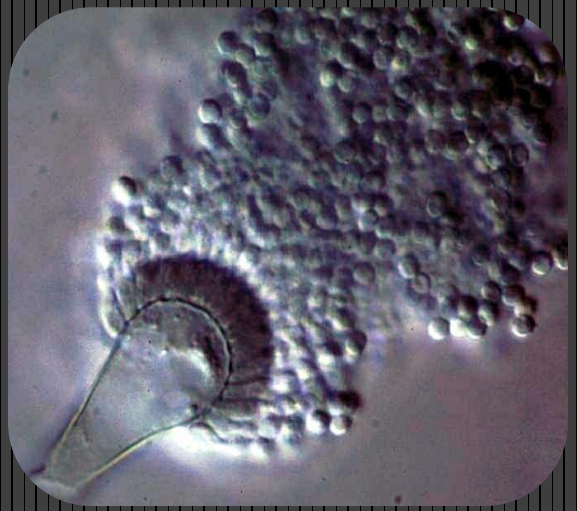
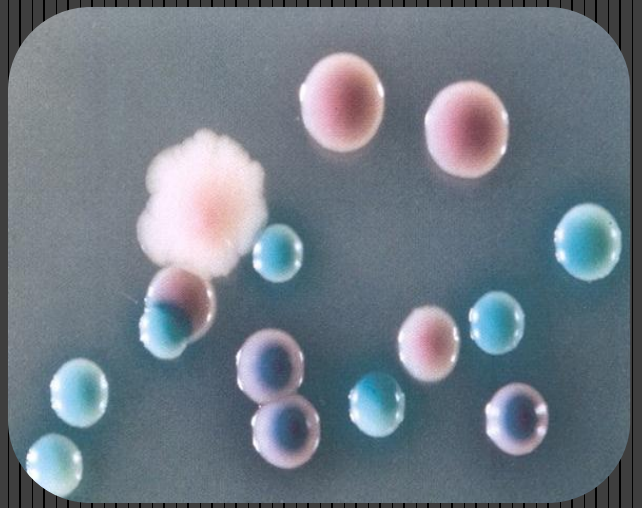
Empiric therapy for invasive fungal infection



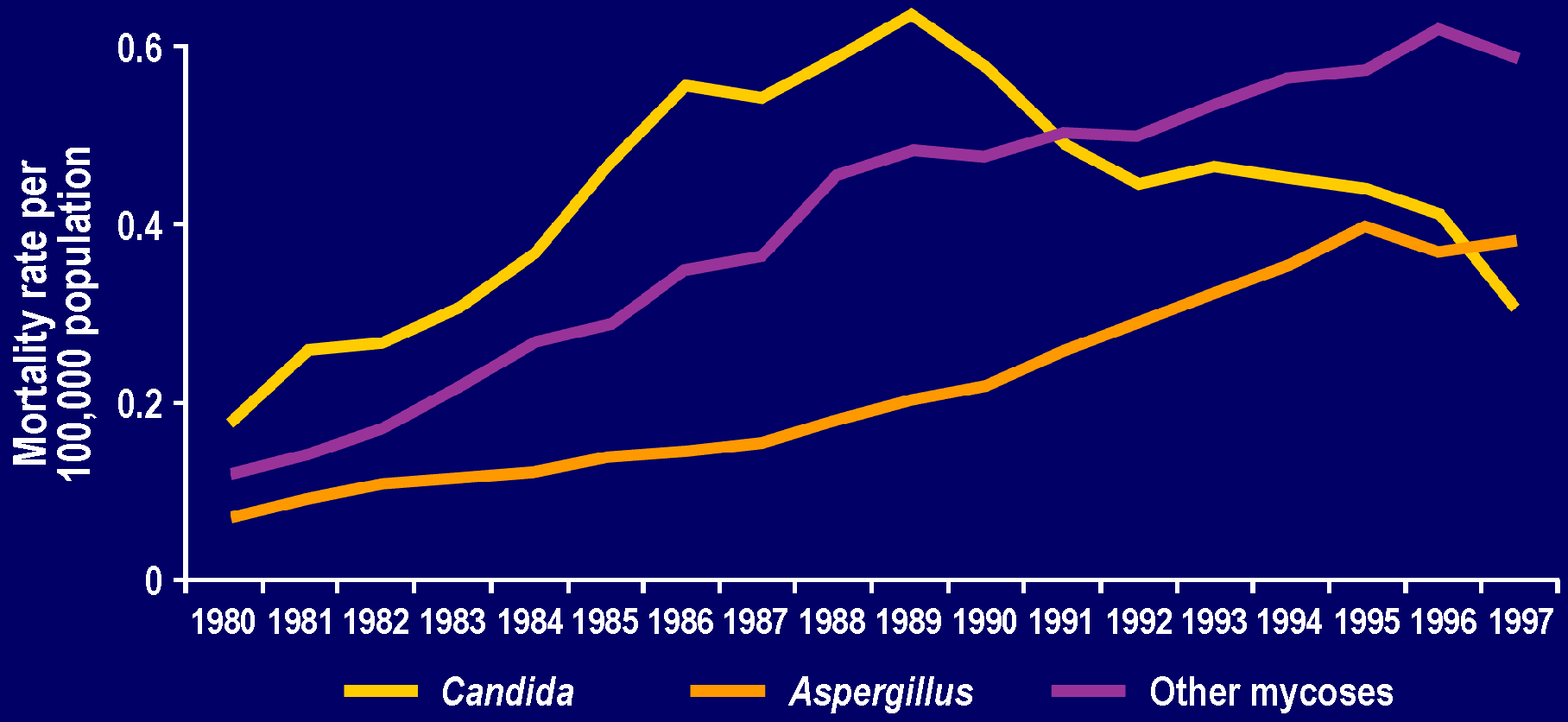


Presentation overview

1. Invasive fungal infection – Global vs Indian scenario
2. Need for empiric therapy
3. Brief introduction to **Liposomal Amphotericin B**
4. Recommendations for use of Liposomal AmB in empiric therapy
5. Candida biofilms, post antifungal effect
6. Re look at published evidence – randomized trials with Liposomal AmB
7. Take home message

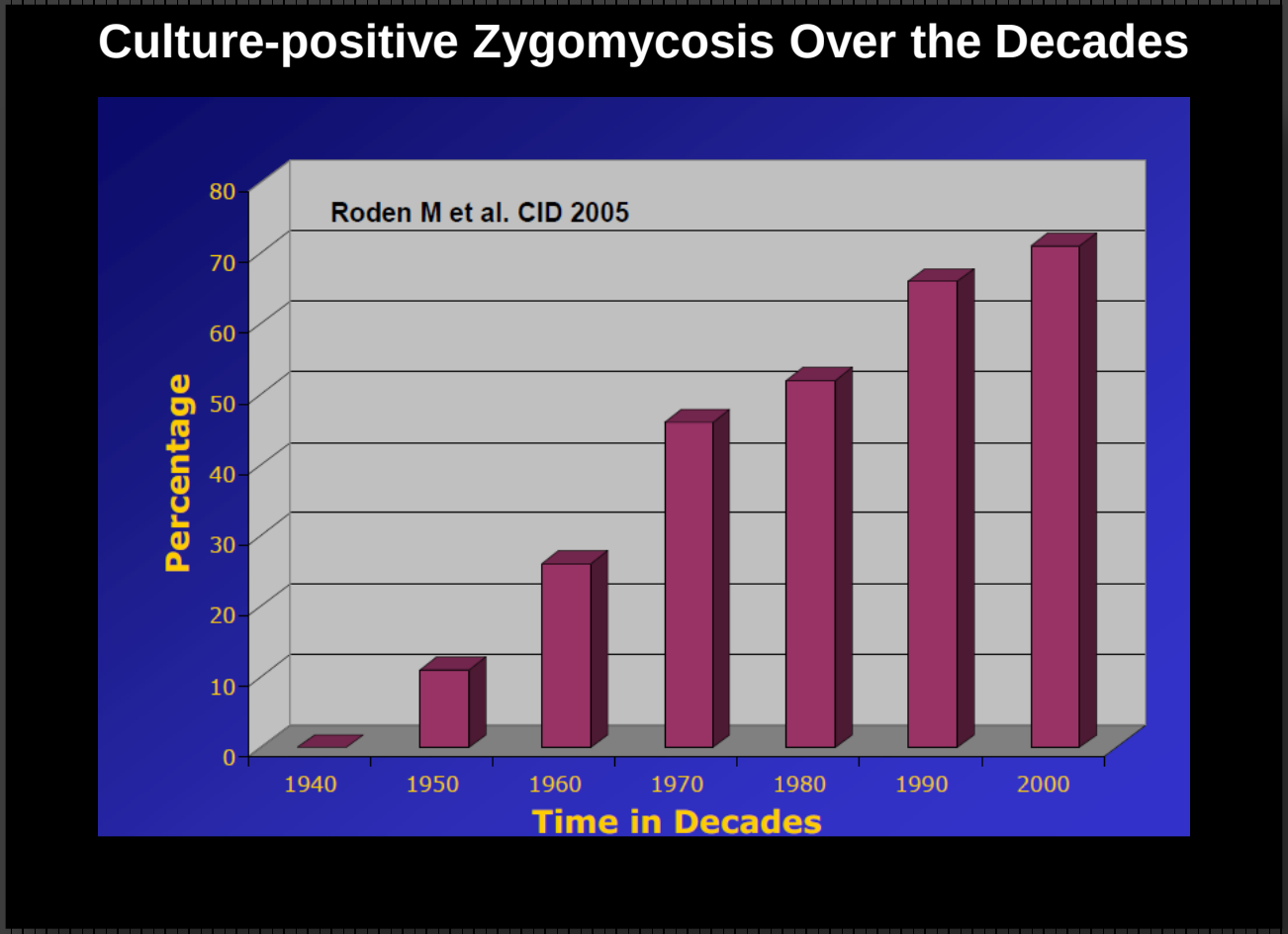
Invasive fungal infection - The global scenario

Mortality Due to Invasive Mycoses

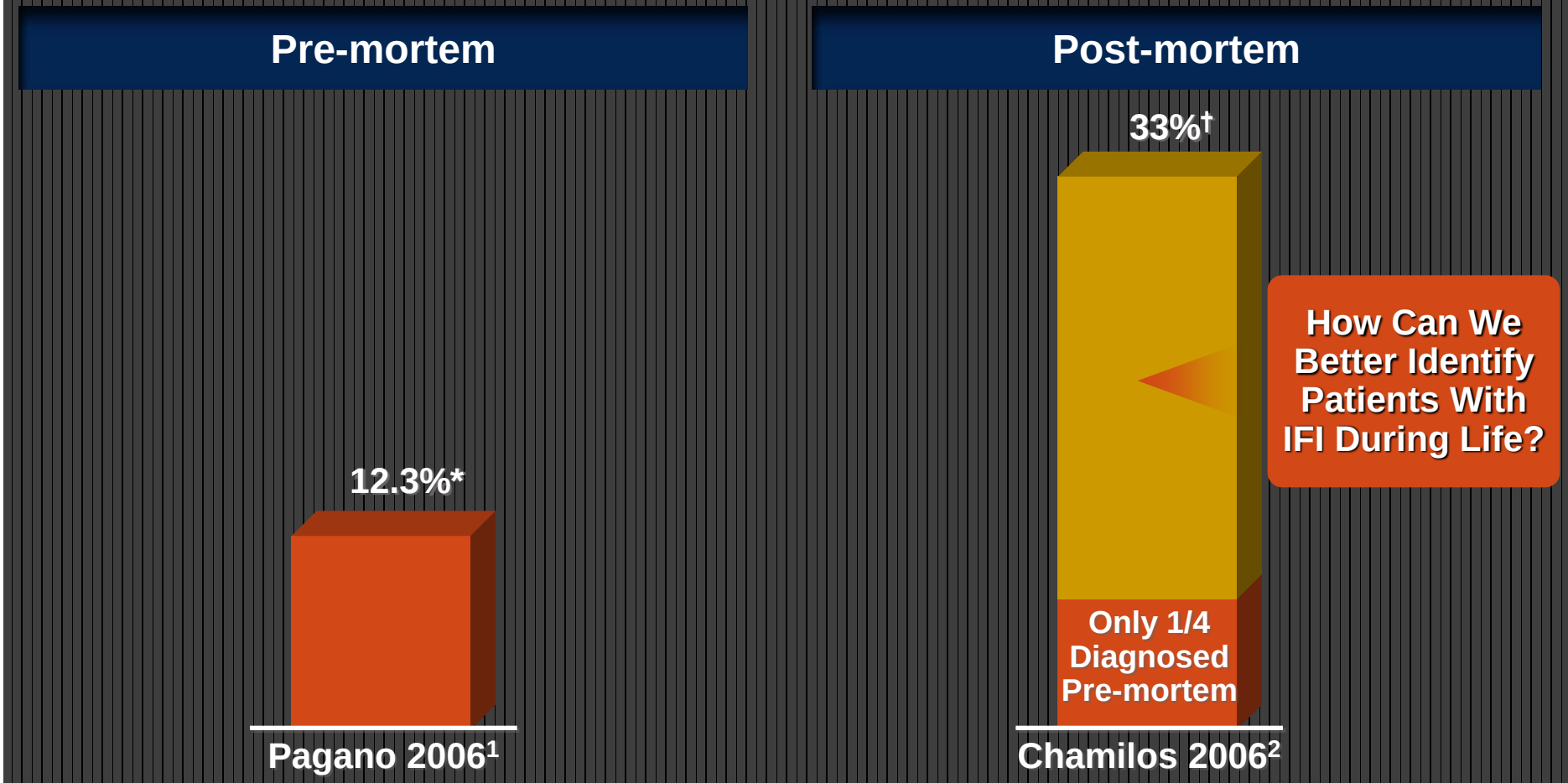


Adapted from McNeil MM et al. *Clin Infect Dis*. 2001;33:641-647.

How rare are the “rare pathogens”?



The Majority of IFIs Are Identified Post-mortem



*Incidence of moulds and yeasts in AML patients (7.9% due to moulds).
†Prevalence of invasive moulds and *Candida* (22% due to moulds).
1. Pagano L et al. *Haematologica*. 2006;91:1068-1075. 2. Chamilos G et al. *Haematologica*. 2006;91:986-989.

How different is the Indian scenario?

Indian scenario – Invasive fungal infection

- Tropical climate with heavy rainfall & humidity - Ideal for fungi to grow
- Expansion & construction work in and around hospitals
- Estimated HIV cases 3 – 6 million
- More than 30 million diabetic – at increased risk
- Misuse of systemic steroids and broad spectrum antibiotics
  - Over the counter dispensing by chemists
  - Misuse by untrained health professionals

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Indian scenario – Invasive fungal infection

- Few diagnostic mycology laboratories
- Handful of centers carry out routine autopsies
- Limited data in country to assess the burden of fungal infection
- Changing pattern of fungal species involved
  - Candida tropicalis and other non albicans candida…. predominant in major centers
  - India is emerging as the "Capital of invasive zygomycosis" of the world

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Problem bugs – Indian scenario

Invasive candidiasis

- Majority cases reported from ICUs
- 30 – 90% cases of non albicans candida reported in Indian hospitals
- Candida tropicalis most common form of non albicans species in Indian scenario
- *C. guilliermondii* , *C. krusei* are other frequently observed species
- Resistance to azoles is rising – matter of concern

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Invasive aspergillosis

- Exact prevalence of aspergillosis not known
- *A flavus* more common in Indian scenario.
  - Western world – *A. fumigatus* more common

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Zygomycosis

- World's highest number of cases reported from India
- Acquired by inhalation of the fungal spores
- Lung - single most common site of involvement in disseminated zygomycosis.
- Associated risk factors – cancer, antibiotic and steroid use, diabetes, deferoxamine/desferrioxamine therapy transplantation and its associated immunosuppressive therapies.

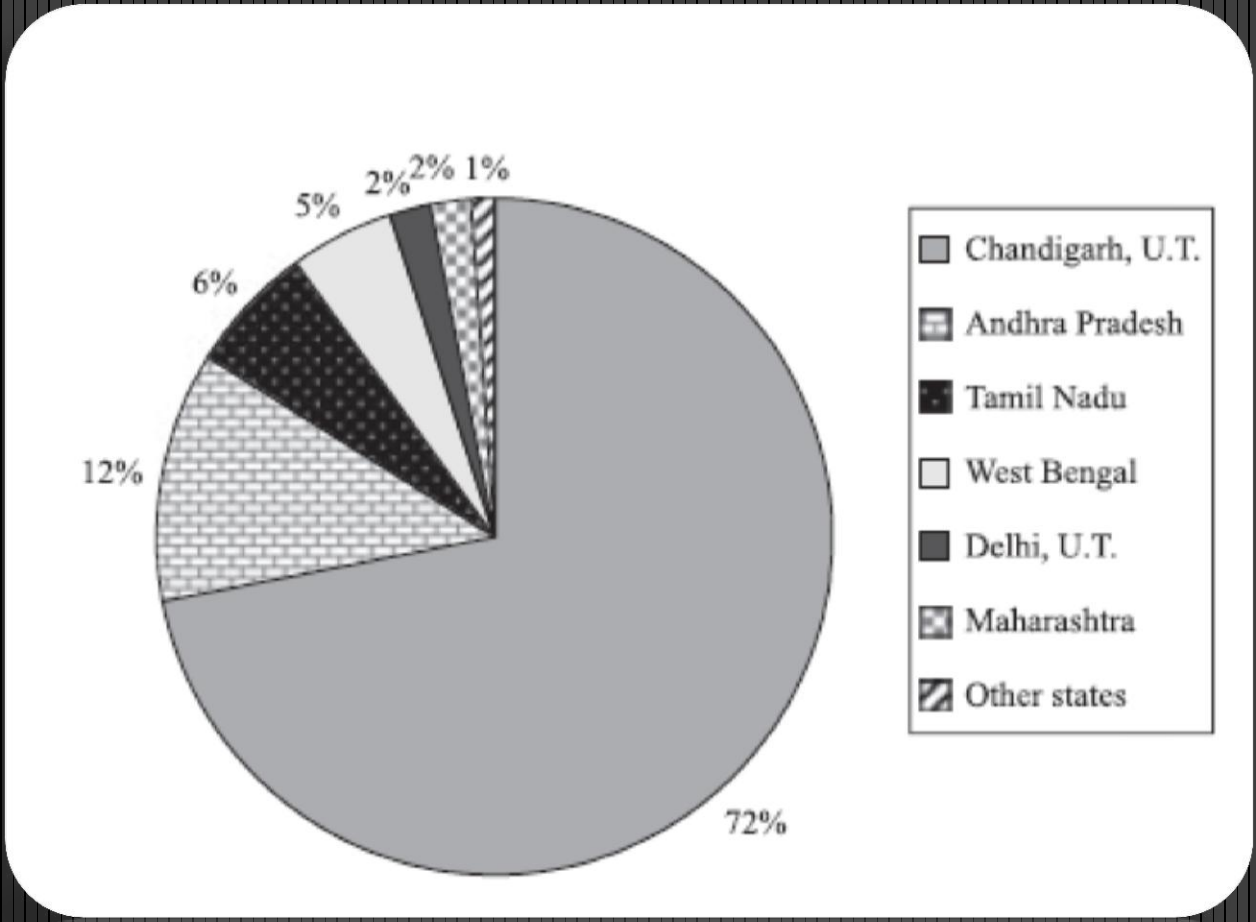
Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Zygomycosis

- 70% of the reported cases diagnosed at a single medical center, IPGMER, Chandigarh.
- Attributed to
  - Better awareness
  - Expertise and infrastructural facilities
  - No particular regional preponderance.
- Actual prevalence in India much higher than reported

Gaur et al. Mycoses (2007), 50, 247–254

State wise percentage distribution of 461 reported cases of zygomycosis



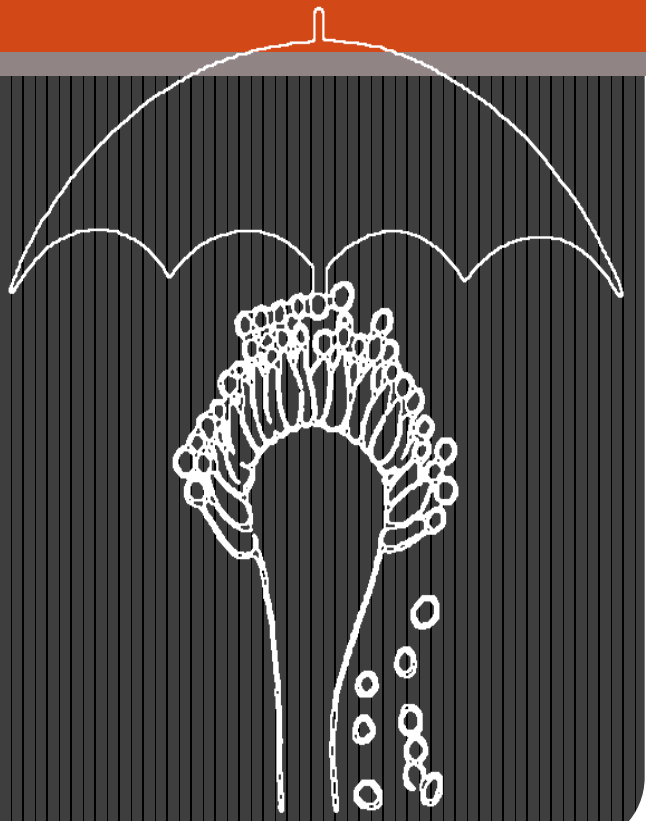
Gaur et al. Mycoses (2007), 50, 247–254

Cryptococcosis

- Frequency in India increased drastically in 80s & 90s with AIDS epidemic
  - Related to increase in number of reported HIV cases
  - Incomplete anti retroviral coverage in many cases
- 42% rise in incidence since 1970 (reported from tertiary care hospital in north India)

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Empirical antifungal therapy



Need for empirical antifungal therapy

High incidence and fatality rates for invasive fungal infections

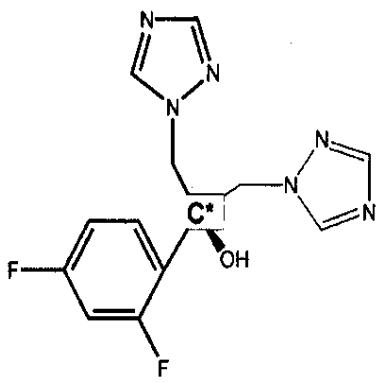
Insufficient diagnostics

- **Culture-based methods**
  - Helpful only with *Candida*, but even then 10% false negative
  - Almost never diagnostic for invasive Aspergillus infections
- **Non-culture based methods (GM, PCR)**
  - Still high false negative rate

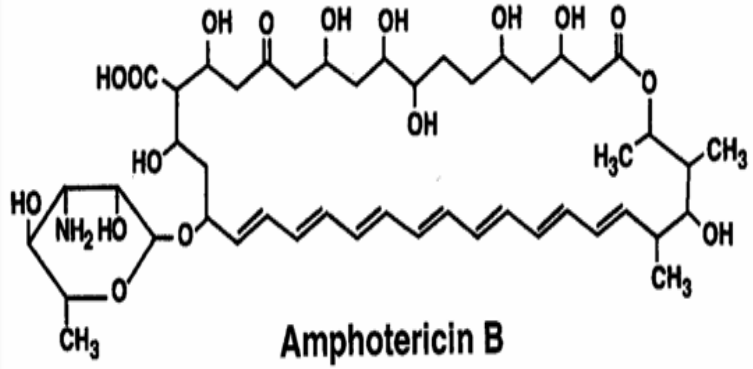
Many diagnosed too late or only at autopsy

Late treatment greatly reduces success rates

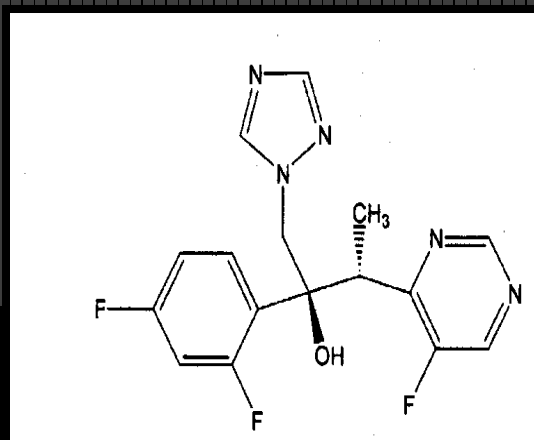
Which antimycotic drug for empirical therapy?



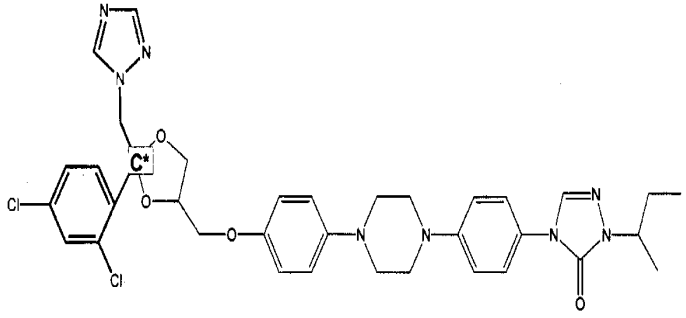
Fluconazole



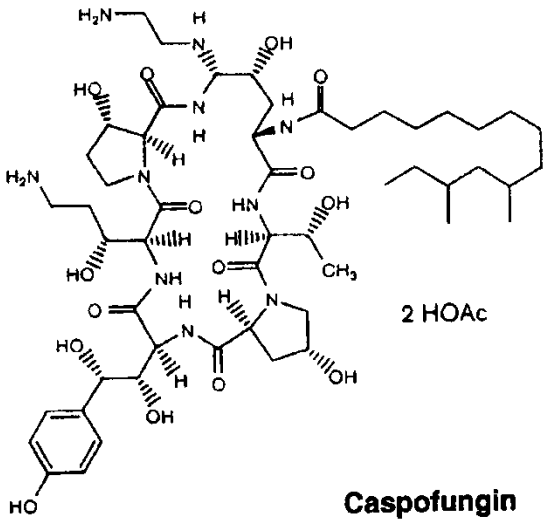
Amphotericin B



Voriconazole



Itraconazole



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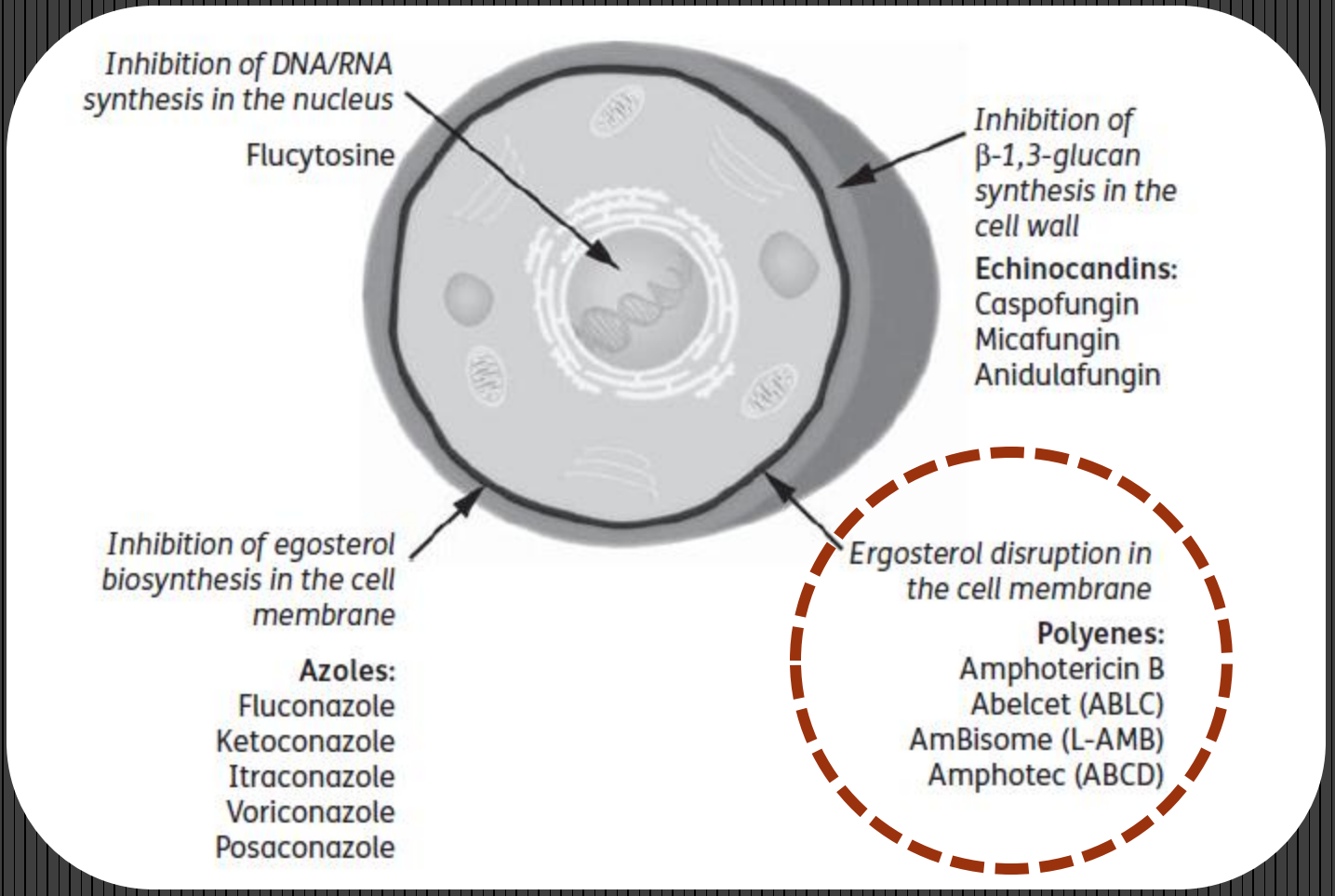
Caspofungin

The (small) world of antifungals



Liposomal amphotericin B

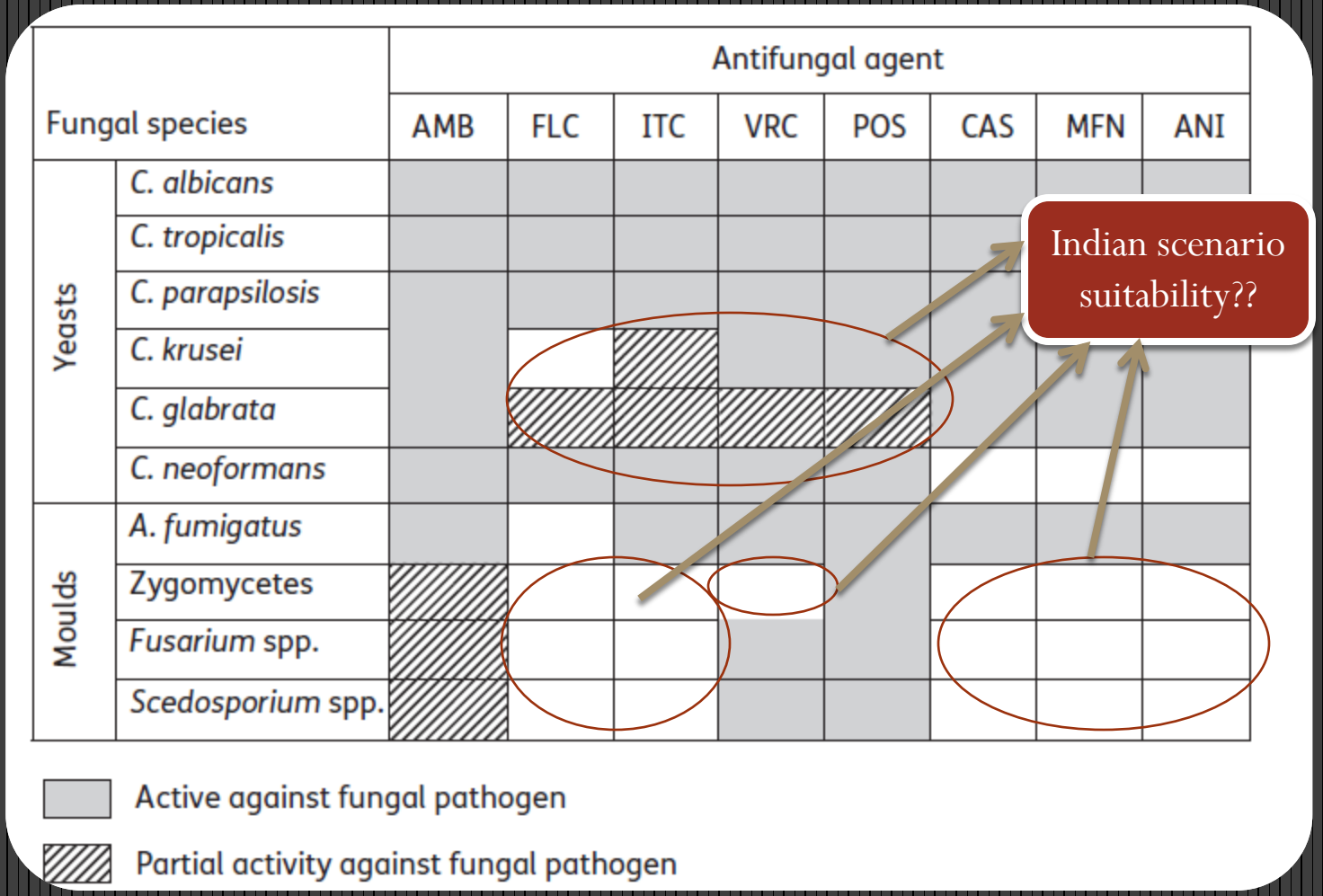
Role in empiric therapy

Mehanism of action - Liposomal amphotericin B

- Mediated through binding to ergosterol,
- Liposomal AmB has affinity to fungal cell wall
- Amphotericin B released from disrupted Liposomal structure at site of infection – damages fungal cell wall
- Results in the formation of aqueous and non-aqueous channels in fungal cell membrane
  - Increase membrane permeability.
  - Cellular components, flow throughthese pores
  - Leading to the loss of membrane potential and ultimately, cell death

Journal of antimicrobial chemo 2002, 49. supp S1

Systemic antifungals – Spectrum & Gaps



J Antimicrob Chemother 2011; 66: 457–465

Recommendations

Liposomal Amphotericin B for empiric therapy

US FDA approval for empiric therapy

Molecules	Granted approval
Amphotericin B	YES
Liposomal Ampho B	YES
Voriconazole	NO
Posaconazole	NO
caspofungin	YES
Micafungin	NO
Anidulafungin	NO

IDSA Guidelines – Status of Liposomal Ampho B for Empiric therapy

- Invasive candidiasis - Non neutropenic
  - LFAmB (3–5 mg/kg daily) as alternative if there is intolerance to other antifungals or limited availability of other antifungals
  - Level of evidence - (B-III).
- Invasive candidiasis - neutropenic patients
  - LFAmB (3–5 mg/kg daily)
  - **Level of evidence (A-I),**

IDSA Guidelines – Status of Liposomal Ampho B for Empiric therapy

- Invasive aspergillosis - Empiric & pre emptive therapy Liposomal AmB;
- **Level of evidence – (A -1)**[1]

1. IDSA Guidelines for Aspergillosis • **CID 2008:46 (1 February) • 327**

EMEA criteria for empirical antifungal therapy in neutropenic patients

Criteria for the approval of antifungals for empiric antifungal therapy

	Broad spectrum	Efficacy in proven infections	Adequate clinical trials
Conv. AmB	Yes	Yes	Yes
Liposom. AmB	Yes	Yes	Yes
Fluconazole	No	No (*Candida* only)	Yes
Itraconazole	Yes	Yes	Yes
Voriconazole	Yes	Yes	No
Caspofungin	Yes	Yes	Yes

Glasmacher, 2004

Polyenes in empiric therapy

- Polyenes valuable in empirical therapy
  - broad spectrum of fungicidal activity against yeasts and moulds
  - Only antifungal - fungicidal against both yeasts & moulds
  - Low incidence of resistance.
  - Lower toxicity than conventional amphotericin

Candida bio films

Considerations for empiric therapy……..

Bio films

- Biofilms - most prevalent type of microbial growth in nature
- Crucial to the development of clinical infections
- Associated with high-level antimicrobial resistance[1]
- Up to 40% of patients with *Candida* isolated from intravenous catheters have underlying fungemia[2]
- Mortality rate of patients with catheter-related candidemia approaches 40% [2]

1. Trends Microbiol 2001. **9:**34–39.
2. Arch. Intern. Med 1995. **155:**2429–2435

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2002, p. 1773–1780 Vol. 46, No. 6
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.6.1773–1780.2002

Antifungal Susceptibility of *Candida* Biofilms: Unique Efficacy of Amphotericin B Lipid Formulations and Echinocandins

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Received 24 January 2002/Returned for modification 5 March 2002/Accepted 18 March 2002

Biofilms, likely the predominant mode of device-related microbial infection, exhibit resistance to antimicrobial agents. Evidence suggests that *Candida* biofilms have dramatically reduced susceptibility to antifungal drugs. We examined antifungal susceptibilities of *Candida albicans* and *Candida parapsilosis* biofilms grown on a bioprosthetic model. In addition to conventional agents, we determined if new antifungal agents (triazoles, amphotericin B lipid formulations, and echinocandins) have activities against *Candida* biofilms. We also explored effects of preincubation of *C. albicans* cells with subinhibitory concentrations (sub-MICs) of drugs to see if they could modify subsequent biofilm formation. Finally, we used confocal scanning laser microscopy (CSLM) to image planktonic- and biofilm-exposed blastospores to examine drug effects on cell structure. *Candida* biofilms were formed on silicone elastomer and quantified by tetrazolium and dry weight (DW) assays. Susceptibility testing of fluconazole, nystatin, chlorhexidine, terbenafine, amphotericin B (AMB), and the triazoles voriconazole (VRC) and ravuconazole revealed resistance in all *Candida* isolates examined when grown as biofilms, compared to planktonic forms. In contrast, lipid formulations of AMB (liposomal AMB and AMB lipid complex [ABLC]) and echinocandins (caspofungin [Casp] and micafungin) showed activity against *Candida* biofilms. Preincubation of *C. albicans* cells with sub-MIC levels of antifungals decreased the ability of cells to subsequently form biofilm (measured by DW; $P < 0.0005$). CSLM analysis of planktonic and biofilm-associated blastospores showed treatment with VRC, Casp, and ABLC resulted in morphological alterations, which differed with each agent. In conclusion, our data show that *Candida* biofilms show unique susceptibilities to echinocandins and AMB lipid formulations.

Post antifungal effect – (PAFE)

PAFE

- Pharmacodynamic parameter - refers to suppression of fungal regrowth persisting after short exposure to, and subsequent removal of, an antifungal drug.

Importance of PAFE

Antifungal drugs showing fungicidal activity, tend to possess longer PAFE compared to fungistatic drugs.

Post-drug exposure effects are important to understand and optimize **drug efficacy in vivo**

Journal of Antimicrobial Chemotherapy (2004) **53**, 386–389
DOI: 10.1093/jac/dkh066
Advance Access publication 16 January 2004

JAC

A comparative study of the post-antifungal effect (PAFE) of amphotericin B, triazoles and echinocandins on *Aspergillus fumigatus* and *Candida albicans*

Elias K. Manavathu*, Mayur S. Ramesh, Inthumathi Baskaran, Latha T. Ganesan and Pranatharthi H. Chandrasekar

Antifungal drug[a]	PAFE ± S.D. (h)	
	A. fumigatus ($n = 5$)[b]	*C. albicans* 90028[c]
Amphotericin B	7.5 ± 0.70	5.3 ± 1.15
Itraconazole	0.5 ± 0.0	≤0.5
Voriconazole	0.5 ± 0.0	≤0.5
Posaconazole	0.75 ± 0.35	≤0.5
Ravuconazole	0.38 ± 0.17	≤0.5
Caspofungin	≤0.5	5.6 ± 0.57
Micafungin	≤0.5	5.0 ± 1.0

1. Amphotericin B known to be fungicidal against filamentous fungi, including *A. fumigatus.*
2. A brief exposure of drug to fungal cells produces a prolonged Post AF Effect.
3. Echinocandins, known fungistatic agents against *A. fumigatus,* do not elicit permanent injury to the fungal cell.
4. As soon as the drug is removed, the cells recover immediately and resume growth and multiplication.

May have a clinical relevance in empiric therapy???

Evidence from published data

Liposomal AmB vs Conventional AmB – empiric therapy

- 687 patients randomized
- L-AmB – 3 mg/kg
- Ampho B Conv– 0.6 mg/kg/day

- **Results**
  - Rates of successful treatment & survival similar
  - L-AmB associated with fewer proven
  - breakthrough IFIs [3.2%]) AmB-D (27 patients [7.8%], $P = 0.009$).

Walsh TJ, et al. Group. *N Engl J Med*. 1999;340(10):764–771.

Liposomal Amp B vs caspofungin in empiric therapy

- 1095 patients with persistent fever and neutropenia
  - Overall success rates 33.9% for caspofungin and 33.7% for L-AmB
  - Breakthroughfungal infections were similar in the two groups
  - Resolution of fever during the period of neutropenia was comparable.
  - Caspofungin improved survival (92.6% and 89.2%; $P = 0.05$) and response rates in patients with IFIs
  - Caspofungin better tolerated

Walsh TJ, *N Engl J Med*. 2004;351(140):1391–1402

Liposomal Amp B vs caspofungin in empiric therapy

- Authors comments……

- *Caspofungin was as effective as L-AmB*

Walsh TJ, *N Engl J Med*. 2004;351(140):1391–1402

NCCN Guidelines - 2009

Formulation	Spectrum
Liposomal AmB	Borad spectrum antifungal activity Candid, Aspergillus species, Zygomycetes, rare moulds, cryptococcus neoformans, dimorphic fungi
Caspofungin	Active against Candida & Aspergillus species. Not reliable or effective against other fungal infections

Liposomal Amp B vs Voriconazole in empiric therapy

- Multicenter trial among febrile neutropenic patients.
- 837 patients randomized
- Voriconazole failed to meet pre-specified criteria for noninferiority to L-AmB.
- Upon prespecified criteria, voriconazole was inferior to L-AmB with overall success rates of 26% with voriconazole and 30.6% with L-AmB (95% confidence interval: -10.6 to 1.6).

Walsh TJ,. *N Engl J Med*. 2002;346(4): 225–234.

Liposomal Amp B vs Voriconazole in empiric therapy

- *Despite the widespread use of voriconazole as empiric therapy and prophylaxis of IFIs, voriconazole is not FDA approved for these indications……*

P. Chandrasekhar et al. Infection and Drug Resistance 2012:5 9–16

Posaconazole

- Based on available data, approved for prophylaxis of invasive *Aspergillus and Candida infections* in high-risk, severely immunocompromised adult patients.
- Effective against Zygomycetes
  - May be useful as step-down therapy after initial treatment with amphotericin B.

Take home message

- Increased incidence of fungal infections in India
- Higher incidence of non albicans candida in Indian scenario
- World's highest number of zygomycosis reported from India
- Diagnosing these rare emerging IFIs is more difficult than diagnosing common IFIs
- Growing concern over resistance to newer antifungal agents …. e.g. azoles and echinocandins
- Need today
  - Good diagnostic mycology laboratory for rapid diagnosis
  - Refinement of antifungal strategy based on Indian scenario

Arunalok Chakrabarti; Jpn J med Mycol, Vol 49, 165 – 172, 2008

Take home message

- The oldest antifungal drugs, polyenes, remain useful in the treatment of IFIs
- Often considered the "Gold standard" because of
  - Their broad-spectrum activity
  - Only antifungal agent – fungicidal to both yeasts & moulds
  - Low rates of documented resistance
  - Established clinical track record
- Liposomal amphotericin B significantly reduces nephrotoxicity potential of amphotericin B

Chandrasekar , J Antimicrob Chemother 2011; 66: 457–465

Thank You