Role of Amp B in Mucormycosis and Challenges

Introduction

- Mucormycosis is an invasive fungal infection (IFI) first described by Paulltauf A in 1885.
- Mucormycosis are the group of invasive infection caused by filamentous fungi of the Mucoraceae family.
- Mucormyscosis also known as Zygomycosis and Phycomycosis is a rare opportunistic fungal infection with a fulminant course and high Mortality rate.
- *Rhizopus* species are the most common causative organisms.
- The Rhinocerbral variant of Mucormyscosis involves facial,orbital,paranasal sinus and cerebral regions.

A. MALLIS, S.N. MASTRONIKOLIS *Rhinocerebral mucormycosis: an update*, 2010; 14: 987-992

Different types of Mucormycosis

- Based on the Clinical presentation and particular site of involvement six manifestations of the disease can be described:
- Rhino cerebral (ROC),
- Pulmonary
- Cutaneous
- Gastrointestinal
- Disseminated
- Localized infection

A. MALLIS, S.N. MASTRONIKOLIS *Rhinocerebral mucormycosis: an update*, 2010; 14: 987-992

Different types of Mucormycosis

- Rhino cerebral Mucormycosis (RCM)
- Rhino Orbital (ROC)
- Rhino Maxillary (ROM)

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Common Causative Organisms

- Mucormycosis-causing species are the filamentous fungi of mucoraceae family of the order mucorales,subphylum Mucormycotina.
  - *Mucor*
  - *Cunninghamella*
  - *Apophysomyces*
  - *Absidia*
  - *Saksenaea,*
  - *Rhizomucor, and other species.*

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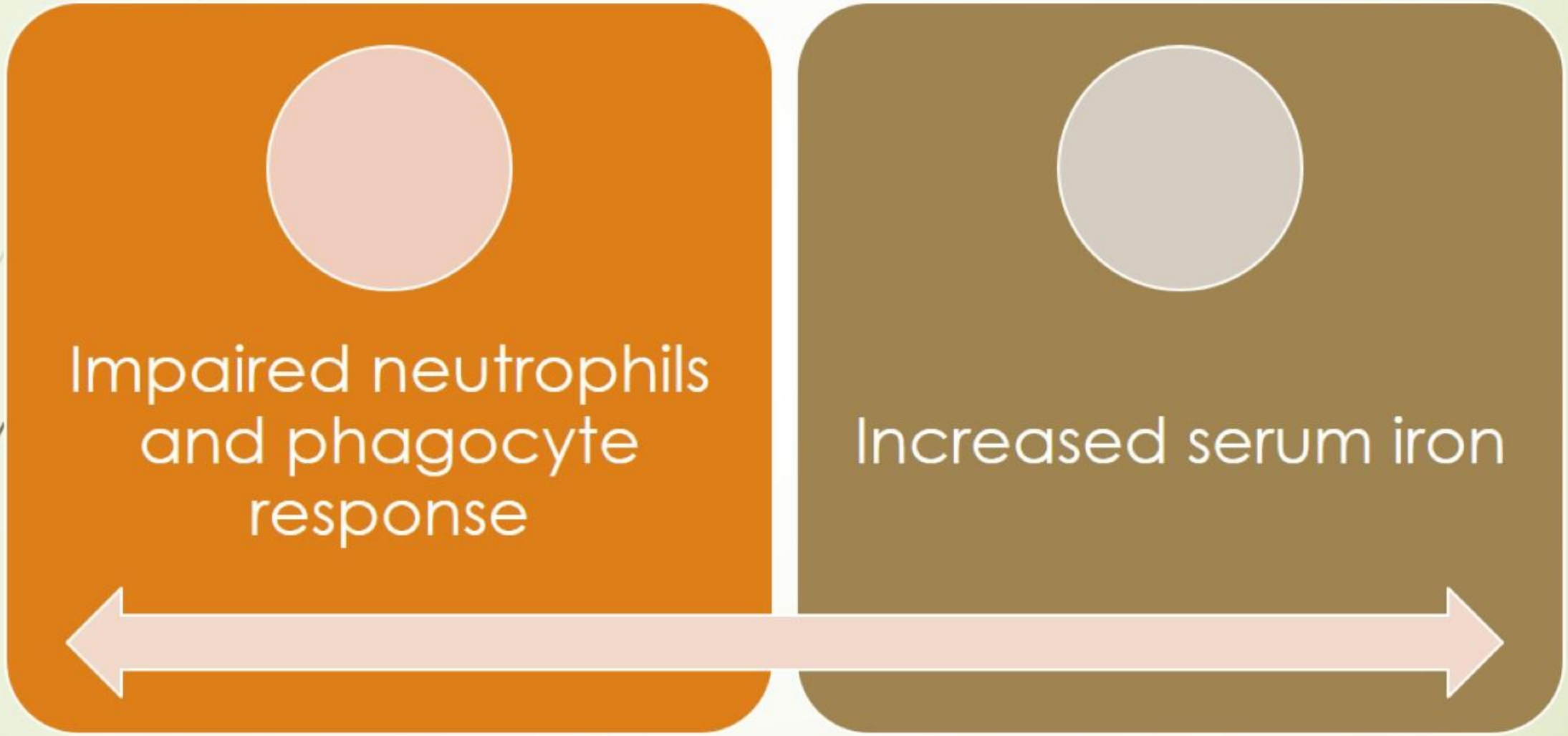
Prevalence & incidence of Mucormycosis

- *Ress et al* reported an annual incidence rate of 1.7 cases per million people in the united states.
- *Biter et al* reported an average annual incidence rate of 0.9 per million people in France.
- The Rhinocerbral accounting for 30-50% of all cases of Mucormyscosis
- Overall Mucormyscosis Prevalence of 0.14 cases per 1000 population in India.
- A Meta analysis of all the zygomycosis cases reported from India, *Diwakar et al.* describe an overall prevalence of ROC (58%), Cutaneous (14%), Pulmonary (6%), Disseminated(7%), Gastrointestinal (7%) and Isolated renal(7%).

A. Chakraborty and R. Singh Mycoses, 2014, 57 (Suppl. 3), 85–90

A. MALLIS, S.N. MASTRONIKOLIS *Rhinocerebral mucormycosis: an update*, 2010; 14: 987-992

Pathophysiology of RCM



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Risk factors for Mucormycosis

- Diabetic Patients
- Neutropenia Patients
- Patients with haematological malignancies
- Increased serum Iron
- Immunocompromised state due to organ transplantation
- Haematological malignancies
- Chronic Corticosteroid treatment
- Hemochromatosis

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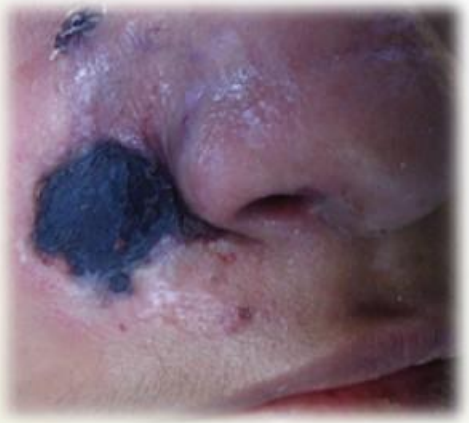
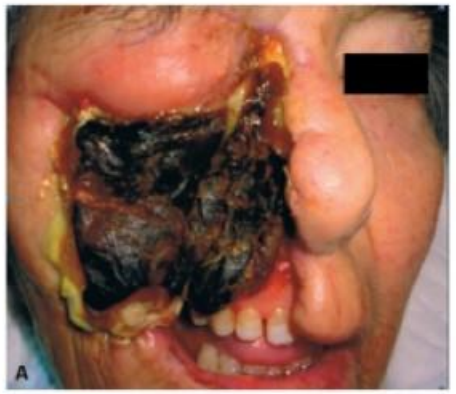
Clinical Presentation of Rhinocerbral Mucormycosis

- Initially Sinusitis/ Orbital cellulitis
- Blackened Necrotic eschars of hard plate or Nasal Cavity.
- Facial Pain
- Unilateral facial swelling





A. MALLIS, S.N. MASTRONIKOLIS *Rhinocerebral mucormycosis: an update*, 2010; 14: 987-992

Diagnosis of Rhino cerebral Mucormyscosis

- Histopathological examinations.
- Fungal cultures can provide confirmation.
- Molecular detection of zygomycetes.
- Cerebral spinal fluid analysis.
- CT Scans is used to evaluate the progression of diseases.
- MRI Scan for the extent of Disease due to fungal invasion of soft tissues.

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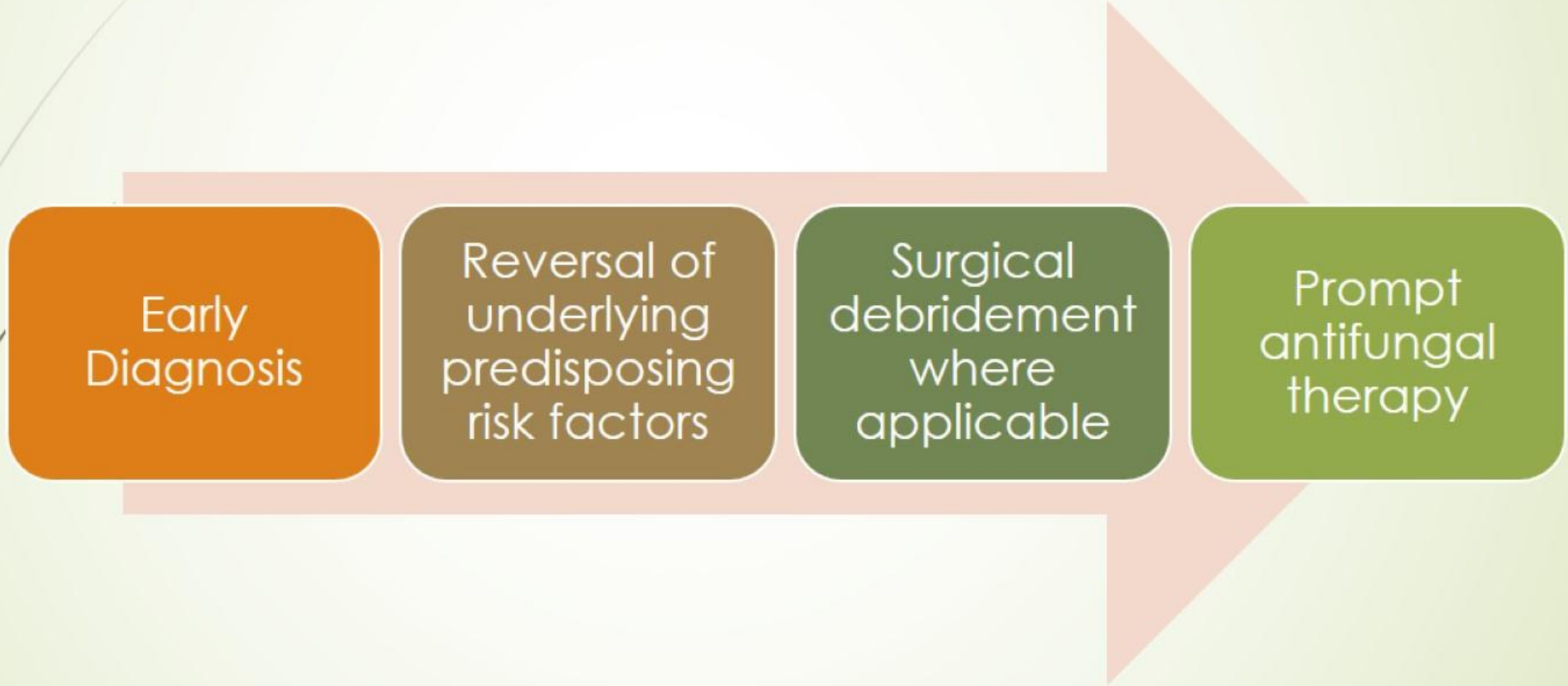
Clinical Microbiology and Infection, Volume 20 Supplement 3, April 2014

Therapeutic goals for Mucormycosis



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Recommendations on targeted first line treatment of Mucormycosis in adult

ESCMID and ECMM

Population	Intention	Intervention	QOE
Any	To Increase survival rates	Surgical Debridement	II u
Any	To cure and to increase survival rates	Surgical Debridement in addition to antifungal treatment	II u
Immunocompromised Any	To Increase survival rates. To cure and to increase survival rates	Immediate treatment initiation Amphotericin B, Liposomal > 5 mg /kg	II u
CNS	To cure	Amphotericin B, Liposomal 10 mg/kg, Initial 28 days	II
Any Except CNS	To cure	Amphotericin B lipid Complex 5 mg /kg	II u
Any	To cure	Posaconazole 4 * 200 mg /day or 2 * 400 mg /day	II u
Any	To cure	Lipid Based Amphotericin Plus Capsofungin	II u

II Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–control analytic studies preferably from more than one centre); from multiple time series; u Uncontrolled trial

Recommendations as per ESCMID & ECMM for Mucormyscosis

- In patients with Mucormyscosis Surgery whenever possible is strongly recommended with Medical treatment.
- **LAmB (Liposomal Amphotericin B)** is the **drug of choice** and the dose should be at least 5mg/kg/day

- Note: Use ABCD is Discouraged

Clinical Microbiology and Infection, Volume 20 Supplement 3, April 2014

First line Antifungal options for Mucormycosis
Primary Antifungal therapy

Drug	Recommended Dosage	Advantages	Limitations
AmB	1.0-1.5 mg/kg/day	> 5 decades clinical experience inexpensive: only licenced agent for the treatment of Mucormyscosis	Highly toxic: poor CNS penetration
LAmB	5-10 mg/kg/day	**Less nephrotoxic than AmB an d ABLC** improved outcomes vs. AmB in murine models and retrospective clinical review	Cost
ABLC	5-7.7 mg /kg/day	Less nephrotoxic than AmB murine and retrospective clinical data suggest benefits of combination therapy with Echinocandins	**More Nephrotoxic than LAmB**. Possibly less efficacious than other option as monoteharpy particularly CNS infection

Primary therapy should generally includes polyenes, non polyenes regimens may be for patients who refuse polyenes therapy for a patients with mild disease in relatively immunocompetent hosts that can be surgically eradicated.

Combination Therapy for Mucormycosis ، CID 2012:54 (Suppl 1

Salvage & Combination Therapy for Mucormyscosis

- Salvage Therapy may be necessary because of **refractoriness** of diseases, or because of **Intolerance towards previous antifungal therapy.**
  - **Posaconzole 200mg/four times a day**

- Combination of LAmB with Caspofungin: When patient is intolerant to Polyenes or Does not respond to monotherapy.

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Primary Combination Therapy for Mucormyscosis

Drug	Recommended Dosage	Advantages & Studies	Disadvantages
Caspofungin plus Lipid polyene	70 mg iv load then 50 mg /day for > weeks; 50 mg/m2 iv for children	Synergistic in murine disseminated Mucormyscosis retrospective clinical data suggested superior outcomes with combination caspofungin lipid- polyene therapy for rhino-orbital-cerebral Mucormyscosis	Clinical data of combination therapy are very limited.
Micafungin OR Anidulafungin plus Lipid polyene	100 mg /day for > 2 weeks;micafungin 10 mg/kg/day for low birth weight infants; anidulafungin 1.5 mg /day for children	Synergistic with LAmB in murine model of disseminated Mucormyscosis.	No clinical data
Deferasirox plus lipid polyenes	20 mg/kg po qd for 2-4 weeks	Highly fungicidal for mucorales in vitro; synergistic with LAmB in murine model of disseminated Mucormyscosis.	Phase 2 is ongoing

Combination Therapy for Mucormycosis ₀CID 2012:54 (Suppl 1

Treatment of Rhino cerebral Mucormycosis

- Surgical Intervention
- Antifungal therapy (AMP) (LAMP)
- Iron Chelation Therapy (Deferasirox and Defriprone)
- Adjunctive therapy (Granulocyte stimulating factor and hyperbaric oxygen).

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Treatment Strategy for RCM

- Surgical approach
- **Polyene based** therapy as the main course of action.
- Recommended starting doses for the **lipid formulation of amphotericin are 5-7.5 mg/kg/day** with higher dosages (up to 10 mg/kg/day) recommended for CNS involvement.
- Absence of supportive clinical evidence on the effectiveness of various combination treatments.
- Iron chelation therapy and posaconazole should be considered in cases of refractory infection or polyene intolerance.

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LIPID amphotericin B formulations in use

- Amphotericin B Lipid Complex (ABLC)
- Amphotericin B Colloidal Dispersion (ABCD)
- Liposomal Amphotericin B (LAMB)

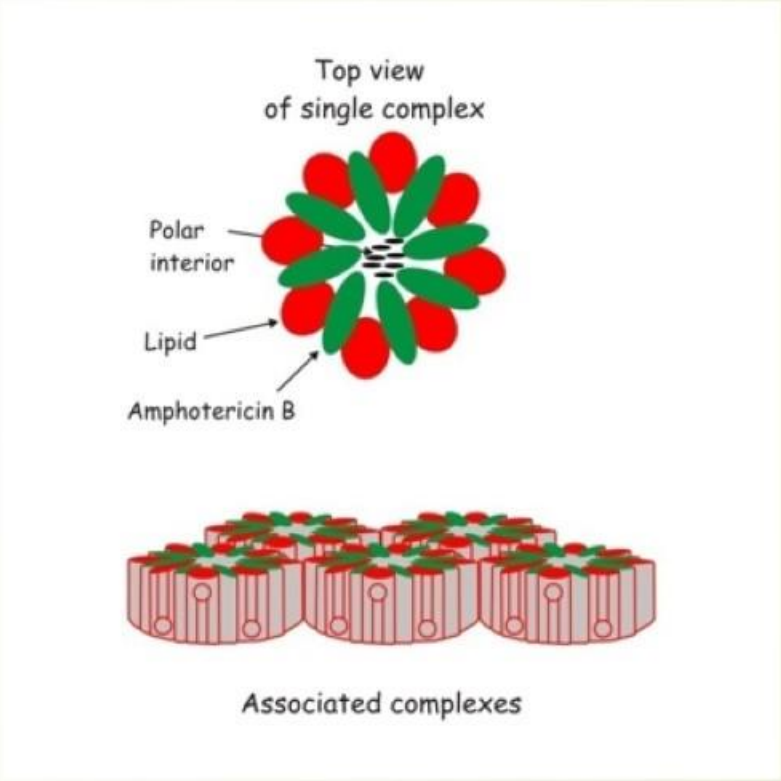
Neil R. H. "Drugs Drugs DOI 10.1007/s40265-016-0538-7

Amphotericin B Lipid Complex (ABLC)

- Ribbon-like configuration of ABLC is a tightly packed complex of amphotericin B with the lipid.

- This complex provides decreased **amount of free drug** and may thus be responsible for the reduced **toxicity of ABLC**

- **Nephrotoxicity** due to ABLC is less frequent compared to AMB



Ribbon-like particles

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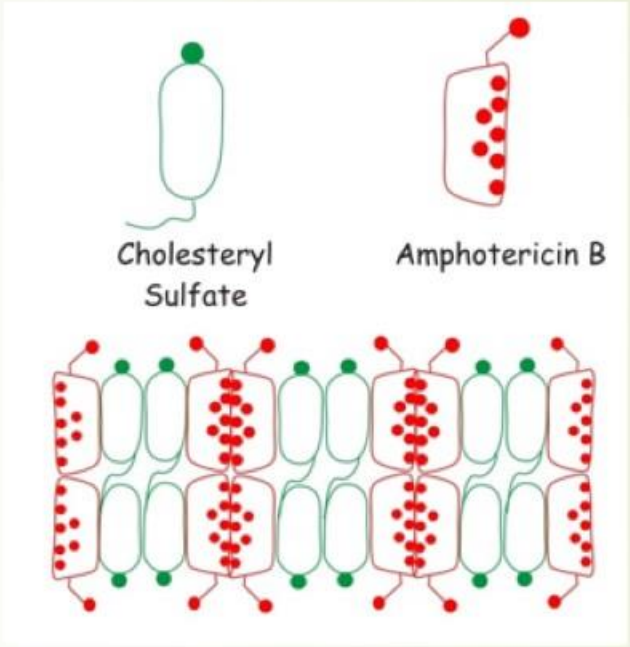
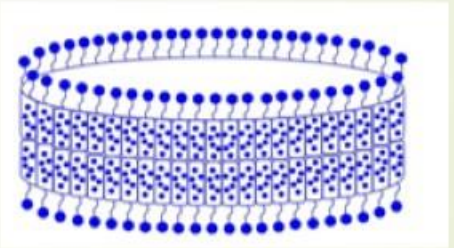
Amphotericin B Colloidal Dispersion (ABCD)

- ABCD is composed of amphotericin B complexed with cholesteryl sulfate.
- It is a disk-like structure.
- **Nephrotoxicity** due to **ABCD** is less frequent compared to **AMB.**
- High incidence of **acute infusion-related toxic reactions (hypoxia and chills)** due to ABCD compared to the other lipid formulations.





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Liposomal Amphotericin B

- LAmB is a safe and effective agent for a wide range of medically important opportunity fungal pathogens including:
  - Aspergillosis
  - Cryptococcal Meningitis
  - invasive candidiasis
  - Mucormyscosis.
- Encapsulation of amphotericin B in liposomes
- Better tolerability profile
- No compromise on antifungal activity

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Amphotericin B Lipid preparations
The efficacy-toxicity ratio

Efficacy

Lipid formulations > AmB d

Nephrotoxicity

L AmB < ABLC < ABCD< AmB d

Infusion related toxicity

L AmB < ABLC < ABCD< AMB d

Bottom-line – All have nephrotoxicity

L AmB scores –

Lesser infusional reaction

Lesser nephrotoxicity

ABLC: Amphotericin B Lipid Complex
ABCD: Amphotericin B Colloidal Dispersion

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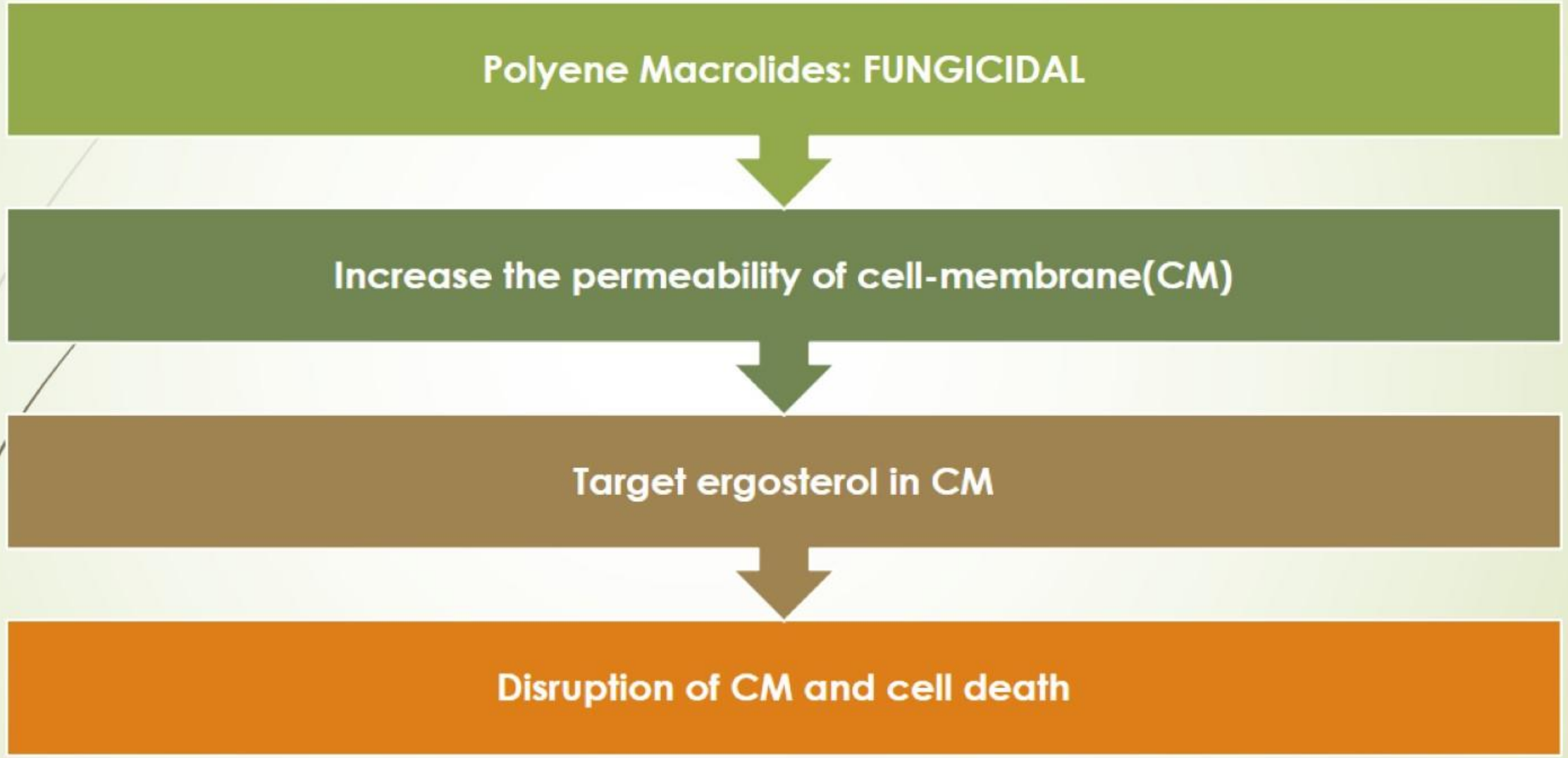
Mechanism of Action



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A COMPARISON OF AMPHOTERICIN B, LIPOSOMAL AMPHOTERICIN B AND OTHER LIPID FORMULATIONS

Parameter	Amphotericin B	Amphotericin B Lipid Complex (ABLC)	Amphotericin B Colloidal Dispersion (ABCD)	Liposomal Amphotericin B (unilamellar)	Liposomal Amphotericin B (mulitlamellar)
Size (nm)	0.035	1.6–11	0.11–0.14	**<0.080**	500-6000
Structure	Miscelles	Ribbon-like	Disc-like	**Liposomes**	Liposomes
Dose (mg/kg)	0.25–1	5	3-4	**3-5**	3-5
C_{max} (compared to AmB)	High	Lower	Lower	**Higher**	Higher
Infusion-related side effects	Fever, chills and nausea/ vomiting	Fever, chills and nausea/ vomiting	Fever and chills	**Hypokalaemia**	Hypokalaemia
Nephrotoxicity	Higher	Less Nephrotoxicity	Less nephrotoxicity	**Less nephrotoxicity**	Less nephrotoxicity
Sonication	Not required	Not required	Not required	**Not required**	Required

Journal of Antimicrobial Chemotherapy 2002; 49: 31-36 *Leukemia research 1997; 21(3): 183-188*

LAmB in Mucormyscosis

- LAmB is first line treatment of infection caused by Mucorales
- Clinical data with the use of LAmB in invasive Mucormyscosis are extremely limited.
- Dosages of at **least 5 mg/kg/day** are generally used.
- One prospective, nonrandomized study using **10 mg/kg/day LAmB** (with surgery in two-thirds of cases) demonstrated a **45 % response rate.**
- High mortality rates of mucormycosis, combinations of LAmB with an **azole** (posaconazole or isavuconazole) and/or an **echinocandin,** warrant study in clinical trials.

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Clinical Study

Improved outcome of zygomycosis in patients with haematological diseases?

Treatment of mucormycosis with liposomal amphotericin B (LAmB) was associated with a 67% survival rate, compared to 39% survival when patients were treated with AmB (p=0.02).

Leuk Lymphoma. 2004 Jul;45(7):1351-60.

Primary treatment of zygomycosis with liposomal amphotericin B: analysis of 28 cases

- The median patient age was 44 years and 71% were male.
- Success as defined by complete or partial positive response was noted in 32% of the cases.
- Concomitant surgery was performed in 46% of the cases, with similar response rates (31%).

Overall survival was 39%. L-AMB was effective as primary therapy in only some patients in this cohort of highly immunocompromised individuals with invasive zygomycosis underscoring the importance of host response and the need for further advances for treatment of this lethal infection.

Med Mycol. 2010 May;48(3):511-7.

Maximum tolerated dose study of LAmB for Mucormycosis

- Open-label, multicentre, sequential dose escalation trial for the assessment of the safety, tolerance, plasma pharmacokinetics, and MTD of intravenous L-AMB.

TABLE 2 Baseline fungal infections and sites

Organism	Site	Total [n (%)]	7.5 mg/kg [n (%)]	10 mg/kg [n (%)]	12.5 mg/kg [n (%)]	15 mg/kg [n (%)]
Aspergillus	Lungs	31 (70.5)	5 (62.5)	7 (70.0)	4 (57.1)	**15 (78.9)**
	Sinuses	3 (6.8)		1 (10.0)	1 (14.3)	**1 (5.3)**
	Other[a]	3 (6.8)		2 (20.0)		**1 (5.3)**
	Skin	2 (4.5)	1 (12.5)	1 (10.0)		
Zygomycete	Skin	2 (4.5)			1 (14.3)	**1 (5.3)**
	Lungs	1 (2.3)	1 (12.5)			
	Sinuses	1 (2.3)			1 (14.3)	
	Paronychia	1 (2.3)	1 (12.5)			

These findings indicate that L-AMB at dosages as high as 15 mg/kg/day follows nonlinear saturation-like kinetics, is well tolerated, and can provide effective therapy for aspergillosis and other filamentous fungal infections.

Antimicrob Agents Chemother. 2001 Dec;45(12):3487-96.

Combination Clinical study

A randomized, double-blinded, placebo-controlled trial: Deferasirox–LAmB Therapy for Mucormycosis.

- N= 20 patients with proven or probable mucormycosis were randomized to receive treatment with:
- Group A : LAmB plus deferasirox (20 mg/kg/day for 14 days).
- Group B: LAmB plus placebo.
- The primary analyses were for safety and exploratory efficacy.

Patients with mucormycosis treated with deferasirox had a higher mortality rate at 90 days. Population imbalances in this small Phase II study make generalizable conclusions difficult. Nevertheless, these data do not support a role for initial, adjunctive deferasirox therapy for mucormycosis.

Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis

- 41patients with biopsy-proven ROCM were identified over 12 years; 23 (56%) of these patients were Hispanic, and 34 (83%) were diabetic
- **Group 1** Polyene caspofungin therapy
- **Group 2** Amphotericin B lipid complex
- Results Showed that had inferior success **(37% vs. 72%; P = .03)** and a higher **clinical failure rate (45% vs. 21%; P = .04),** compared with patients who received other polyenes. However, patients treated with **amphotericin B lipid complex plus caspofungin had superior success** (100% vs. 20%; P = .009) and survival time (P = .01), compared with patients who received amphotericin B lipid complex alone

Combination polyene-caspofungin therapy represents a promising potential alternative to polyene monotherapy for patients with ROCM. Randomized, prospective investigation of these findings is warranted

Contraindication of LAmB

- LAmB is contraindicated in those patients who have demonstrated or have known **hypersensitivity** to amphotericin B deoxycholate or any other constituents of the product unless, in the opinion of the treating physician, the benefit of the therapy outweighs the risk.

Warnings And Precautions

- Anaphylaxis and **anaphylactic reactions** have been reported in association with liposomal amphotericin B infusion.
- Allergic type reactions, including severe **infusion-related reactions**, can occur during administration of amphotericin containing products, including liposomal amphotericin B.

Summary

- **Rhinocerebral** form of the diseses has been the most common accounts for **30 % to 50%** of all cases of mucormycosis.
- Based upon superior Safety and efficacy, lipid formulations of Amphotericin B have become the **Standard treatment for mucormycosis**.
- Posoconazole may be useful as **salvage therapy** but can not be recommended as **Primary therapy**.
- Combination of LAmB with Caspofungin: When patient is intolerant to **Polyenes or Does not respond** to monotherapy