How To Best Use Antifungal Agents

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ESCMID SUMMER SCHOOL 2012

Roadmap

- Epidemiology
- Diagnosis
- Antifungal drugs and therapy

Trends in fungal diseases

- Increasing cases of invasive fungal infections
- Clinical signs/symptoms are non specific: a continuum of clinical presentations
- Poor diagnostic tools
- Replacement of sensitive species by resistant ones
- Increasing use of prophylaxis and empirical therapy
- Increasing drug and hospitalisation costs
- New hosts

Hope, 2005; Denning, 2006; Lass-Flörl, 2007

Fungal infections

Fungi can be both, colonizers and pathogens, hence vigilance is required in the interpretation of:

-superficial cultures

-antigen tests, PCR screening, presence of antibodies and/or metabolites

Lass-Flörl 2005, Walsh 2000, Kontoyiannis 2006

Conventional methods for the laboratory diagnosis of fungal infections might be insensitive and timeconsuming!

Alexander BD , Pfaller MA (2006) Clin Infect Dis. 43:S15-S27

Non culture techniques

Tests	Fungus identification
Galactomannan	Aspergillus species
1-3-ß-D-Glucan	Candia species, Aspergillus species, Pneumocystis jiroveci
Glucurono-xylo-mannan	Cryptococcus neoformans, Cryptococcus gattii
Antibody	Histoplasma and Coccidiodes
PCR	Genus or species-specific

Lass-Flörl, Mycoses 2009

Diagnosis of fungal infections

- **Blood cultures**

Sensitivity: Candida 35% - 60%

- **Antibody**

Sensitivity: Candida 50%, chron. Aspergillose 80%

- **(1,3)-ß-D-Glucan**

No difference between yeasts and molds

- **Mannan -Candida**

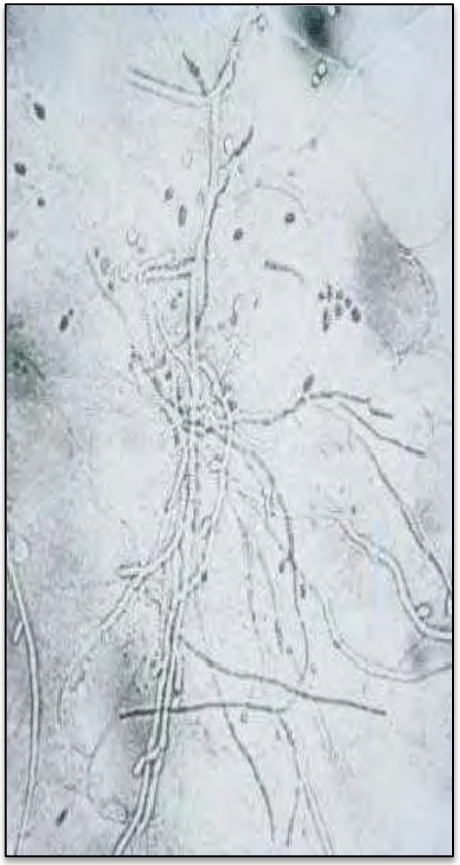
Sensitivity 34%-85%, Specificity 76% -94%

- **Galactomannan -Aspergillus**

Sensitivity 50%-83%, Specificity 64% -94%

- **PCR Polymerase chain reaction**

Sensitivity 45%-85%, Specificity 56% -94%

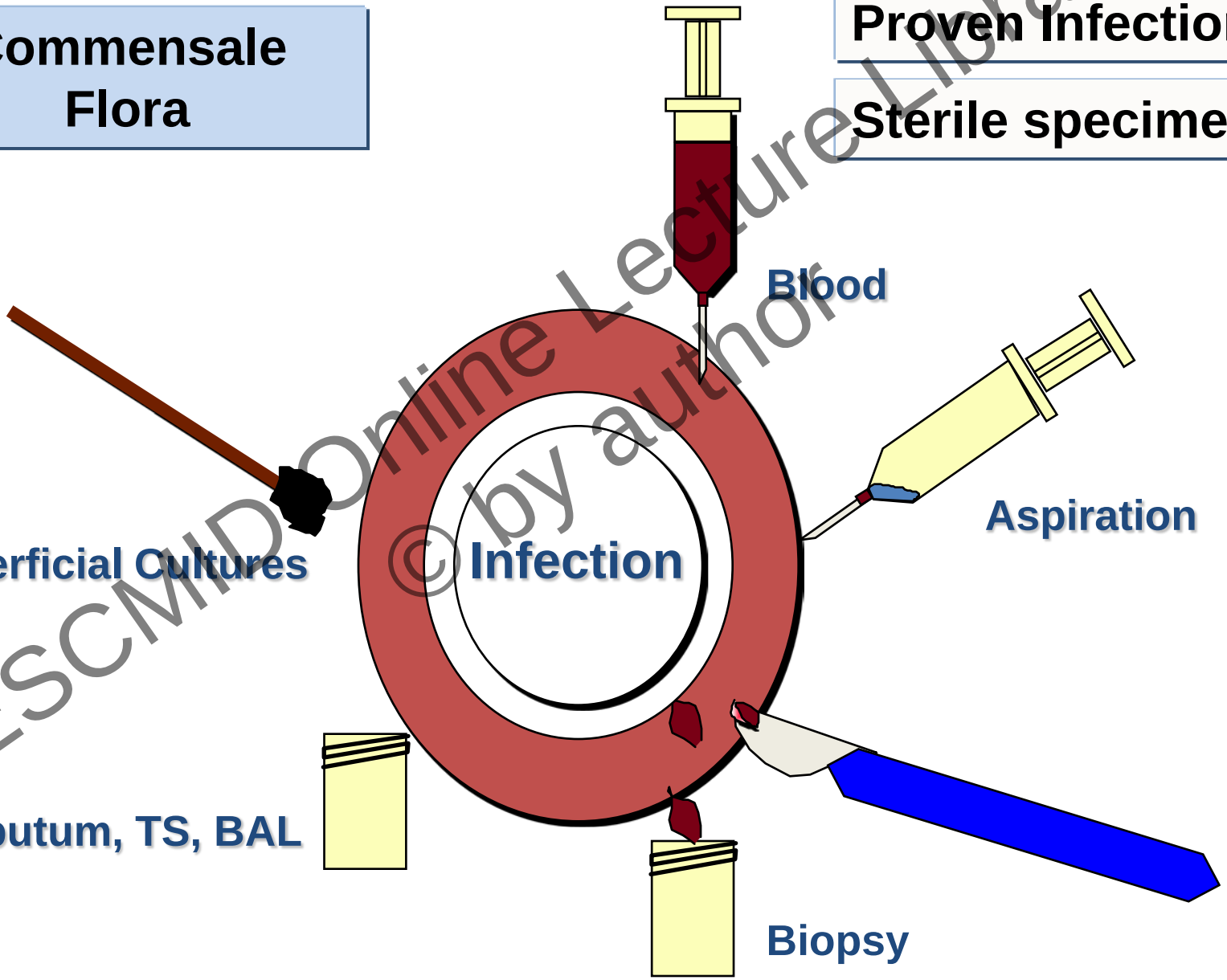


Possible Infection

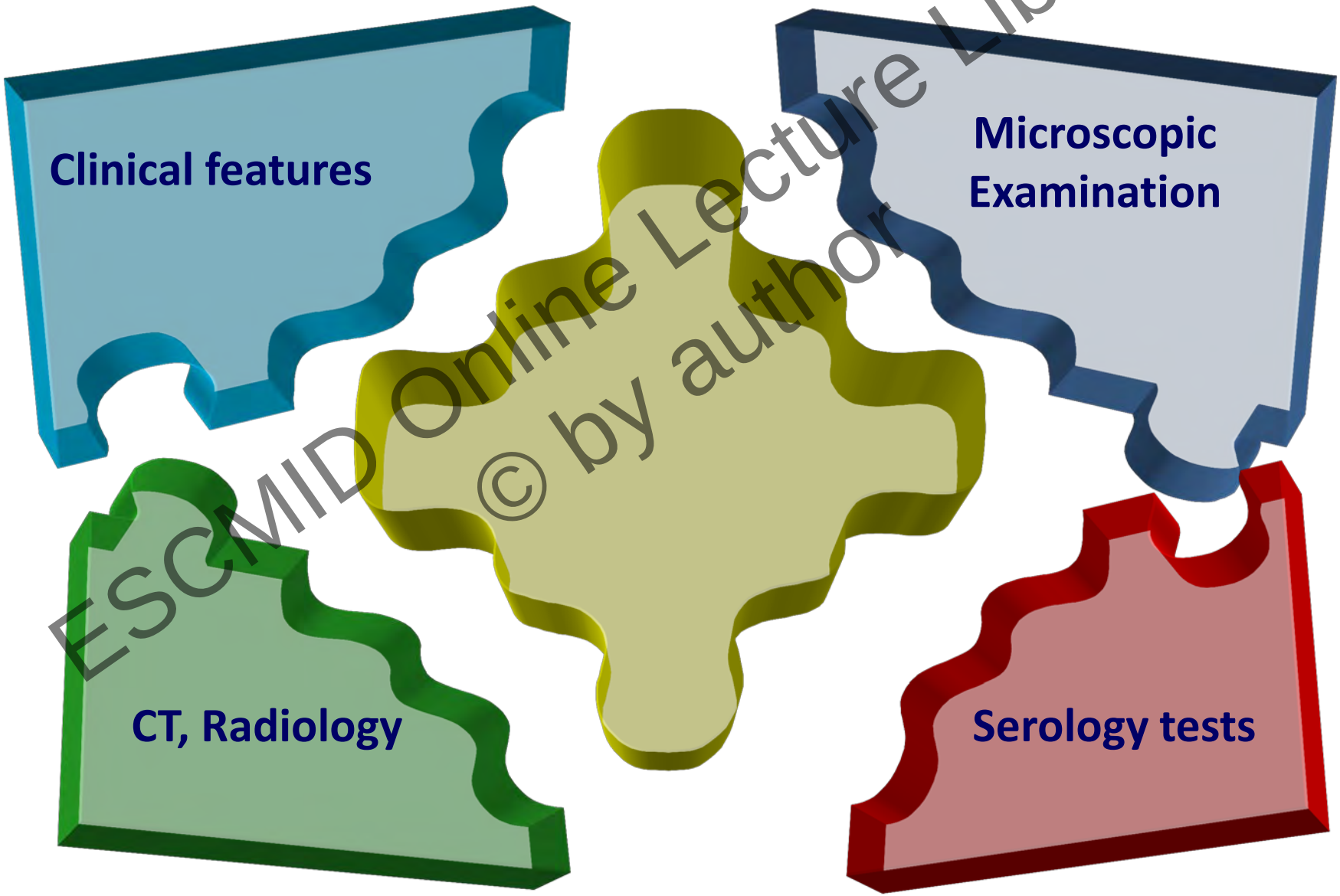
Commensale Flora

Proven Infection

Sterile specimen



„Puzzle diagnosis“



Genus and Species Distribution - what are the concerns?

- C. glabrata: panazole resistant
- C. parapsilosis: MIC ↑ echinocandins
- Aspergillus spp: (pan) azole resistant
- A. terreus: Ampho B resistant
- Zygomyzetes: susceptible to POS and AMPHO B
- Scedosporium prolificans: multidrug resistant
- Fusarium solani: multidrug resistant

Richardson & Lass-Flörl 2008

Prophylaxis	Administration of the antifungal agent at a period of high risk of infection
Empirical treatment	Initiation antifungal in persistently febrile patients with neutropenia (generally 4–7 days in duration) - without a known source and is unresponsive to antibacterial agents
Preemptive therapy	Aims to treat a suspected early IFI but uses radiologic studies, laboratory markers, or both
Treatment of proven IFI	European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria: proven IFI

The echinocandin class

- 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)

- **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 azoles

- Flu: 100-200 mg/d (EC) and 400/d (IC). Load with 2x daily dose.
- Vori: Load with 6 mg/kg q12h x 2 doses. Then, 3-4 mg/kg qd (IC). Oral is 200 mg q12h x 2 dose then 200/d (IC & EC).

- Fluconazole
  - Renal clearance (dose per creatinine)
  - IV and PO: forms are interchangeable
- Voriconazole
  - Hepatic clearance (↓ dose 50% with mild to moderate failure, no data in severe)
  - IV uses cyclodextrin carrier that is cleared by kidneys. Avoid in renal failure
- Safety: Both are quite good
  - Hepatic injury is main risk
- Drug interactions
  - Both have typical range of P450/cytochrome azole problems
    - Voriconazole is more difficult

Voriconazole

- Oral and iv formulations
- Spectrum of activity — Candida spp, Aspergillus, Fusarium
  Pseudoallescheria /Scedosporium
  C. neoformans

  Not active — Zygomycosis, Sporothrix sp.

- Therapy of choice: **Aspergillus**
- Increasingly used as prophylaxis and empiric therapy in neutropenia and bone marrow/stem cell transplant
  - *Are we selecting for Zygomycosis infections?*

- Adverse drug effects:
  hepatotoxicity – follow LFTs!
  visual disturbances
  void IV in pts with CrCl < 50 ml/min

Posaconazole

- **Very broad spectrum**
  - Candida spp, Aspergillus, Zygomycetes, hyahyphomycetes, Fusarium, endemic fungi
- Currently approved indications based on clinical trials
  - Antifungal prophylaxis:
    - **patients with HCST and severe GVHD**
    - **Patients with hematologic malignancies and profound neutropenia secondary to chemotherapy**
- Other uses: salvage therapy of Zygomycosis and other mould infections

The amphotericines

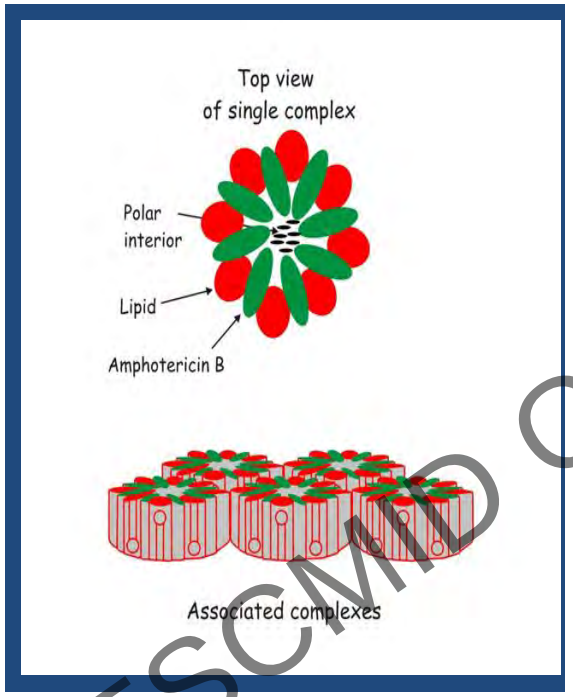
Some patients tolerate one but not another

- 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

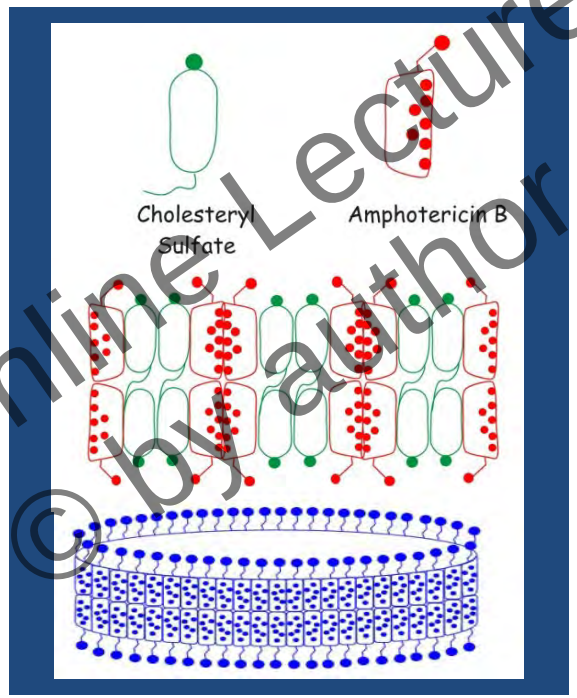
Lipid Amphotericin B Formulations

Abelcet ® ABLC



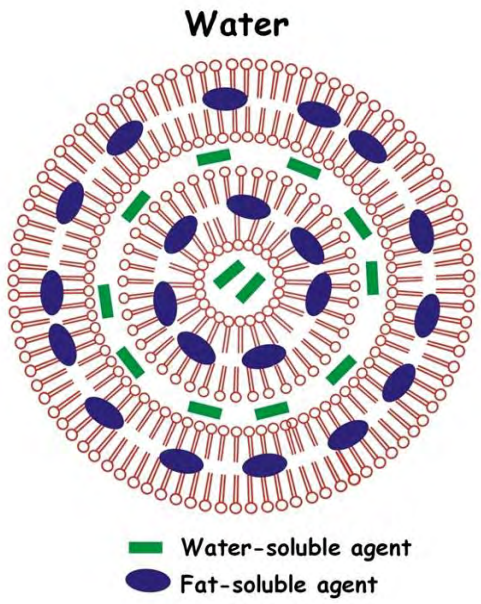
Ribbon-like particles
Carrier lipids: DMPC, DMPG
Particle size (µm): 1.6-11

Amphotec ® ABCD



Disk-like particles
Carrier lipids: Cholesteryl sulfate
Particle size (µm): 0.12-0.14

Ambisome ® L-AMB

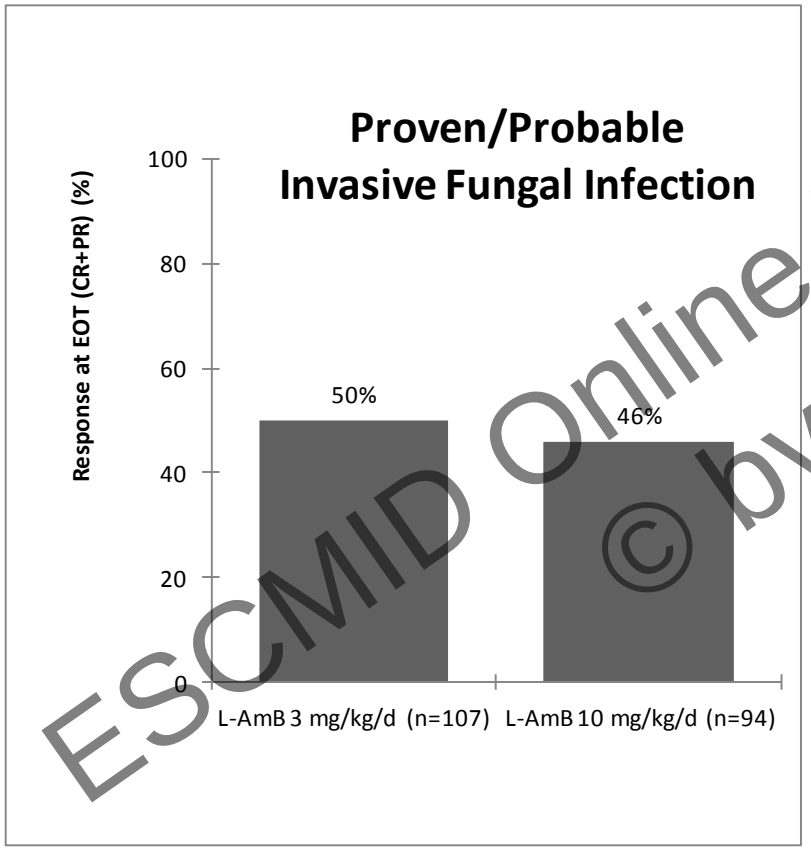


Unilaminar liposome
Carrier lipids: HSPC, DSPG, cholesterol
Particle size (µm) : 0.08

HSPC-Hydrogenated soy phosphatidylcholine
DSPG-Distearoyl phosphitidylcholine

DMPC-Dimyristoyl phospitidylcholine
DMPG- Dimyristoyl phospitidylcglycerol

Efficacy of Liposomal AmB (L-AmB) in Invasive Mycoses: AmBiLoad Trial

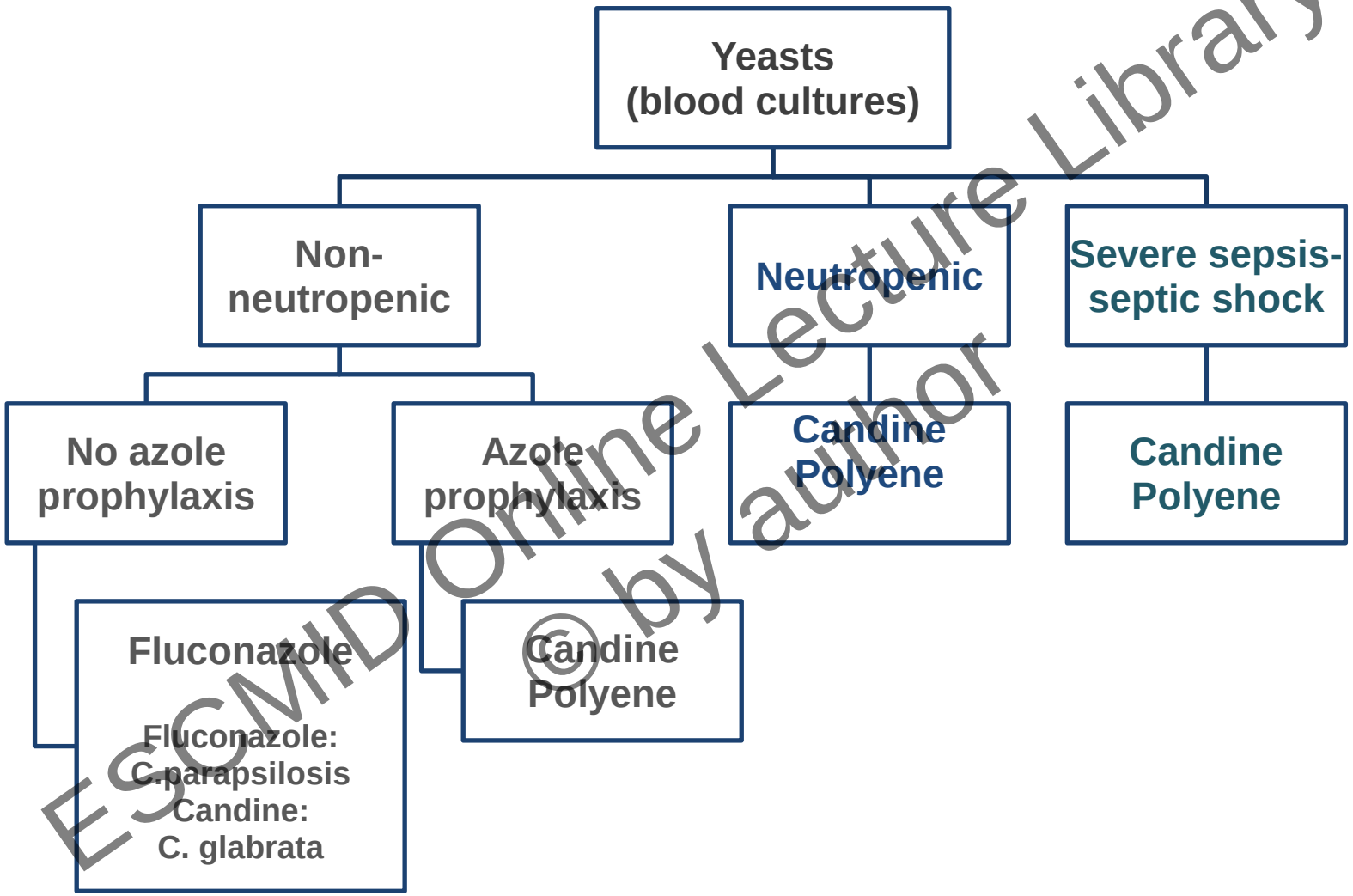


14 day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d

	L-AmB 3	L-AmB 10
IPA	96%	97%
CT Halo	58	60
Allo-SCT	16	19
Neutropenia	71	76
Survival	72	59
Toxicity	20	32

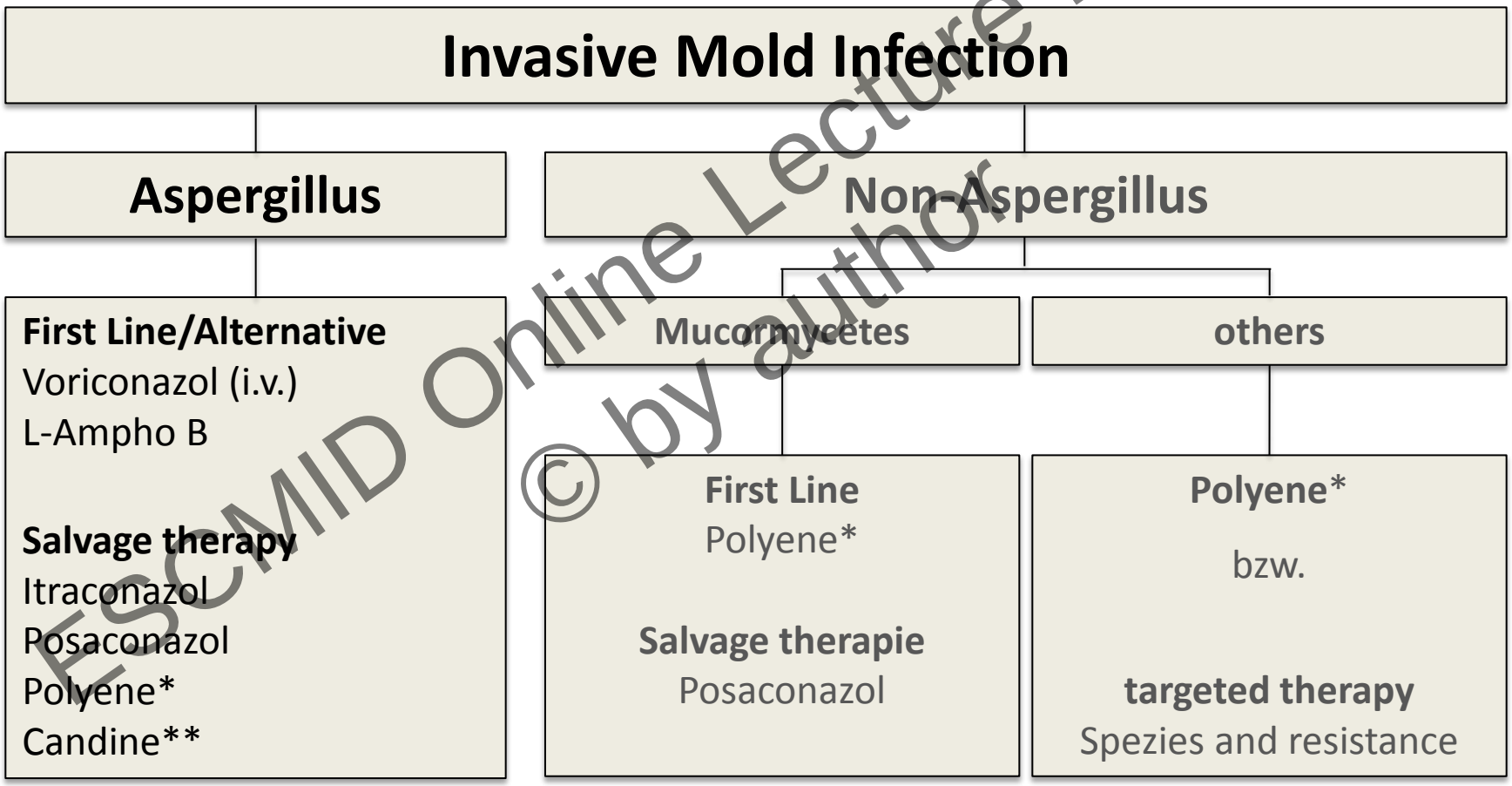
Note: L-AmB=liposomal amphotericin B; CR+PR=complete & partial responses; EOT=End of Therapy; IPA=invasive pulmonary aspergillosis; Allo-SCT=allogeneic stem cell transplant

Cornely et al, 2007

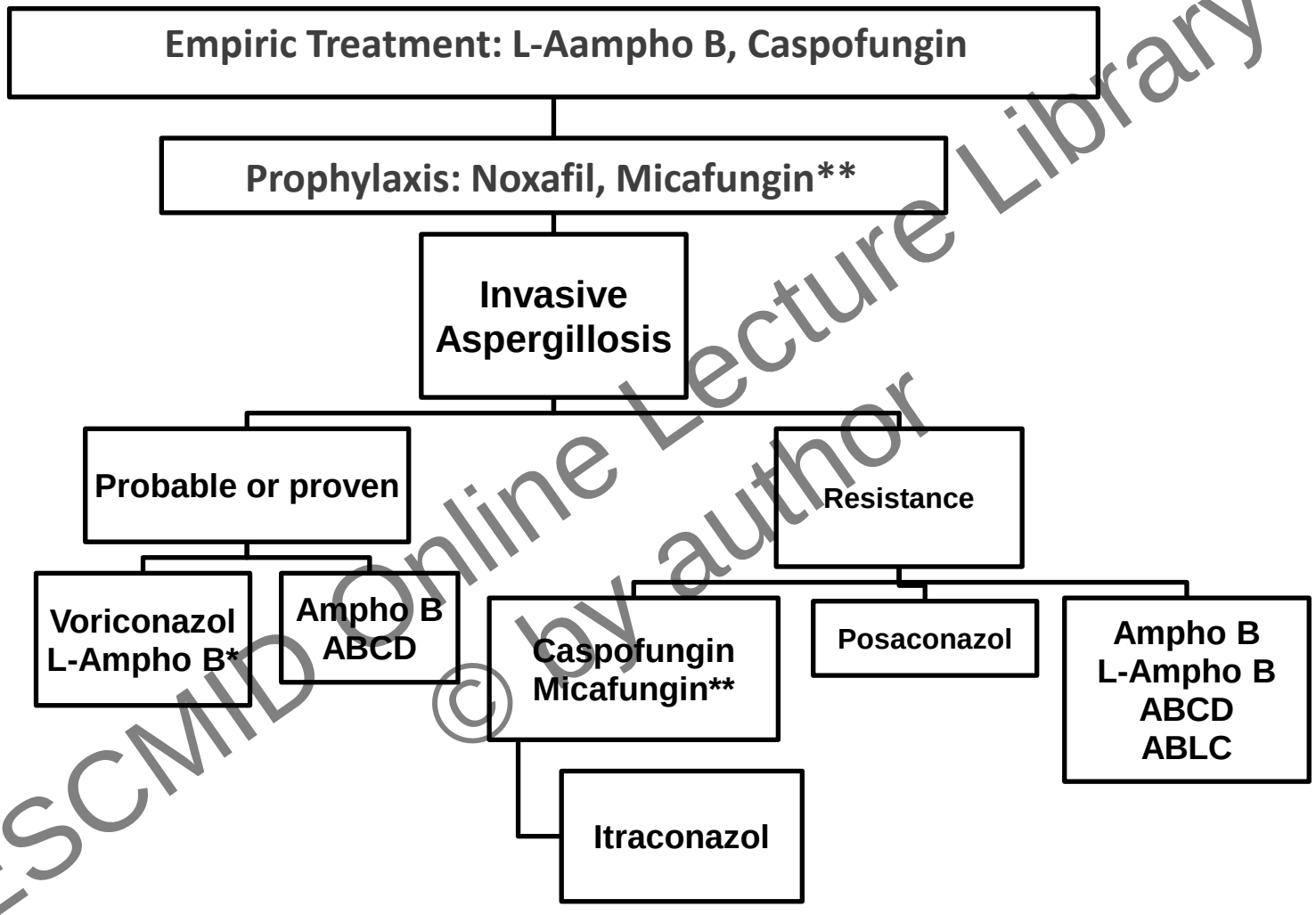


IDSA Guidelines for Candida 2009

Other mold infections IDSA-Guidelines 2009



* Polyene: AmphoB, L-AmphoB, ABLC, ABCD
** Candine: Caspofungin



ABCD: colloidal form
*L-Ampho B: liposomal Ampho B, ECIL 2 Guidelines and DGHO (AII)
ABLC: Lipid complex
** In some countries not licensed for IA

Mod. IDSA Guidelines Aspergillosis 2008

Antifungal Combination Therapy: Considerations

PRO

- Increased activity
- More rapid response
- Broader spectrum
- Prevention of resistance development
- Better tissue distribution
- Reduced toxicity?

CON

- Potential antagonism
- Drug interactions
- Increased toxicity?
- Higher costs

Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus-Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7-1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3-4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7-1.0 mg/kg per day) or liposomal AmB (3-4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4-6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	≥ 1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	≥ 1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	≥ 1 year[c]	C-I

ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

[a] Begin HAART 2-10 weeks after the start of initial antifungal treatment.

[b] In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made – but not encouraged – as substitutes.

[c] With successful introduction of HAART, a CD4 cell count ≥ 100 cells/μL, and low or nondetectable viral load for ≥ 3 months with minimum of 1 year of antifungal therapy.

[d] Inferior to the primary recommendation.

CID 2010; 50: 291-322

How to best use drugs?

- Identify the fungus (yeasts or mold or…)
- Local epidemiology (IBK versus …)
- Previous therapy (azoles or polyenes or…)
- Risk factors
- Severity of clinical presentation
- Underlying diseseas
- PK/PD
- Toxicity

Thank you very much for your attention!