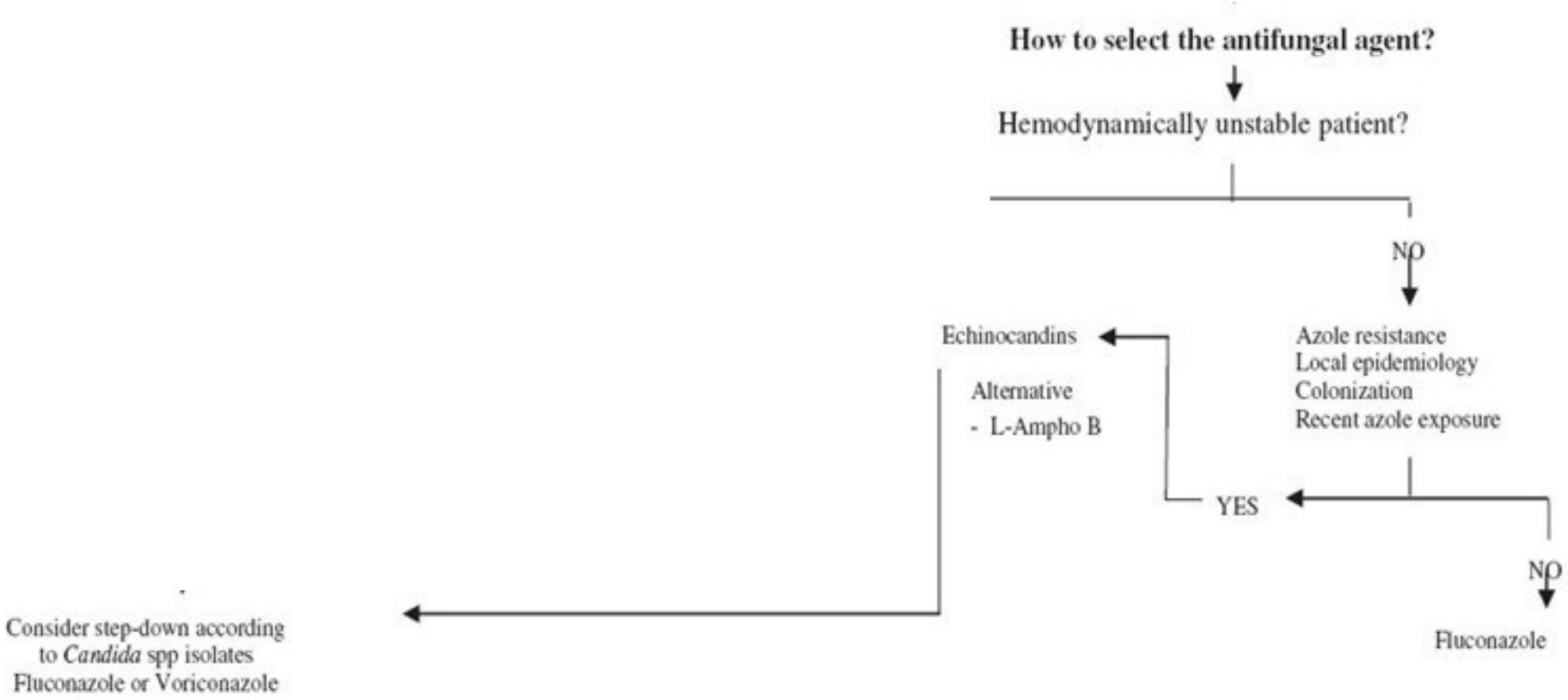
Treatment Strategies in Mycotic Infections

- **Prophylactic treatment**
- **Pre-emptive treatment**
- **Empiric treatment**
- **Definitive treatment** relies on significant invasive fungal infection with microbiological evidence that allows for specific, targeted therapy


Critically ill patient
Fungal infection
Suspected
Risk factors (+)
Clinical signs (-)
Biomarkers (-)
Mycology (-)
Prophylaxis with
Fluconazole
Risk factors (+)
Clinical signs (±)
Biomarkers (+)
Pre-emptive treatment
Risk factors (+)
Clinical signs (+)
Empirical treatment


Critically ill patient
Fungal infection
Proven
Blood cultures (+) or biopsy (+)
Targeted treatment according to
- guidelines
- local epidemiology


Targeted treatment according to
- guidelines
- local epidemiology
How to select the antifungal agent?
Hemodynamically unstable patient?
YES
Echinocandins
Stabilized patient?
Susceptible isolate?
Consider step-down according to *Candida* spp isolates
Fluconazole or Voriconazole


How to select the antifungal agent?
Hemodynamically unstable patient?
NO
Azole resistance
Local epidemiology
Colonization
Recent azole exposure
YES
NO
Fluconazole
Echinocandins
Alternative
- L-Ampho B
Consider step-down according
to *Candida* spp isolates
Fluconazole or Voriconazole

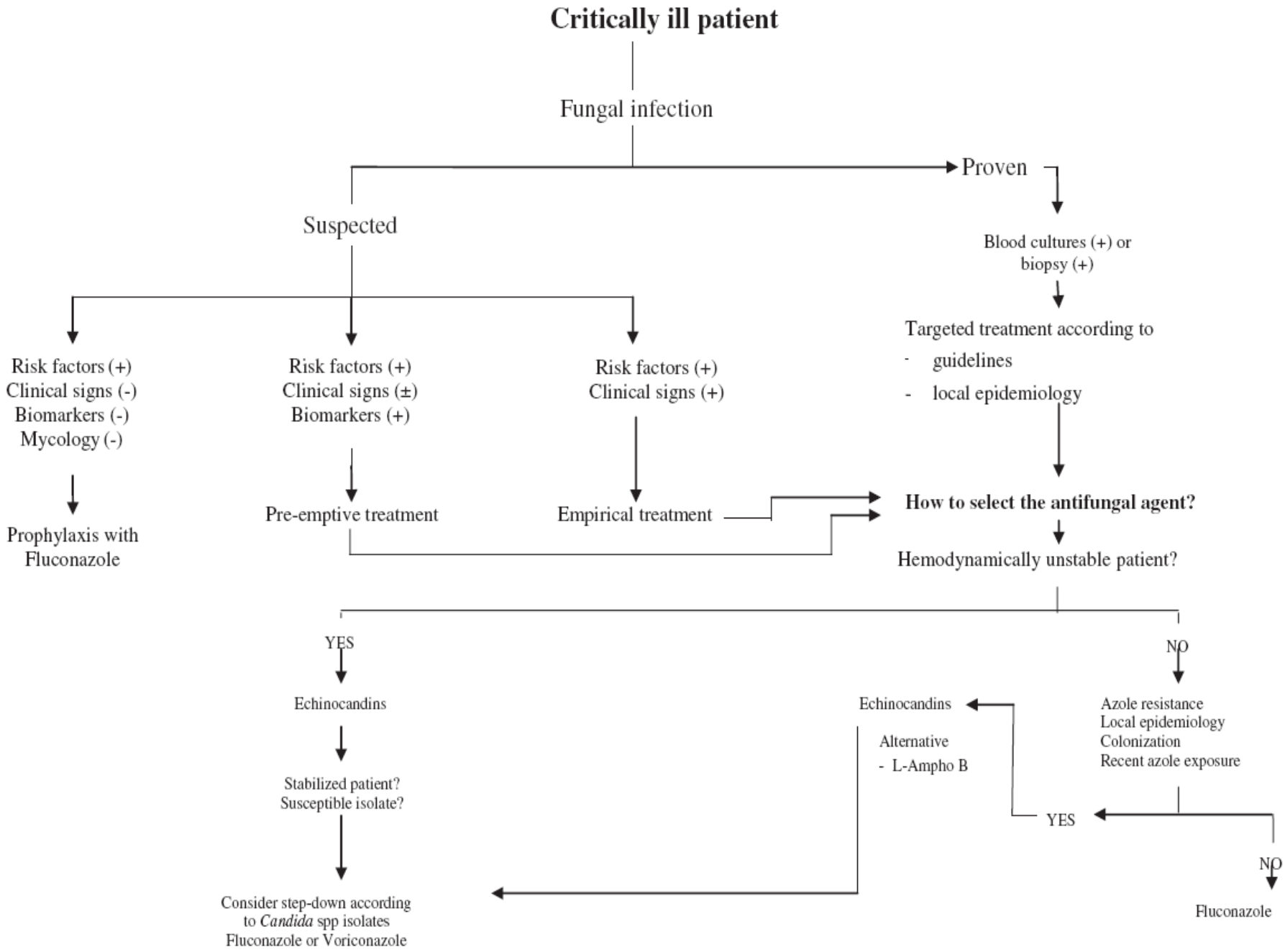

Critically ill patient
Fungal infection
Proven
Suspected
Blood cultures (+) or biopsy (+)
Targeted treatment according to
- guidelines
- local epidemiology
Risk factors (+)
Clinical signs (-)
Biomarkers (-)
Mycology (-)
Risk factors (+)
Clinical signs (±)
Biomarkers (+)
Risk factors (+)
Clinical signs (+)
Prophylaxis with Fluconazole
Pre-emptive treatment
Empirical treatment
How to select the antifungal agent?
Hemodynamically unstable patient?
YES
NO
Echinocandins
Stabilized patient?
Susceptible isolate?
Consider step-down according to Candida spp isolates
Fluconazole or Voriconazole
Echinocandins
Alternative
- L-Ampho B
Azole resistance
Local epidemiology
Colonization
Recent azole exposure
YES
NO
Fluconazole

Table 6 ESCMID Guidelines for initial treatment of candidemia and invasive candidemia [79]

Compound	SoR	QoE	Comments
Echinocandins	A	I	Broad spectrum, safety, few drug-drug interactions, activity against *C glabrata* and *C krusei*, rare resistance
Anidulafungin 200*/100 mg daily			
Caspofungin 70*/ 50 mg daily			
Micafungin 100 mg daily			
Voriconazole	B	I	Narrower spectrum than echinocandins, drug interactions, i.v. administration associated with renal failure
Fluconazole	C	I	Limited spectrum, inferiority to anidulafungin in patients with high APACHE II score
Polyenes			Similar efficacy to
Amphotericin B liposomal	B	I	echinocandins, more adverse events, higher toxicity
Amphotericin B lipid complex	C	IIa	
Amphotericin B colloidal dispersion	D	IIa	
Amphotericin B deoxycholate	D	I	

SoR, strength of recommendation; QoE, quality of evidence.

Table 4 Treatment options for systemic *Candida* infections in non-neutropenic patients according to the 2009 IDSA guidelines [47]

Type of infection	Initial treatment options
Candidemia	Fluconazole (loading dose 800 mg, followed by 400 mg daily), echinocandins or alternatively liposomal amphotericin B or voriconazole). Echinocandins are preferred for patients with moderately severe to severe illness or with recent azole exposure; fluconazole is recommended for patients who are less critically ill and with no recent azole exposure.
Pyelonephritis	Fluconazole, alternatively liposomal amphotericin B
Endophthalmitis	Amphotericin B plus 5-flucytosine or fluconazole (for less severe infections). Surgical intervention is an important adjunct
Endocarditis	Liposomal amphotericin B or echinocandin
Suppurative thrombophlebitis	Liposomal amphotericin B or fluconazole or echinocandin
CNS infection	Liposomal amphotericin B with or without 5-flucytosine