Treatment of Invasive fungal infections

Vishnu Sharma

DM Clinical Hematology (AIIMS Delhi)

Associate Professor, Medicine

SMS Medical College, Jaipur

Outline

- **What is IFI**
- **Epidemiology**
- **Why in COVID**
- **Antifungal drugs**
- **Treatment of IFIs**
- **Our experience with these patients**
- **Take home message**

What is IFI ?

- "Presence of fungal elements either as mould or yeast in deep tissues of biopsy or needle aspirates that is confirmed on culture and histo-pathological examination can be described as an Invasive Fungal infection (IFI)."

  S. Ascioglu, J. H. Rex, B. de Pauw, et al. Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus. Clinical Infectious Diseases 2002; 34:7-14

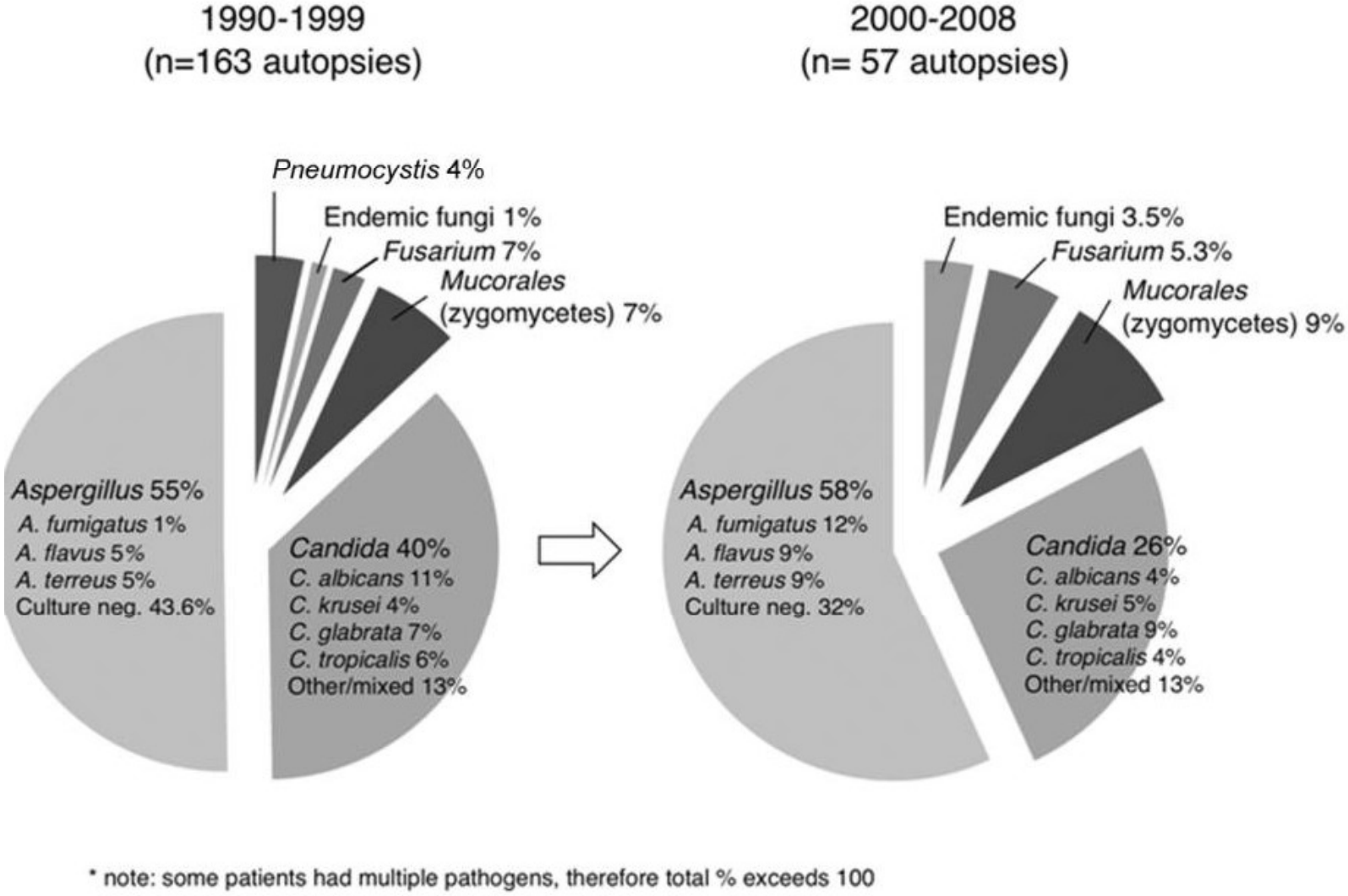
- "Term IFI is used only to characterize **systemic, generalized, deep-seated, visceral** and **severe, life-threatening** fungal infections, in contrast to superficial, local, benign, self-limiting fungal diseases." - Hof H. IFI = invasive fungal infections. What is that? A misnomer, because a non-invasive fungal infection does not exist! International Journal of Infectious Diseases 14 (2010) e458–e459

- "IFIs are those infections where fungi have **invaded in to the deep tissues** and have established themselves resulting in **prolonged** illness, usually are seen in debilitated and **immunosuppressed** individuals."

  Ramana KV et al. **Invasive Fungal Infections: A Comprehensive Review** *American Journal of Infectious Diseases and Microbiology, 2013, Vol. 1, No. 4, 64-69*

Epidemiology of IFIs- A Moving Target

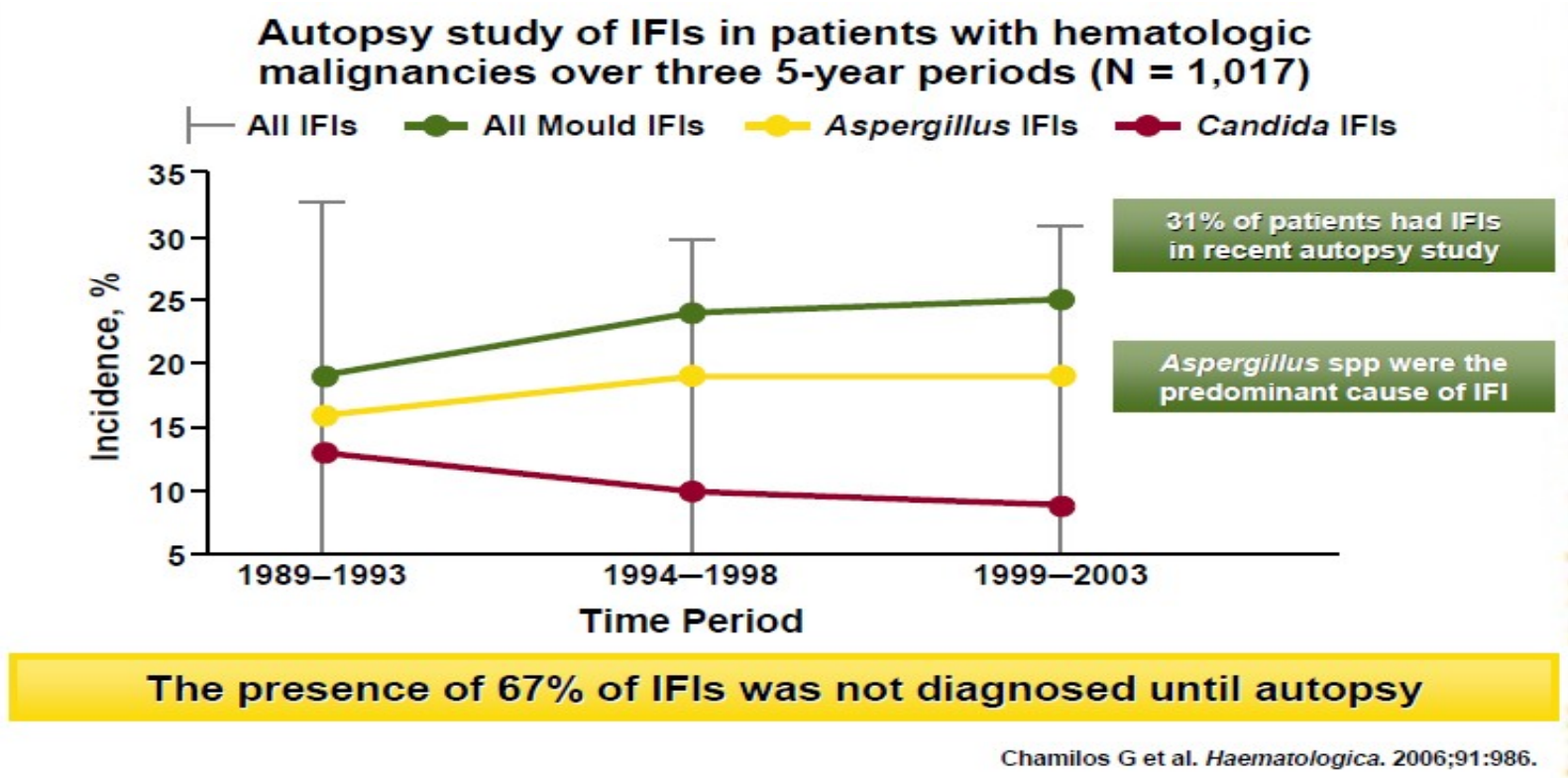
The epidemiological characteristics of IFIs in leukemia patients continue to evolve



Pie charts showing the evolving epidemiology of invasive fungal infections by their prevalence in autopsies of patients with leukemia at M. D. Anderson Cancer Center, Houston, Texas

Leventakos K etal. Clinical Infectious Diseases 2010; 50:405–15

Increase Prevalence of *Aspergillus* in High-risk Patients Over-time



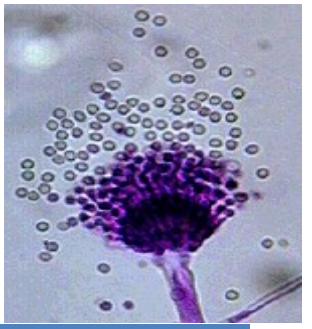
- A single-center, retrospective autopsy study from 1989 through December 2003
- In this study, the prevalence of *Aspergillus* remained higher than *Candida* over time
- In the most recent time period of the study (1999–2003):
  - IFIs were identified in 31% (82/268) of autopsies
  - Only 33% (27/82) of IFIs were diagnosed prior to death
  - 73% (60/82) of IFIs contributed to the cause of death

Chamilos et al. Haematologica. 2006;91:986–989.

Burden of IFI – Indian data

Studies	Incidence
Sharma SK et al. JIDC. 2013 (AIIMS)	**30.3% (n=776)**
Bothra M et al. IJP. 2013 (AIIMS)	14.2% (n=155)
Bakshi S et al. PHO. 2008 (AIIMS)	10% (n=222)
Rajendranath R et al. IJC. 2014 (Adyar)	15.7% (n=115)

Incidence of Invasive Mould infections



Host factors	Incidence (1990s)	Incidence (2000-2015)
Allo BMT	5-10%[1,2]	5-10%[4,5,6]
Auto BMT	0-5%[1,2]	<2%[4,6]
Chemo induced cytopenias	Upto 70%[3]	AML – 11-18%[7,8] ALL - -10%[9]

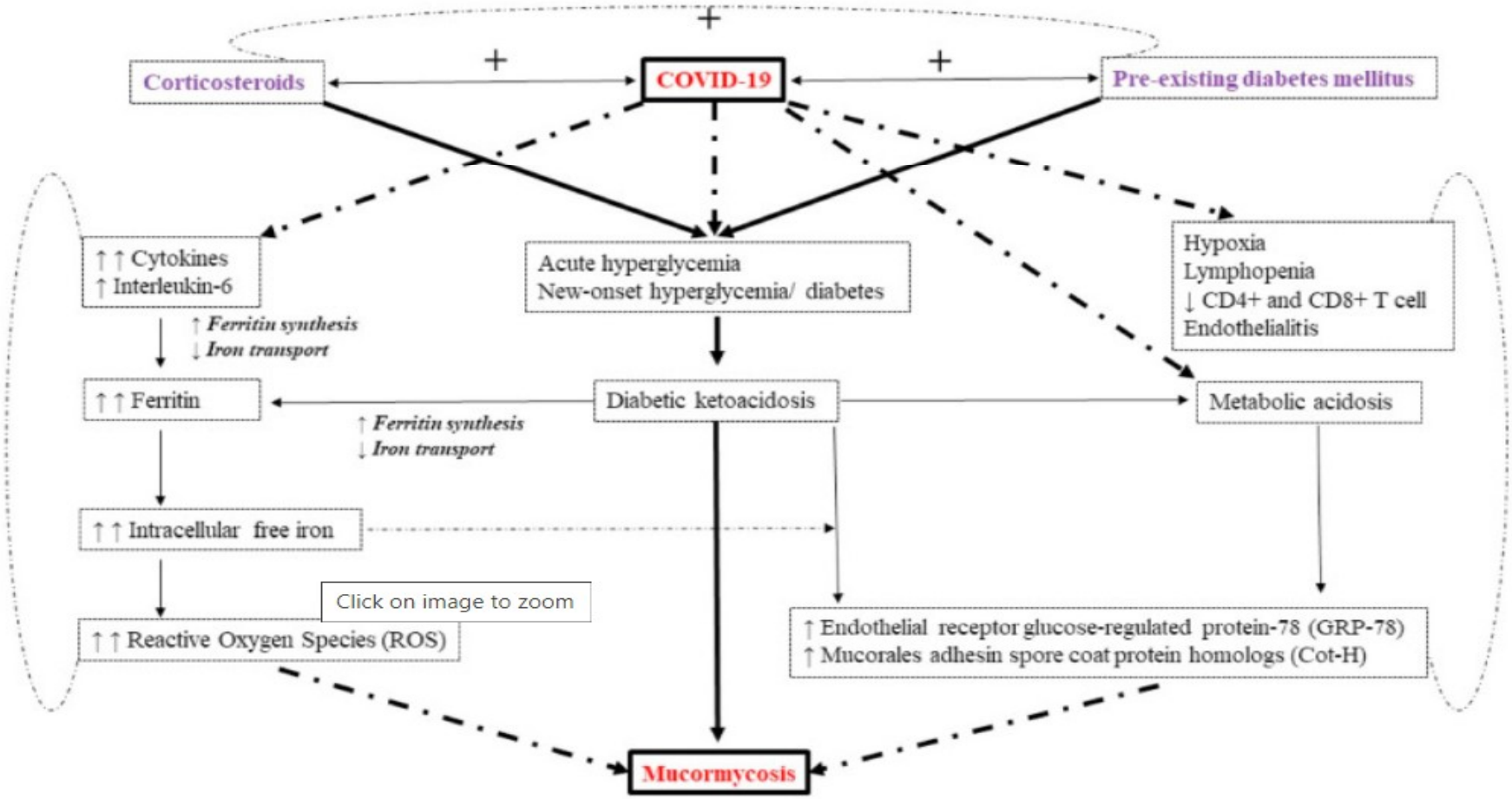
Mortality rate without Rx – 100%[4]

Mortality rate with Rx – Aspergillosis – 40%[10]

Mucorales – 70-80%[4,11]

1. McWhinney PHM, Kibbler CC, Hamon MD, et al. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. Clin Infect Dis 1993; 17: 397-404.
2. Iwen PC, Reed EC, Armitage JO, et al. Nosocomial invasive aspergillosis in lymphoma patients treated with bone marrow or peripheral stem cell transplants. Infect Control Hosp Epidemiol 1993; 14: 131-139.
3. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukaemia. Cancer 1984; 53:411-419.
4. Denning DW. Aspergillosis. Harrison principles of internal medicine. 18th ed, p1346
5. Kontoyiannis DP, Marr KA, Park BJ, et al. *Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. Clin Infect Dis 2010;* ***50: 1091–100***
6. Girmenia C, Raiola AM, Piciocchi A, et al. *Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant 2014;* ***20: 872–80.***
7. Nucci M, Garnica M, Gloria AB, et al. *Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. Clin Microbiol Infect 2013;* ***19: 745–51.***
8. Tang J-L, Kung H-C, Lei W-C, et al. *High incidences of invasive fungal infections in acute myeloid leukemia patients receiving induction chemotherapy without systemic antifungal prophylaxis: a prospective observational study in Taiwan. PloS One 2015;* ***10: e0128410***
9. Doan TN, Kirkpatrick CMJ, Walker P, et al. *Primary antifungal prophylaxis in adult patients with acute lymphoblastic leukaemia: a multicentre audit. J Antimicrob Chemother 2016;* ***71: 497–505.***
10. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. *Clin Microbiol Infect 2016;* ***22: 811.e1–811.e8.***
11. Lortholary O, Gangneux J-P, Sitbon K, et al. *Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). Clin Microbiol Infect 2011;* ***17: 1882–89.***

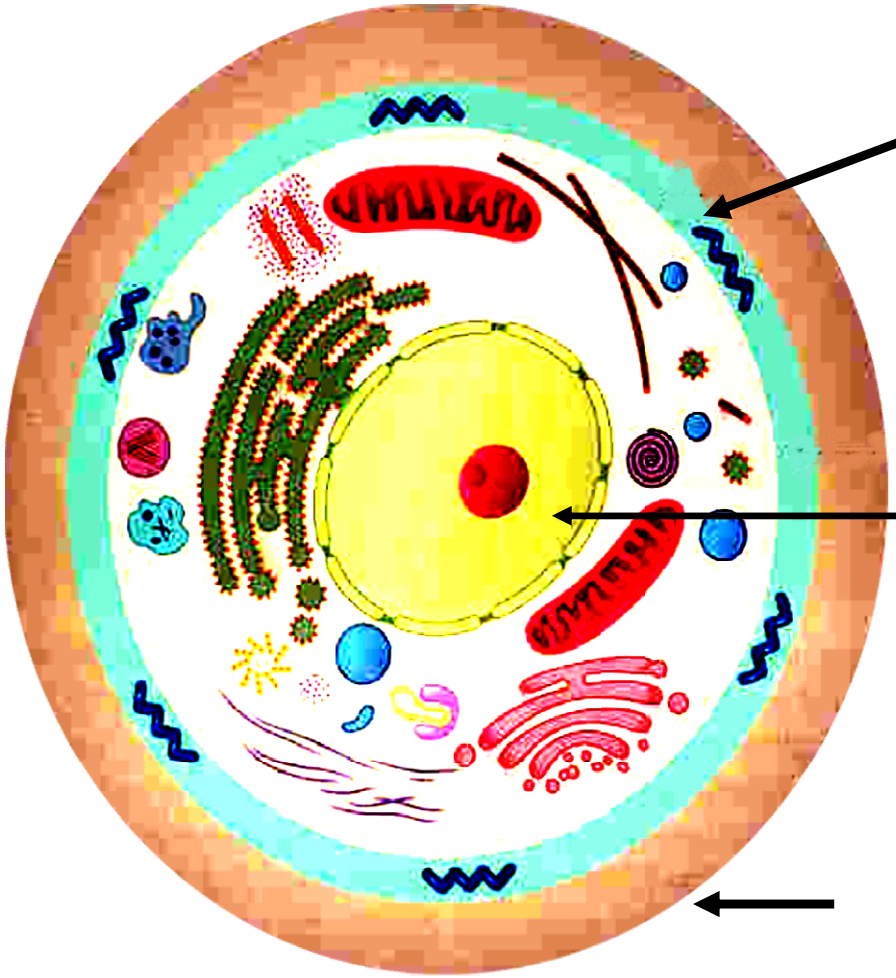
postulated mechanism of increased propensity of having mucormycosis infection in COVID-19 patients



Diabetes Metab Syndr. 2021 May 21

Antifungal Drugs

What are the targets for antifungal therapy?



Cell membrane

Fungi use principally ergosterol instead of cholesterol

DNA Synthesis

Some compounds may be selectively activated by fungi, arresting DNA synthesis.

Cell Wall

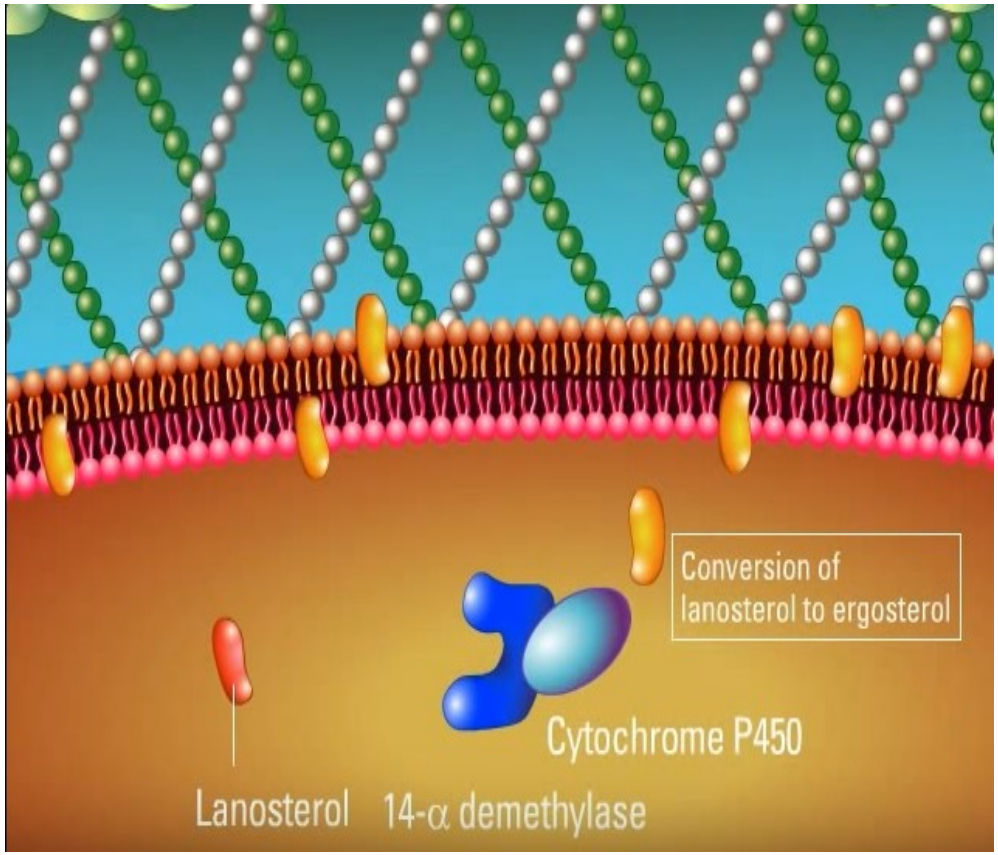
Unlike mammalian cells, fungi have a cell wall

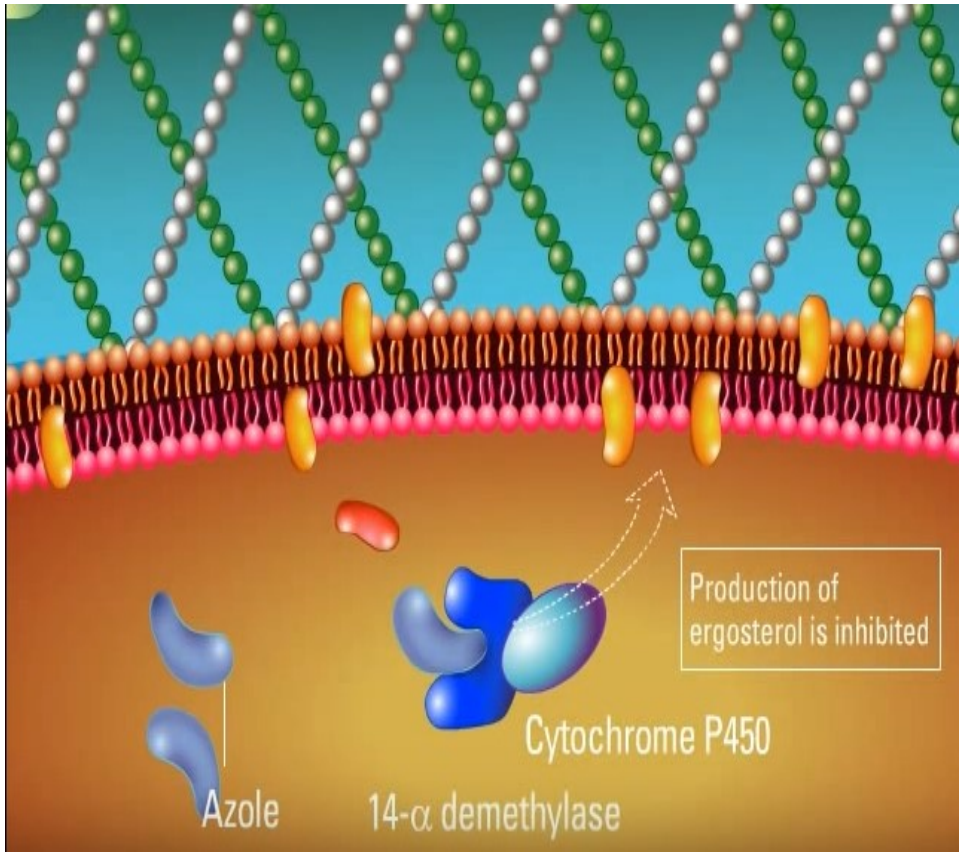
Atlas of fungal Infections, Richard Diamond Ed. 1999
Introduction to Medical Mycology. Merck and Co. 2001

Anti-fungal agents

- Polyenes
  - Amphotericin
  - Amphotericin B Cochleate
- Antimetabolites
  - Flucytosine
- Allylamines
  - Terbinafine
- Azoles
  - Itraconazole
  - Fluconazole
  - Voroconazole
  - Posaconazole
  - Isavuconazole
  - Oteseconazole
- Echinocandins:
  - Caspofungin
  - Micafungin
  - Anidulafungin
  - Rezafungin
- Antimetabolites
  - 5 Flucytosine
- Triterpenoid
  - Ibrexafungerp
- Orotomide
  - Olorofim
- Gwt1 inhibitors
  - Fosmanogepix
  - Manogepix
  - Gepinacin

Azoles – mechanism of action





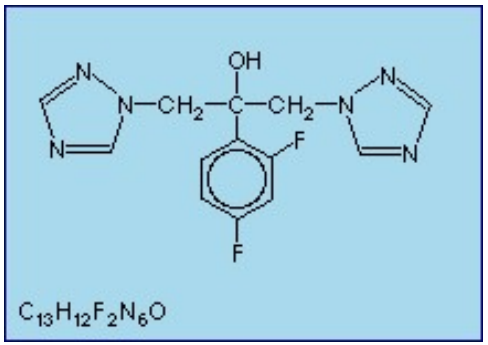
Azole Antifungals for Systemic Infections

- Ketoconazole
- Itraconazole
- Fluconazole
- Voriconazole
- Posaconazole
- Isavuconazole

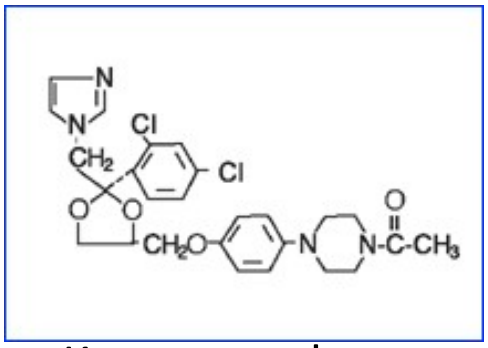
Imidazole

Triazoles

"2nd generation triazole"



Fluconazole



Ketoconazole

Drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole
Dose	Rx – 800mg D1 f/b 400mg OD Prop – 400mg OD	200 TDS – 3days f/b 200 BD	Iv – 6mg/kg BD D1 f/b 4mg/kg bd PO - >40kg – 200bd, <40 – 100bd	Susp – 200mg tds Tab / iv - 300mg iv bd – D1 f/b 300mg OD	Tab/IV- 200mg TDS for 2days F/B 200mg OD
Food inter-		Yes (1hr b4/after)	Yes (1hr b4/after)	With food (for suspn)	No
TDM		1-2	Prop – >0.5 Rx – 1-5.5	Prop – >0.7 Rx - >1	Not recm.
S/E	Gi, hepatic, QTc, skin	Hepatic tox, GI A/E, CHF, CNS depn, neuropathy	Vision, neuro, hepatic, QTc inc., photosens, fluorosis	Hepatic , QTc inc, GI, HypoK+	GI A/E, Hepatotox, headache, fatigue
Liver	Nil	nil	CP – A/B – dec maint dose 50%	nil	No dose adjustment
Renal	CrCL- <50 – 50%	nil	Avoid iv in GFR<50	Avoid iv in GFR<50	No dose adjustment

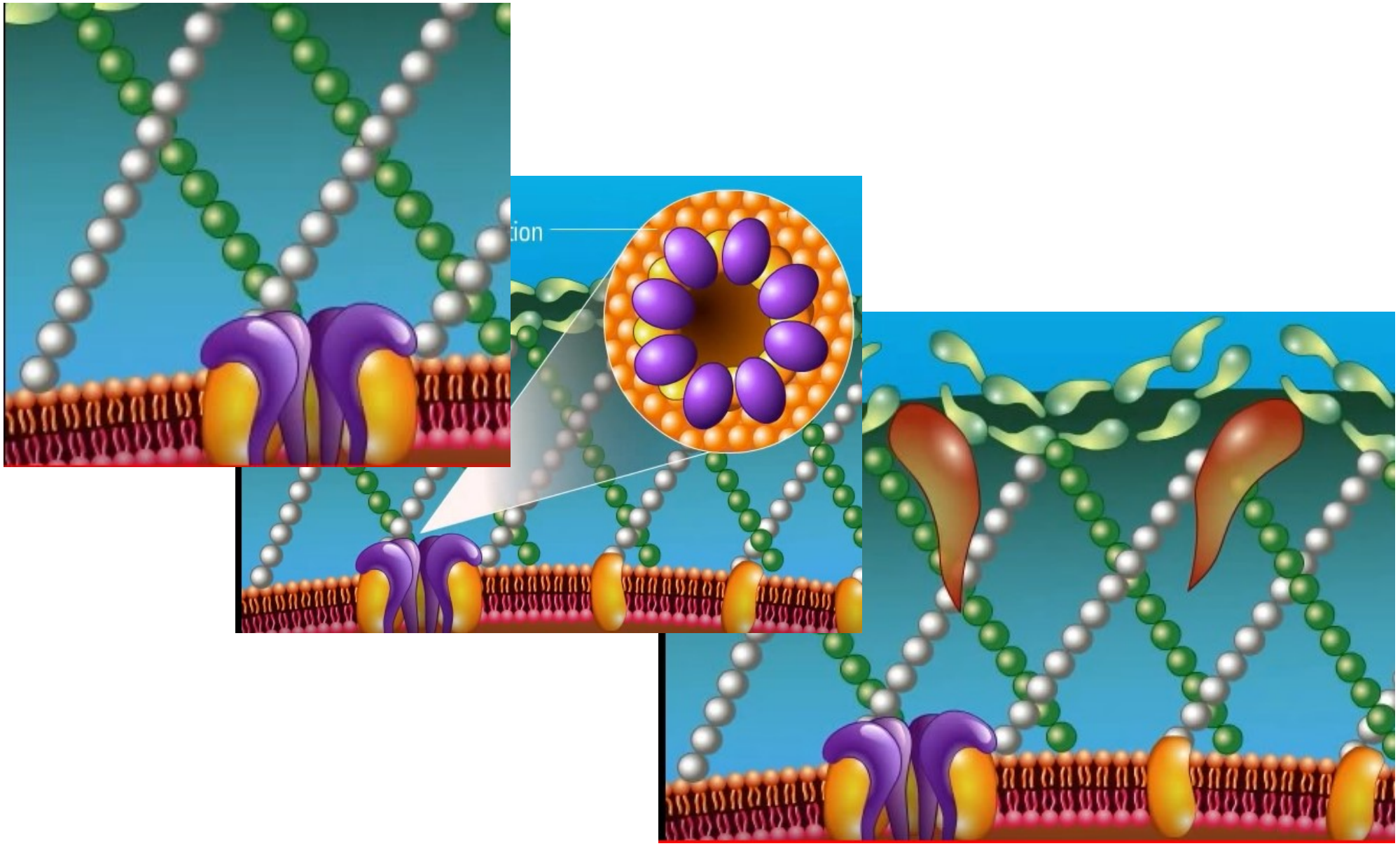
Isavuconazole (Crezemba)

- FDA approved in march 2015 for Rx of IA and IM
- Dose – 200mg TDS for 6 doses f/b 200mg OD

Select Aspects of Azole Pharmacology

Feature	Isavuconazole	Posaconazole	Voriconazole
IV and oral	Yes	Yes	Yes
IV contains cyclodextrin	No	Yes	Yes
Effect on QT interval	Shortens	Prolongs	Prolongs

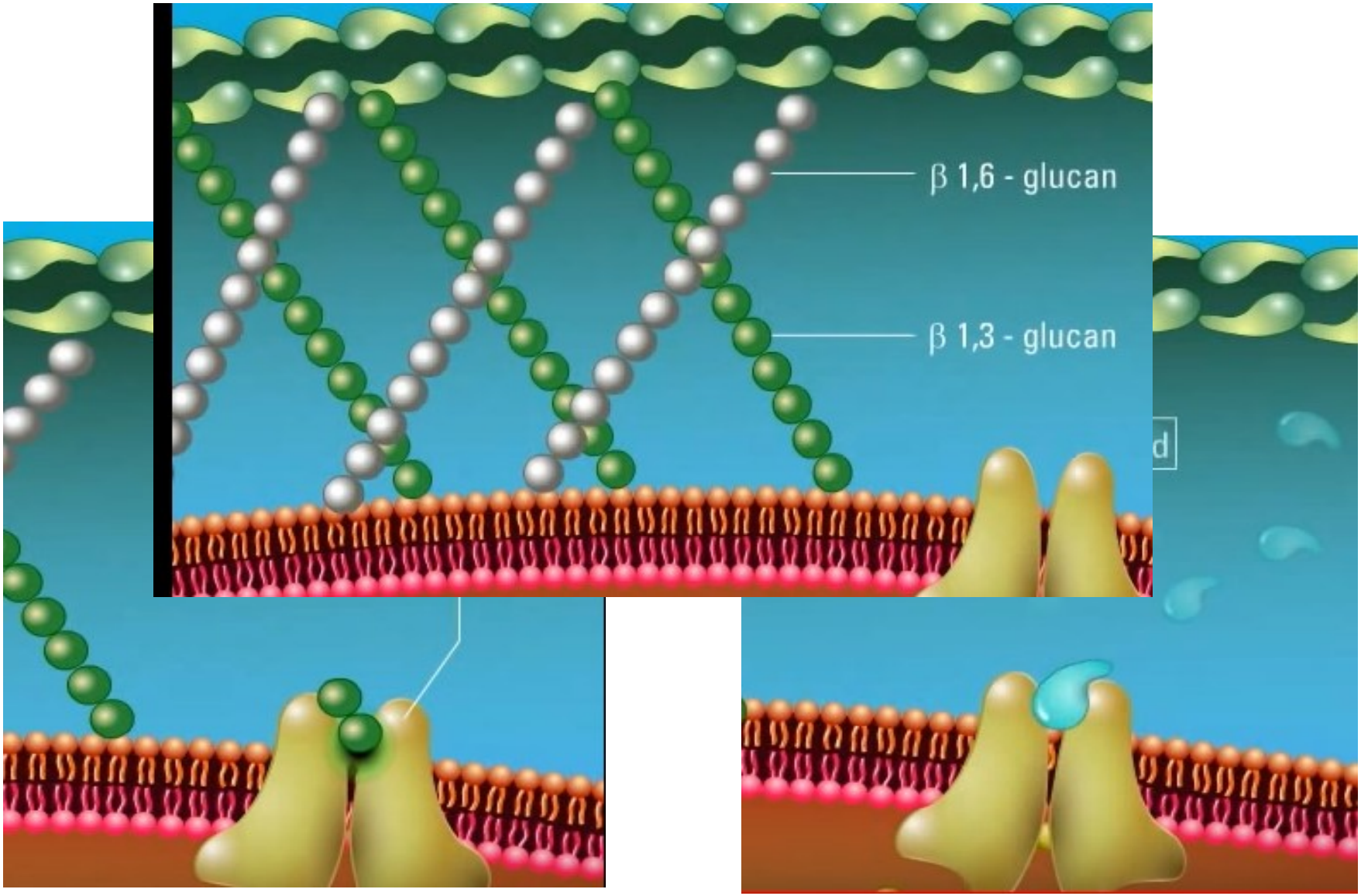
Ampho – B – Polyene - mechanism



Amphotericin B (AmB)

- **FORMULATIONS**
  - Amphotericin B Deoxy cholate (ABDC)
  - Inj Amphotericin B colloid dispersion (ABCD)
  - Inj Amphotericin B lipid complex (ABLC)
  - Inj Liposomal Amphotericin B (L-AmB-S)
- Ophthalmic, CNS, pulmonary and disseminated disease require higher doses.
- Appropriate dose & adequate hydration - as higher doses lead to significant nephrotoxicity.

Echinocandins – mechanism



Echinocandins

Drug	*Indication*	*Dose*	*Duration*
Caspofungin[16]	Esophageal candidiasis	50 mg IV daily	Mean duration in trials 9 days. Range = 7-21 days
	Candidemia and invasive candidiasis	50 mg IV daily	Continued till 14 days after last positive culture
	Febrile neutropenia	70mg IV loading dose on day 1, followed by 50 mg IV daily	Continued till resolution of neutropenia. If fungal infection occurs, then minimum 14 days. To be continued for at least 7 days after symptoms resolve.
	Invasive Aspergillosis	70mg IV loading dose on day 1, followed by 50 mg IV daily	Based on severity of the underlying disease.
Micafungin[17]	Esophageal candidiasis	150 mg IV daily	Mean duration in patients treated successfully = 15 days. Range = 10-30 days
	Prophylaxis of HSCT patients	50 mg IV daily	Mean duration in patients treated successfully = 19 days. Range = 6-51 days
	Candidemia, disseminated candidiasis, candida peritonitis and abscess	100 mg IV daily	Mean duration in patients treated successfully = 15 days. Range = 10-47 days
Anidulafungin[18]	Esophageal candidiasis	100 mg IV loading dose on day 1, followed by 50 mg IV daily	Minimum 14 days and for at least 7 days following resolution of symptoms
	Candidemia and invasive candidiasis	200 mg IV loading dose on day 1, followed by 100 mg IV daily	14 days after last positive culture

Antifungals – imp. concepts -

- Azoles –
- ➢ Prevent ergosterol synthesis in **cell membrane**
- ➢ **Fungistatic** as removal of drug allows regrowth of cell (except voric for aspergillus)
- Polyenes –
- ➢ Attach to ergosterol in **cell membrane** – create pores – cytoplasm with imp nutrients leak out – cell death. Hence , its **fungicidal**
- Echinocandins –
- ➢ Prevent interaction between regulatory and catalytic subunits of b-glucan. So, less b-glucan is formed for **cell wall**.
- ➢ **Cidal for yeasts, but static for moulds**
- ➢ Drug concentrated only on tips of extending hyphae with less effect on remaining less metabolically active fungus

❖ Combination – polyene + azole is fungistatic as ergosterol for polyene action is depleted by azole.

❖ Can use cell wall active (echinocandin) with cell memb active (polyene / azole)

Hoffman R. Hematology Basic principles and practice. 6th edition. Part VIII. Clinical approach to immunocompromised host. Chap 88.p.1386

ECIL-6 recommendations for initial first-line treatment of candidemia

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II
Catheter removal[f]	A II	B II

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017 Volume 102(3):433-444

IDSA 2016 Recommendations for Invasisive Aspergillosis

Condition	Primary therapy	Secondary therapy	Comments
Saprophytic or colonizing syndromes of *Aspergillus*			
Aspergilloma	No therapy or surgical resection	Itraconazole or voriconazole; similar to IPA	The role of medical therapy in the treatment of aspergilloma is uncertain; penetration into preexisting cavities may be minimal for AmB
Chronic cavitary pulmonary aspergillosis	Similar to IPA	Similar to IPA	Innate immune defects demonstrated in most of these patients; long-term therapy may be needed; surgical resection may lead to significant complications; anecdotal response to IFN-γ. Tranexamic acid may be helpful in management of hemoptysis
Allergic syndromes of *Aspergillosis*			
ABPA	Itraconazole	Oral voriconazole (200 mg PO every 12 h) or posaconazole (dosage depends on formulation)	Corticosteroids are a cornerstone of therapy for exacerbations; itraconazole has a demonstrable corticosteroid-sparing effect
Allergic rhinosinusitis caused by *Aspergillus*	Polypectomy and sinus washout with intranasal corticosteroids	Antifungal therapy reserved for refractory or relapsing cases	

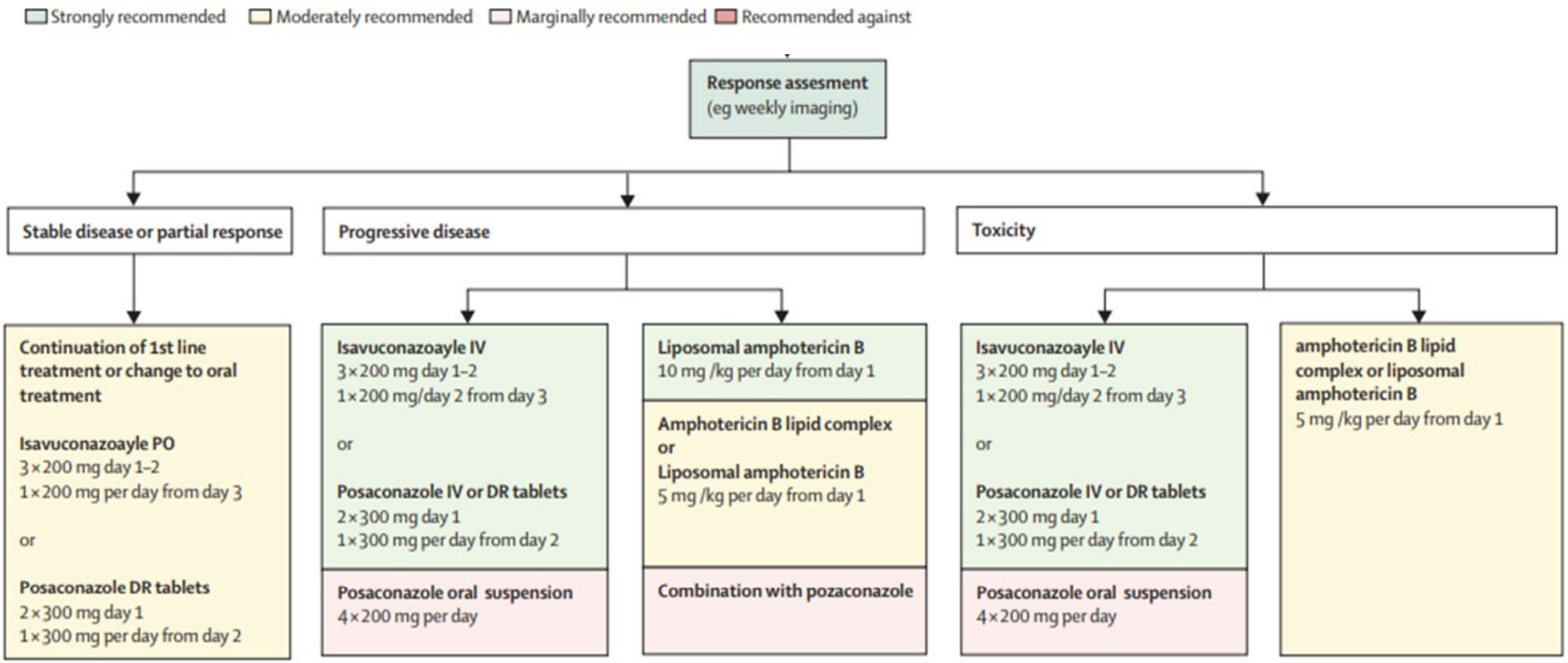
Clinical Infectious Diseases 2016;63(4):e1–60. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

ECIL-6 recommendations for initial first-line treatment of invasive aspergillosis

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017 Volume 102(3):433-444

Global Guideline for Management of Mucormycosis



Lancet Infect Dis 2019. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium

Recommendations on first-line antifungal monotherapy for mucormycosis

	Intention	Intervention	SOR	QOE	Reference
Any	To cure and to increase survival rates	Amphotericin B, any formulation, escalation to full dose over days	D	IIu	Chamilos[1] (N=70, give full daily dose from day 1)
Any	To cure and to increase survival rates	Amphotericin B, liposomal, 5–10 mg/kg per day	A	IIu	Gleissner[144] (N=16, haematology); Pagano[109] (N=5); Cornely[106] (N=4); Pagano[105] (N=44); Rüping[67] (N=21); Shoham[50] (N=28); Skiada[17] (N=130); Lanternier[104] (N=34, 18 haematology, six diabetic); Kyvernitakis[108] (N=41); Stanzani[107] (N=97, increased renal toxicity with cyclosporine)
CNS involvement	To cure	Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days	A	III	Ibrahim[112] (Animal); Lanternier[104] (N=9)
SOT adults	To cure	Amphotericin B, lipid formulation; dose not given	A	IIh	Singh[145] (N=25); Sun[146] (N=14); Lanternier[147] (N=3)
SOT adults	To cure	Amphotericin B, lipid complex; 10 mg/kg per day	A	III	Forrest[114] (N=6, 3 of 6 died)
Any, without CNS involvement	To cure	Amphotericin B, lipid complex; 5 mg/kg per day	B	IIu	Larkin[113] (N=10); Ibrahim[112] (animal); Skiada[17] (N=7)
Haematological malignancy	To cure	Amphotericin B, liposomal; 1–<5 mg/kg per day ± surgery	C	III	Nosari[110] (N=13, 8 of 13 treated, 5/8 died); Li[148] (N=7, 2 of 7 died)
Any	To cure	Isavuconazole PO or IV; 3 × 200 mg day 1–2, 1 × 200 mg/d from day 3	B	IIh	Marty[49] (N=21, 11 haematology, 4 diabetes, overall mortality comparable to amphotericin B formulations)
Any	To cure	Posaconazole DR tablet or intravenously 2 × 300 mg day 1, 1 × 300 mg from day 2	B	IItu	Duarte;[122] Maertens;[124] Cornely;[123] Cornely[125] (higher trough levels than oral suspension, intravenous bridging when oral dosing not feasible)
Any	To cure	Posaconazole oral suspension; 4 × 200 mg/day or 2 × 400 mg/day	C	IIu	Rüping[67] (N–8); Skiada[17] (N–17); Dannaoui[149] (animal, emphasises preference of amphotericin B, liposomal)
Any	To cure	Amphotericin B, deoxycholate, any dose (if alternative therapy available)	D	IIt	Walsh[116] (renal toxicity); Pagano[109] (N=9); Roden[11] (N=532); Ullmann[115] (renal toxicity); Chakrabarti[66] (N=10); Skiada1[17] (N=21)
Orbital mucormycosis	To cure	Retrobulbar injection of amphotericin B deoxycholate in addition to systemic therapy	D	III	Hirabayashi[50] (N=1, post-injection inflammatory response, risk for acute compartment syndrome)

Lancet Infect Dis 2019. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium

ECIL-6 recommendations for initial first-line treatment of mucormycosis

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017 Volume 102(3):433-444

ESMID and ECMM recommendations on targeted first-line treatment of mucormycosis in adult patients

Population	Intention	Intervention	SoR	QoE
Any	To increase survival rates	Surgical debridement	A	IIu
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥5 mg/kg[a]	A	IIu
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days[a]	A	II
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg[a]	B	IIu
Any	To cure	Posaconazole 4 × 200 mg/day or 2 × 400 mg/day[a]	B	IIu
Any	To cure	Lipid-based amphotericin plus caspofungin[a]	C	III
Any	To cure	Amphotericin B, deoxycholate, any dose[a]	D	I

CNS, central nervous system; QoE, quality of evidence;.
[a]Treatment duration is determined on a case-by-case basis and depends, for example, on extent of surgery and organs involved.

European Society of Clinical Microbiology and Infectious Diseases (ESMID) and the European Confederation of Medical Mycology (ECMM) joint clinical guidelines for the diagnosis and management of mucormycosis 2013

Clinical Microbiology and Infection, 2014

Our practice

Induction

1. Ampho B daily for 2-4wks
2. Ideally insert two cannulae separately for
   - Ampho tericin
   - Fluids/injections
3. 500-1000 ml of NS to be given prior to Amphotericin

Salvage therapy

1. Isavuconazole for patients with renal dysfunction
2. Posaconazole as second line

Common side effects **at our site**

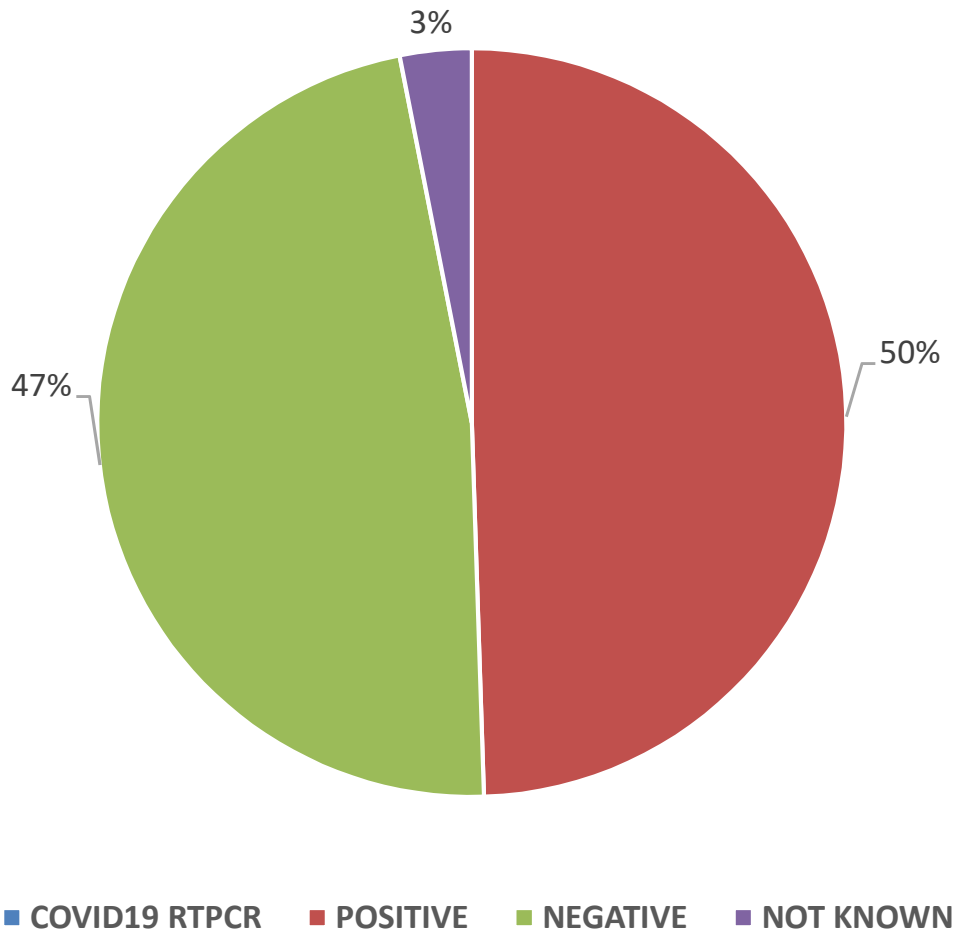
1. Flu like symptoms **(Most common**)
2. Deranged renal function -5.2%
3. Hypokalemia -3.1%

	Name of the drug	Date	Starting time	Ending time	Dose given	Cumulative dose	Serum Electrolytes Na/K/Cl/Mg	Urea/ Creatinine	Premedication	Adverse effects
Day1										
Day2										
…..										

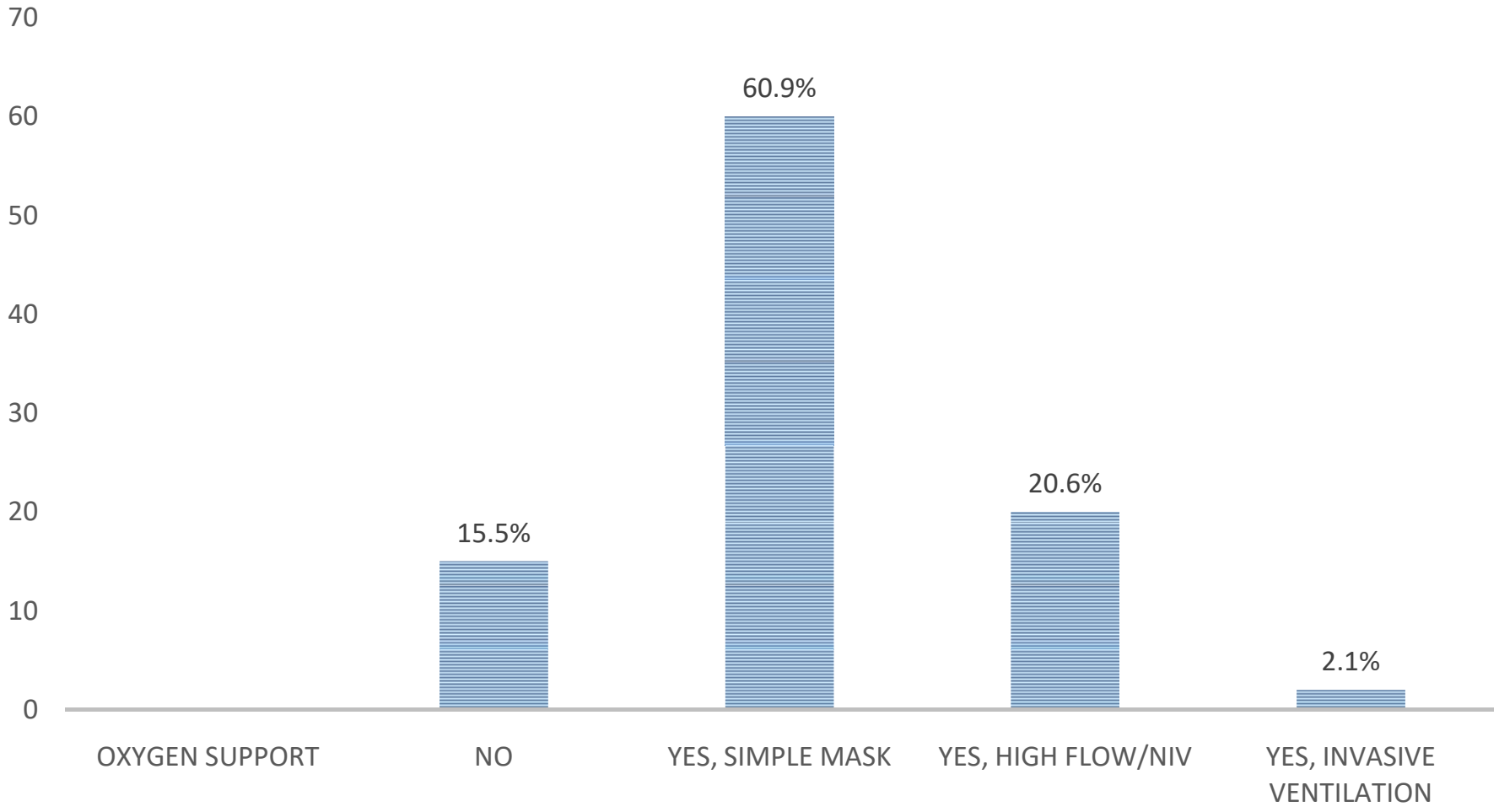
Maintenance

- Tab/Suspension Posaconazole
- Minimum of 6 to 12 weeks depending on extent of disease, site of disease and response

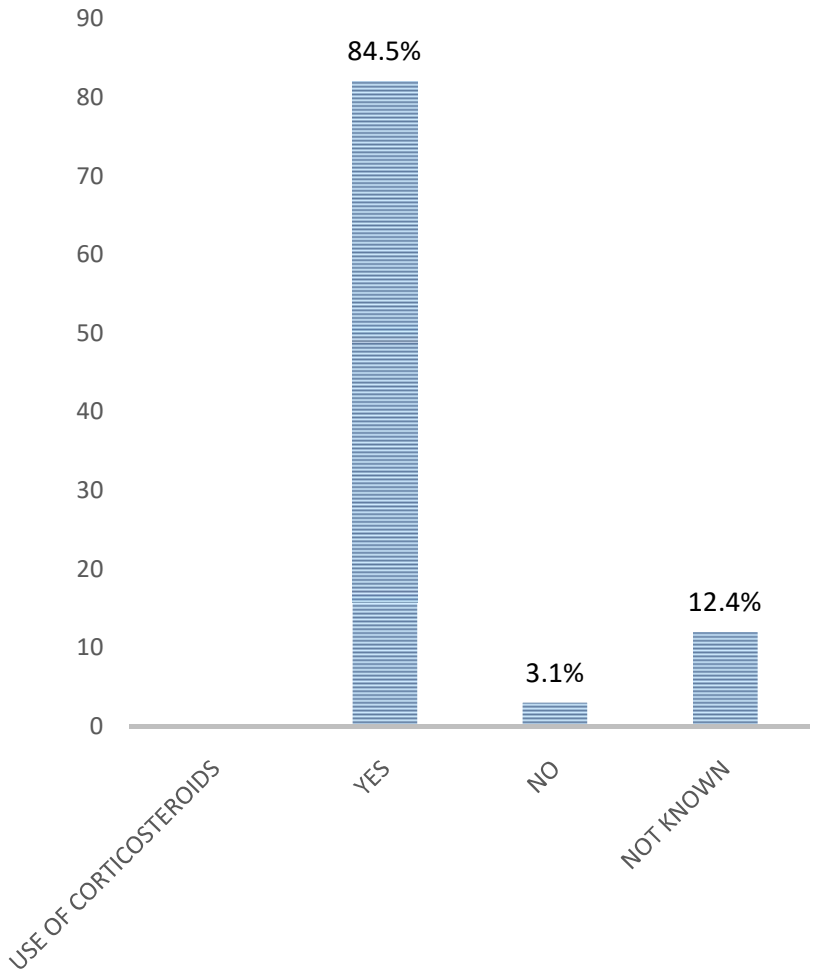
COVID19 RTPCR



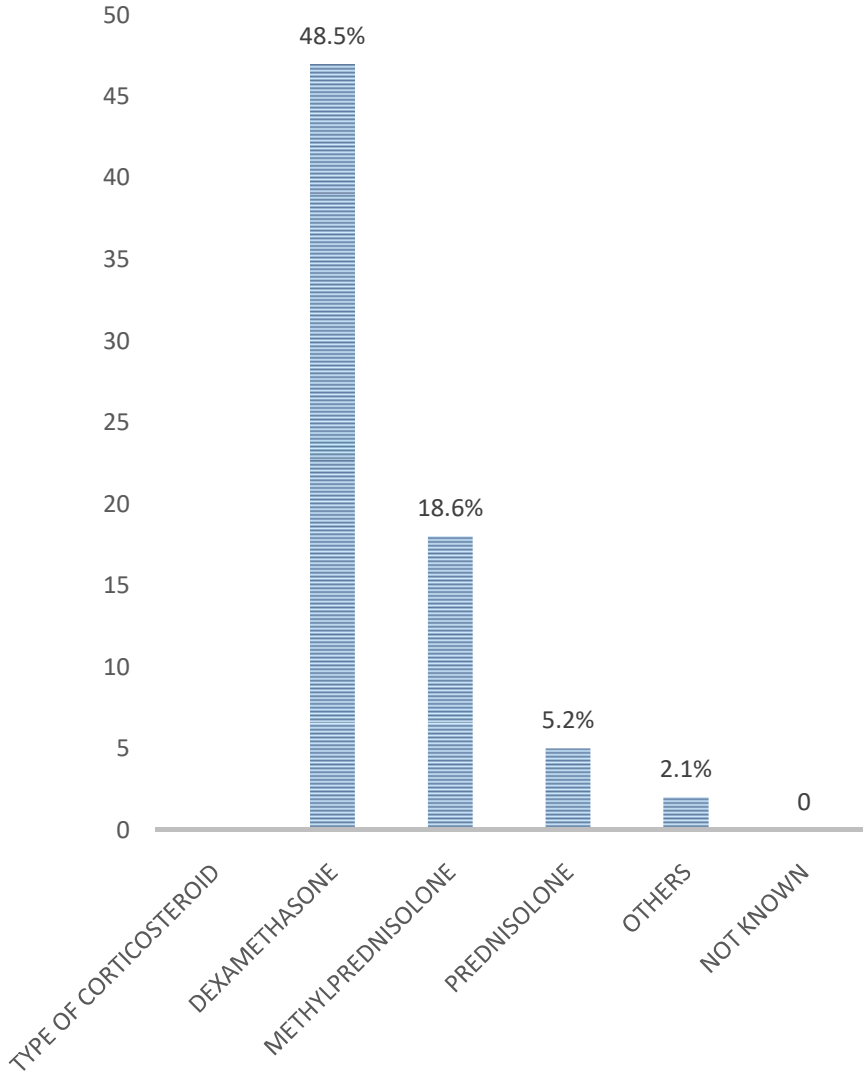
OXYGEN SUPPORT



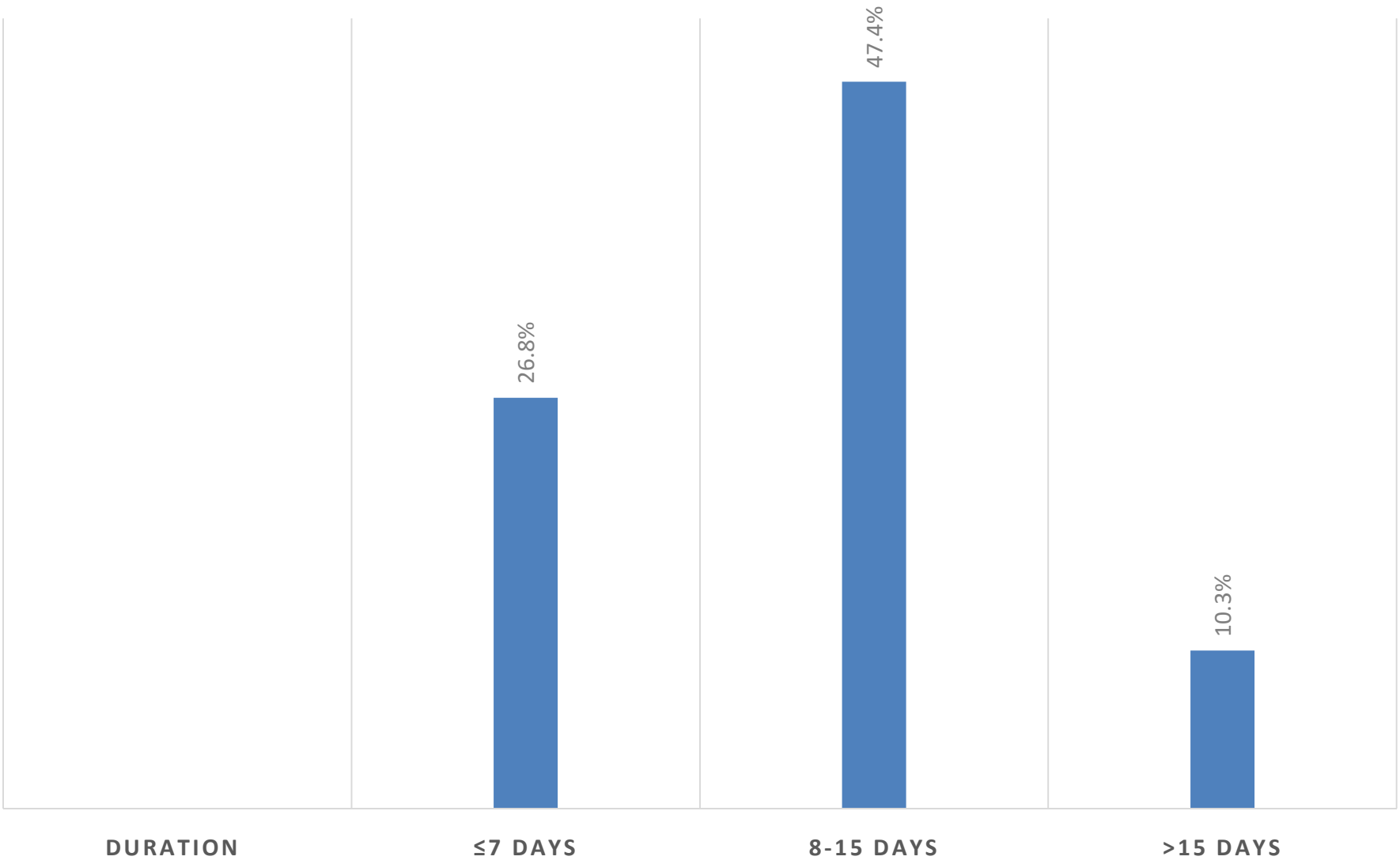
USE OF CORTICOSTEROIDS



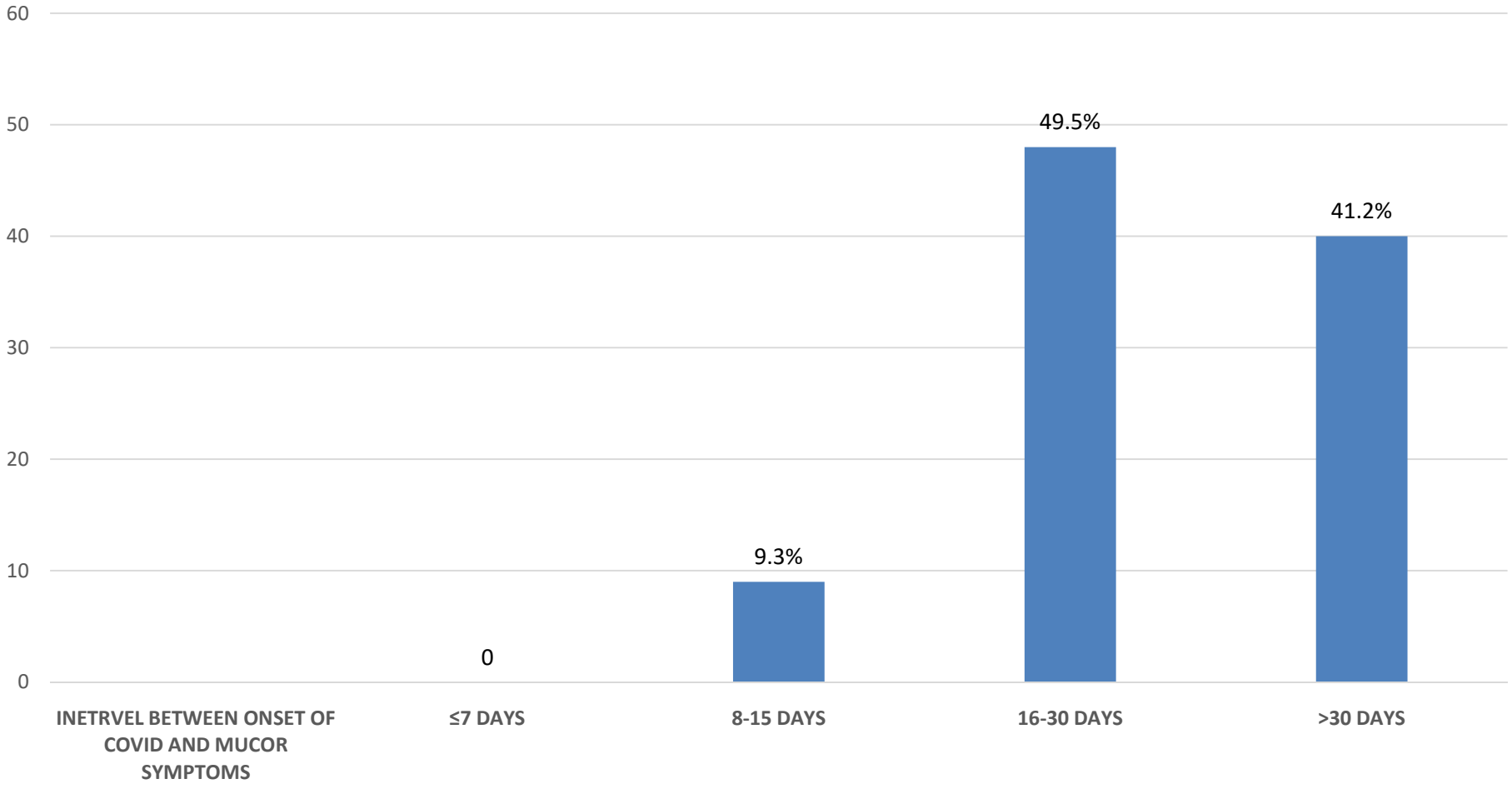
TYPES OF CORTICOSTEROIDS



DURATION OF USE OF CORTICOSTEROIDS



INTERVAL BETWEEN ONSET OF COVID AND MUCOR SYMPTOMS



Take home messages -

- Invasive fungal infections are uncommon in immunocompetent patients
- High index of suspecion is necessary
- Early and prompt treatment is the key,
- Echinocandins are DOC for candida
- Voriconazole is DOC for IA, isavuc / lipo amB – as salvage
- Amphotericin B is first line drug for Mucor, Posa/Isavuc - as salvage

Thank you…