Updates on new Antibiotics and Antifungals

Cytopenia and infectious diseases workshop for hematology fellows

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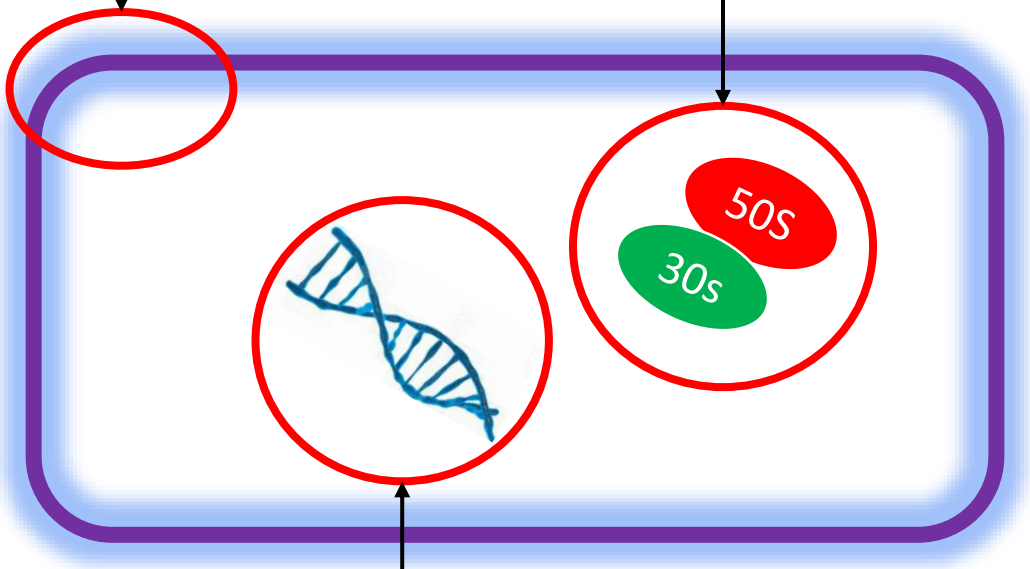
Beta lactams
Vancomycin
Daptomycin

Macrolides (50s)
Clindamycin (50s)
Linezolid (50s)
Chloramphenicol (50s)
Aminoglycosides (30s)
Tetracycline (30s)
Tigecycline (30s)



Quinolones
TMP/SMX
Nitrofurantoin
Metronidazole

Beta lactams
(inhibits cell wall synthesis)

Penicillins

Natural penicillins:
Benzathine pen, pen G

Aminopenicillins:
Amoxicillin, ampicillin

Antistaphylococcal penicillins:
Nafcillin, dicloxacillin

Antipsudomonal penicillins
Piperacillin, Ticracillin

Cephalosporins

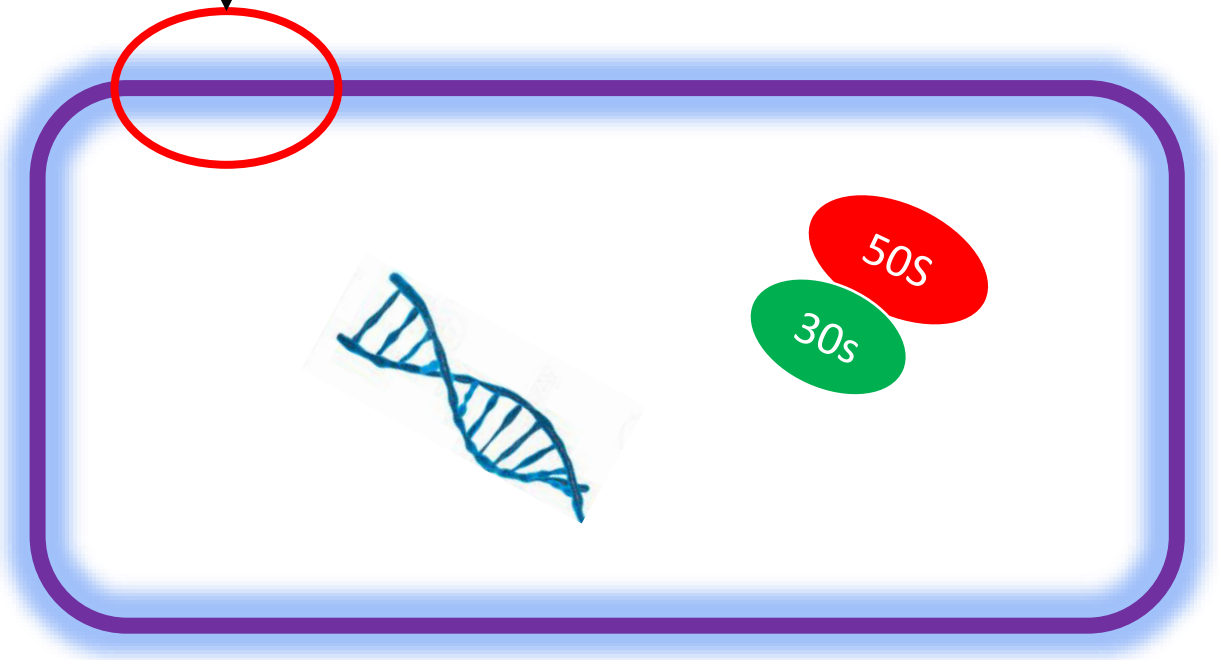
1st Generation:
Cefazolin, Cephalexin

2nd Generation: *Cefotetan*

3rd Generation: *Ceftriaxone, Cefpodoxime, Ceftazidime*

4th Generation: *Cefepem*

5th Generation: *Ceftaroline*



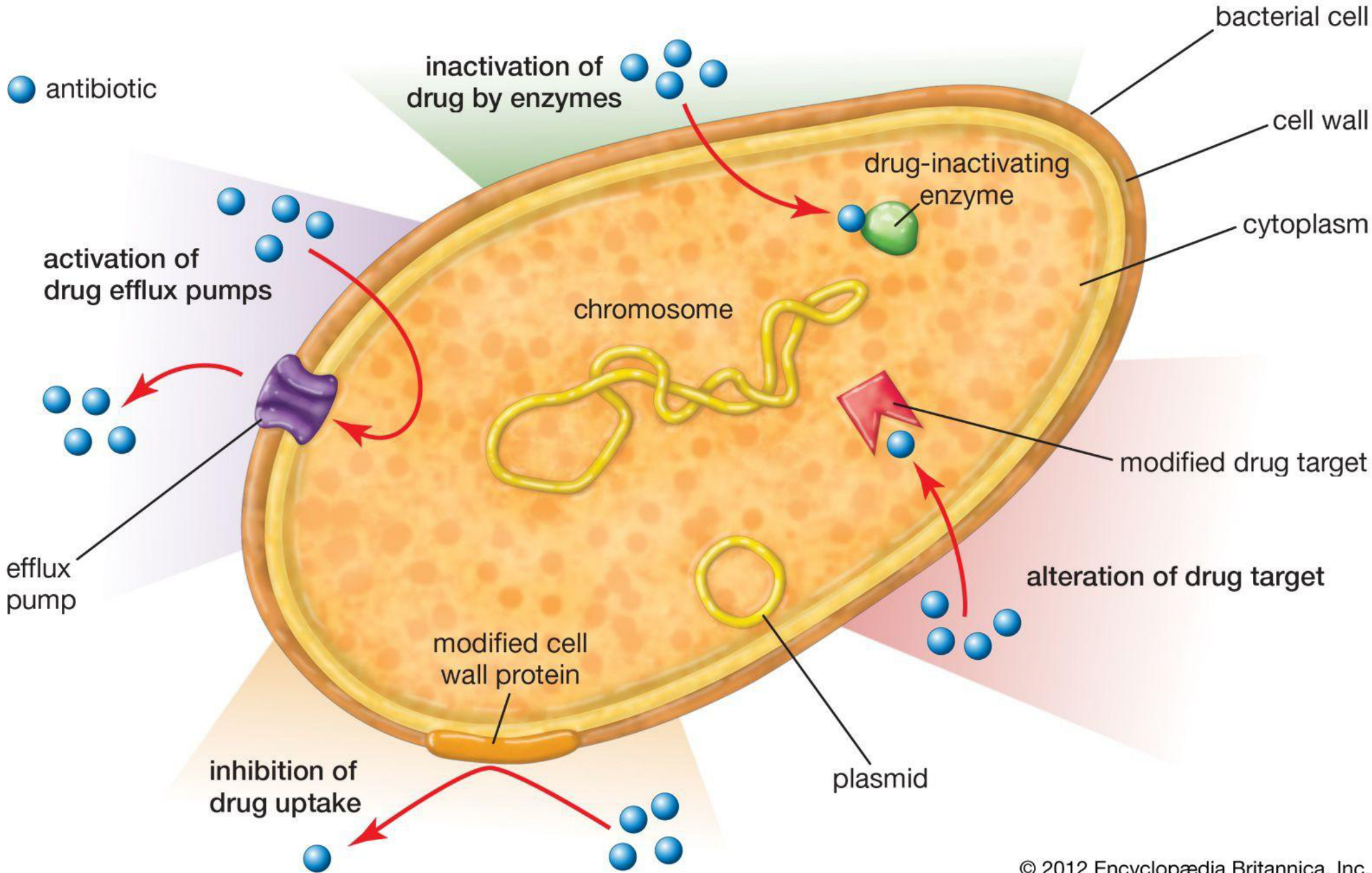
Carbapenems: *Meropenem, Imipenem, Ertapenem*

Monobactams: *Aztreonam*

Penicillin/beta lactamase inhibitor

Augmentin (Amoxicillin+clavulanic Acid)
Unasyn (Ampicillin+sulbactam)
Tazocin (Piperacillin+tazobactam)

Examples of mechanisms of antibiotic resistance



Mechanisms of resistance

TABLE 18.1 Eight Major Mechanisms of Resistance by Antimicrobial Class

	β-LACTAM	AMINO-GLYCOSIDE	CHLORAM-PHENICOL	MACROLIDE	SULFONAMIDE	TETRACYCLINE	TRIMETHOPRIM	QUINOLONE	GLYCOPEPTIDE	LINOSAMIDE; STREPTOGRAMIN	RIFAMPIN
Enzymatic inactivation	+++	+++	+++	+ (gram-negative)	–	–	–	+	–	–	–
Decreased permeability	+ (gram-negative)	+ (gram-negative)	+ (gram-negative)	++ (gram-negative)	–	+ (gram-negative)	+ (gram-negative)	+ (gram-negative)	++ (gram-negative)	+ (gram-negative)	–
Efflux	+	+	+	++	–	+++	–	+	–	–	–
Alteration of target site	++	++	–	+++	++	+ *(Helicobacter pylori)*	+++	+++	+++	+++	+++
Protection of target site		–	–	–	–	++	–	+	–	–	–
Overproduction of target	–	–	–	–	++	–	++	–	+	–	–
Bypass of inhibited process	–	–	–	–	+	–	+	–	–	–	–
Bind up antibiotic	–	–	–	–	–	–	–	–	++	–	–

TABLE 18.2 Ambler Classification of β-Lactamases

CLASS	ACTIVE SITE	ENZYME TYPE	SUBSTRATES	EXAMPLE
A	Serine	Penicillinases:		
		Broad-spectrum	Benzylpenicillin, aminopenicillins, carboxypenicillins, ureidopenicillins, narrow-spectrum cephalosporins	PC1 in *Staphylococcus aureus* TEM-1, SHV-1 in *Escherichia coli, Klebsiella pneumoniae,* other gram-negative bacteria
		Extended-spectrum (β-lactamase)	Substrates of broad-spectrum plus oxymino-β-lactams (cefotaxime, ceftazidime, ceftriaxone) and aztreonam	In Enterobacteriaceae: TEM-derived, SHV-derived, CTX-M–derived; PER-1, VEB-1, VEB-2, GES-1, GES-2, IBC-2 in *Pseudomonas aeruginosa*
		Carbapenemases	Substrates of extended-spectrum plus cephamycins and carbapenems	KPC-1, KPC-2, KPC-3 in *K. pneumoniae;* NMC/IMI, SME family
B	Metallo-β-lactamases (Zn^{2+})	Carbapenemases	Substrates of extended-spectrum plus cephamycins and carbapenems	NDM-1 in Enterobacteriaceae, IMP, VIM, GIM, SPM, SIM lineages in *P. aeruginosa, Acinetobacter* spp.
C	Serine	Cephalosporinases	Substrates of extended-spectrum plus cephamycins	AmpC-type enzymes in Enterobacteriaceae, *Acinetobacter* spp.
D	Serine	Oxacillinases:		
		Broad-spectrum	Aminopenicillins, ureidopenicillin, cloxacillin, methicillin, oxacillin, and some narrow-spectrum cephalosporins	OXA-family in *P. aeruginosa*
		Extended-spectrum	Substrates of broad-spectrum plus oxymino-β-lactams and monobactams	OXA-derived in *P. aeruginosa*
		Carbapenemases	Substrates of extended-spectrum plus cephamycins and carbapenems	OXA-derived in *Acinetobacter* spp.

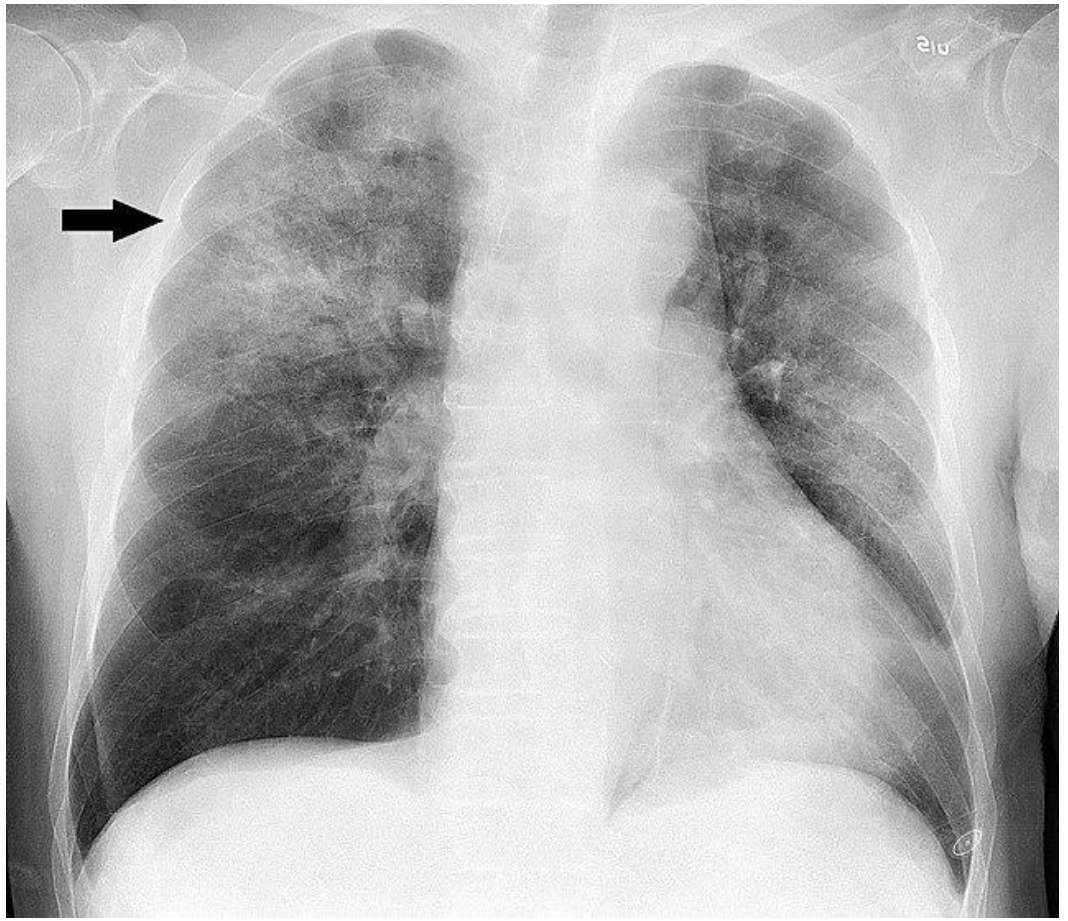
בן 85, MDS, אבחנה של acute leukemia, חום ונויטרופניה (ANC 100) לאחר אינדוקציה, קיבל טיפול בטזוצין, החום המשיך, מדדי דלקת בעליה, יציב הימודנמית. הותחל מרופנם, תחת מרופנם עדיין החום ממשיך. לציין מטוש רקטלי בקבלה – KPC (נשאות).
בזוג תרביות דם צמיחה של *klebsiella pneumonia* עמידה לטזוצין וקרבפנמים (KPC). **מה לעשות?**

- **<u>Treatment options for KPC:</u>**
- Ceftazidime-**Avibactam**
- Aztreonam-**Avibactam**
- Imipenem-**Relebactam**
- Meropenem-**Vaborbactam**
- **Cefiderocol**
- Colistin
- Tigecycline

בן 71, COPD עם ברונכאקטזיות, DLBCL רפרקטורית לטיפול, טופל בתאי-CAR-T. יומיים אחרי החזרת התאים, חום גבוה, קוצר נשימה, ועליה במדדי דלקת, לחץ דם גבולי, הותחל טיפול אמפירי במרופנם והועבר לטיפול נמרץ. בטיפול נמרץ קיבל אקטמרה. החום המשיך, דה-סטורציה, הורדם והונשם. צלום חזה:

Pseudomonas aeruginosa

Antibiotics	Susceptibility
Ceftazidime	R
Piperil	R
Pip/tazo	R
Meropenem	R
Imipenem	R
Ciprofloxacin	R



איך מתקדמים?

Treatment options for MDR *Pseudomonas aeruginosa*

- Imipenem relebactam
- Ceftazidime-**Avibactam**
- Ceftolozane-tazobactam
- **Cefiderocol**

בן 63, מושתל מח עצם מתורם זר, יום 12 לאחר ההשתלה, עדיין חום ונויטרופני לסירוגין, על מרופנם 10 ימים. ביומיים האחרונים, חום ממושך, עליה במדדי דלקת, צמיחה בלחץ הדם. תרביות דם נלקחו, מה לעשות?

Current treatment options for Stenotrophomonas

TMX-SMX

Levofloxacin

Minocycline and Tigecycline

Cefiderocol

Ceftazidime-Avibactam + Aztreonam

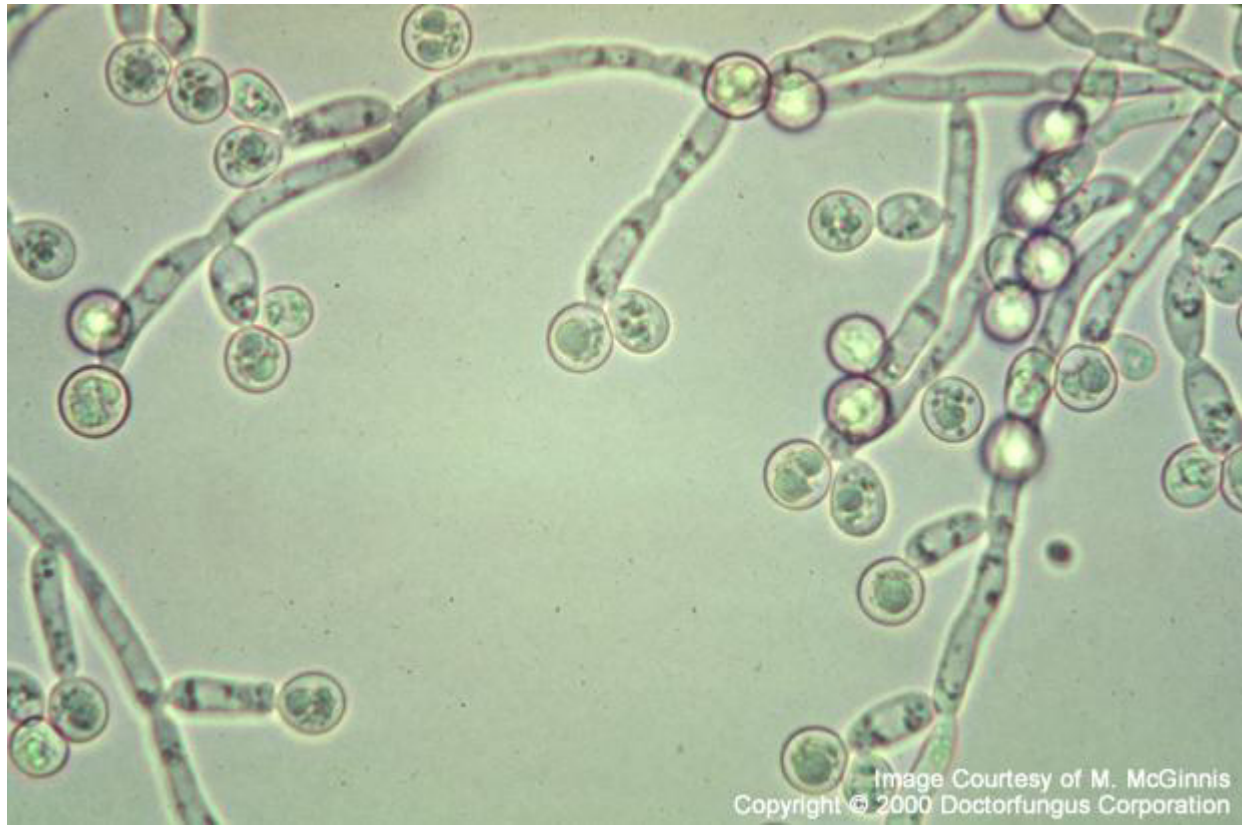
Current treatment options for CRAB

- Colistin
- Tigecycline
- Cefiderocol
- Ampicillin-sulbactam

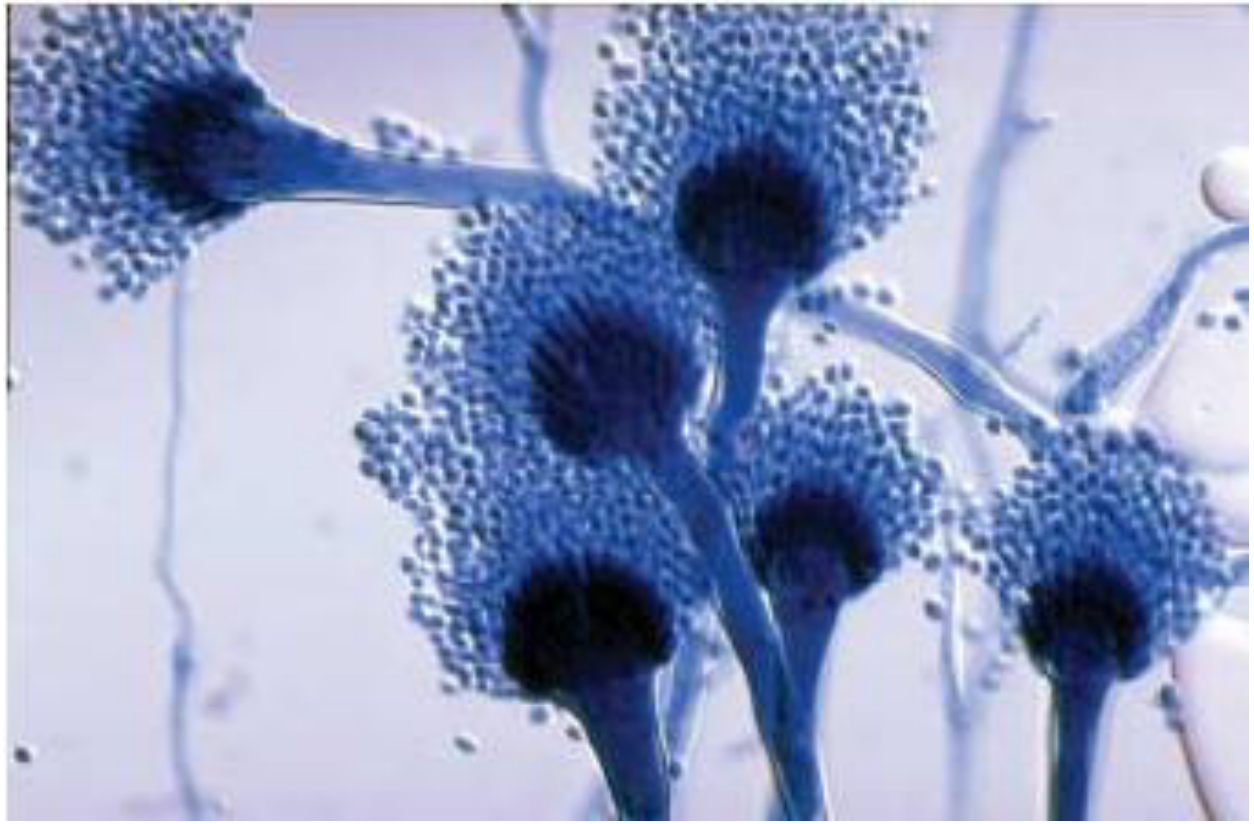
Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam[1]						
Ceftolozane-tazobactam[1]						
Eravacycline[1,2]						
Fosfomycin (intravenous)						
Imipenem-relebactam[3]						
Meropenem-vaborbactam[1]						
Plazomicin[1,4]						
Polymyxin B[1,5] or Colistin[1,5]						
Tigecycline[1,2]						

Medically important fungi

Yeasts



Molds



Dimorphic Fungi

Histoplasma, Blastomyces, Coccidioides, Paracoccidioides, Talaromyces, Sporotrix schenckii

Invasive fungal infections

- **Invasive candidiasis**
- **Invasive aspergillosis**
- **Mucormycosis**

Invasive candidiasis

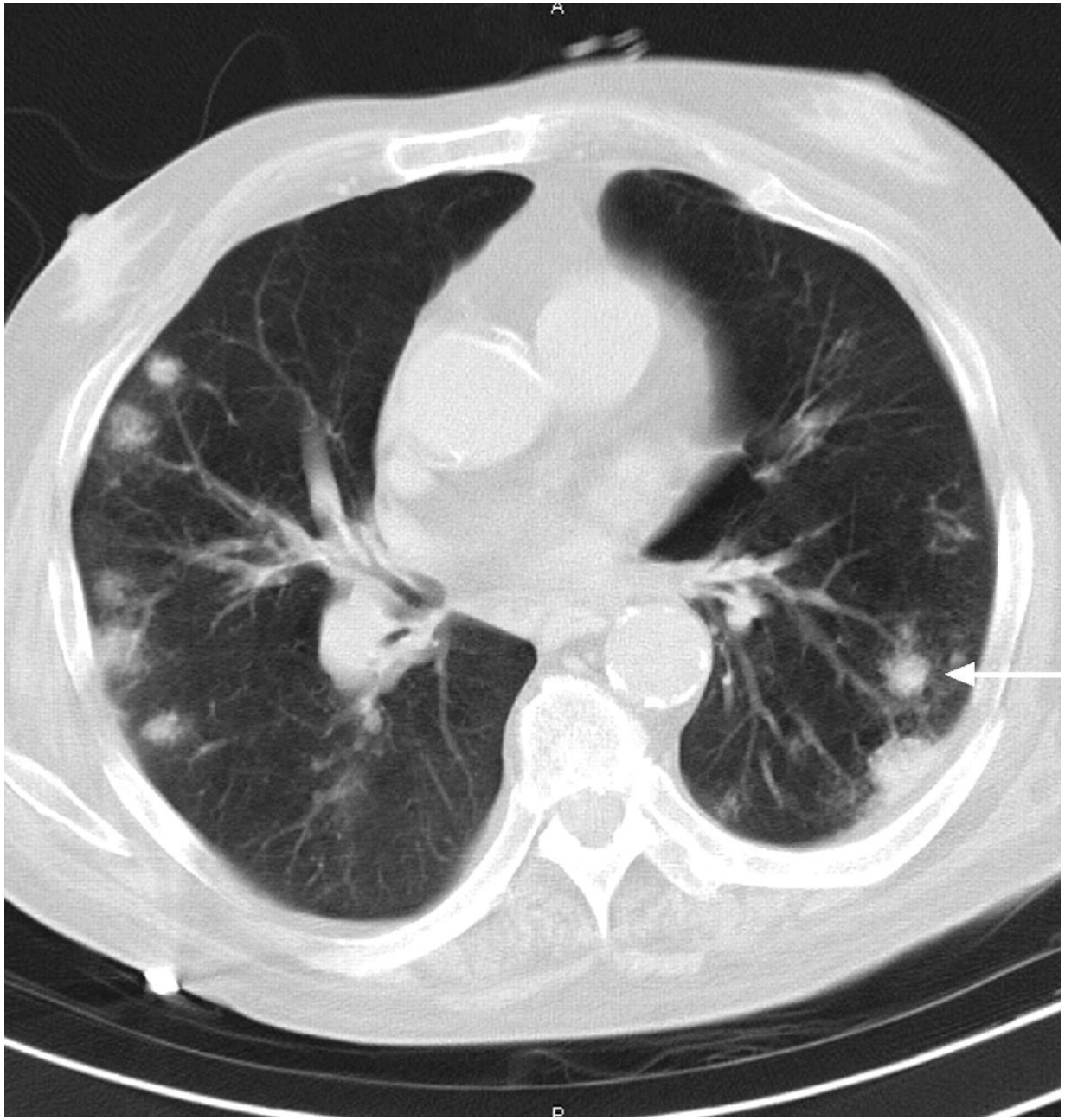
- Frequent colonizers of GI tract and skin (emerged as **nosocomial pathogens**)
- **Fourth** most frequent causes of BSI in hospitalized patients in US
- Most frequent mycotic disease in hospitalized patients
- Global incidence ~750,000 cases annually **(2-21 cases per 100,000)**
- Highest mortality rate among leading bloodstream isolates **(~40%)**
- Invasive candidiasis = deep-seated candidiasis and candidemia

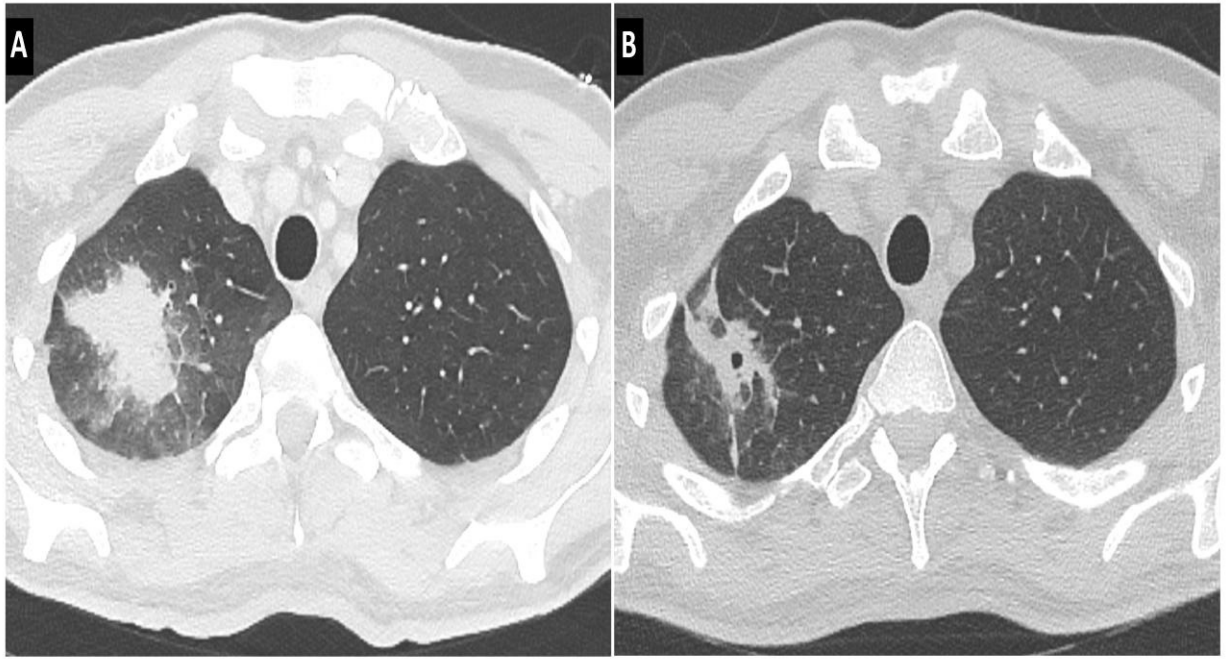
Invasive candidiasis

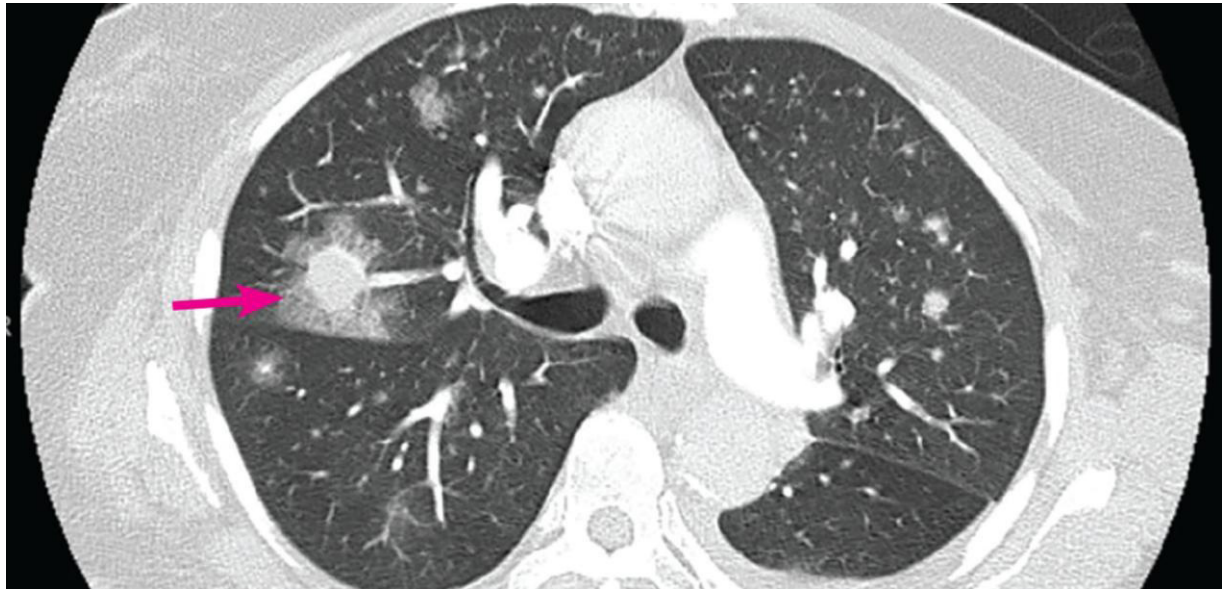
- **Risk factors:**
  - ✓Exposure to broad-spectrum antibiotics and chemotherapy,
  - ✓Major abdominal surgery
  - ✓Organ transplantation
  - ✓Prolonged stay in ICU
  - ✓Vascular catheters and prosthetic heart valves
  - ✓parenteral feeding

Invasive aspergillosis

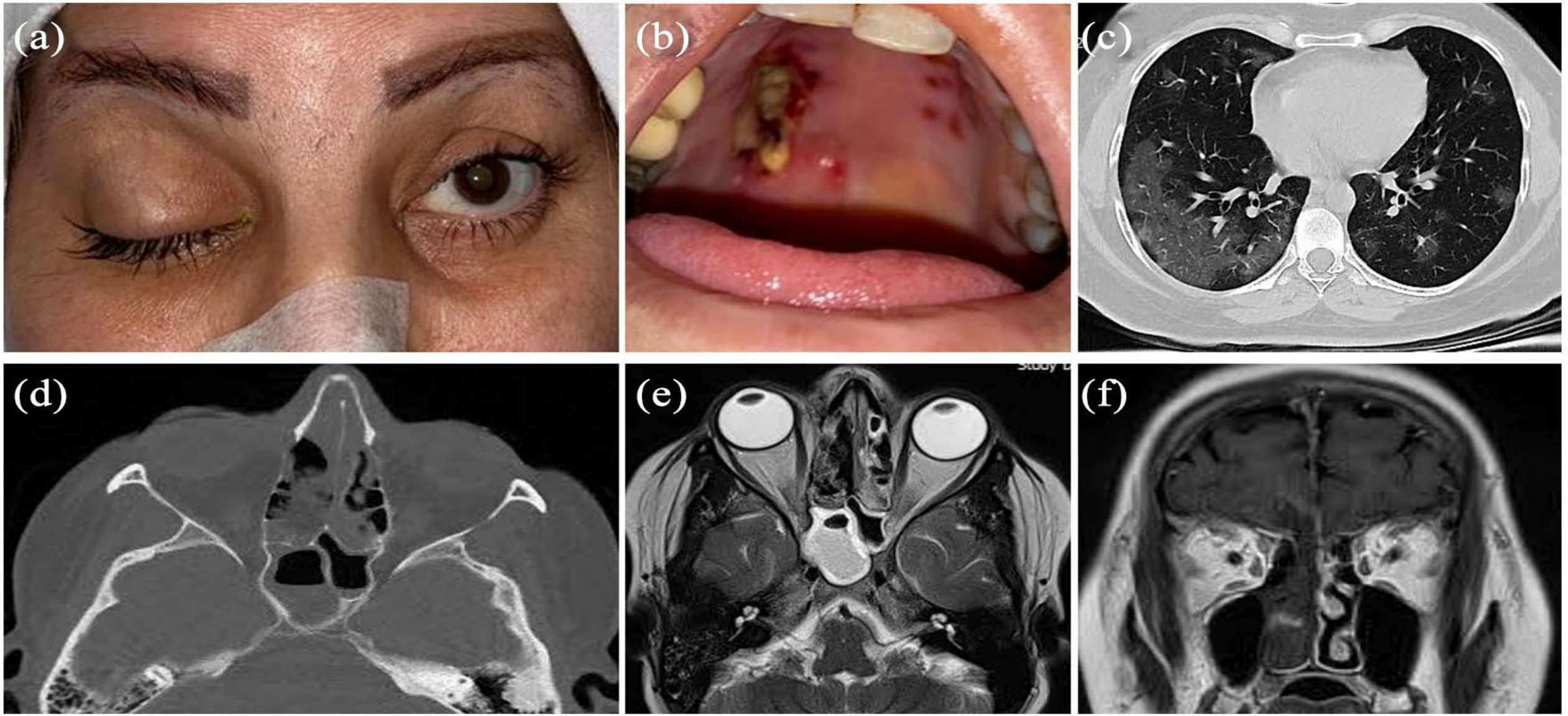
- *Aspergillus* important cause of life-threatening infection in ICH
- **At-risk population**: prolonged neutropenia, HSCT, SOT, inherited/acquired immunodeficiencies, corticosteroid
- 3 major forms of aspergillosis:
  - Invasive aspergillosis (invasive pulmonary aspergillosis, Aspergillus sinusitis, disseminated aspergillosis)
  - Chronic forms of aspergillosis
  - Allergic forms of aspergillosis




A
B



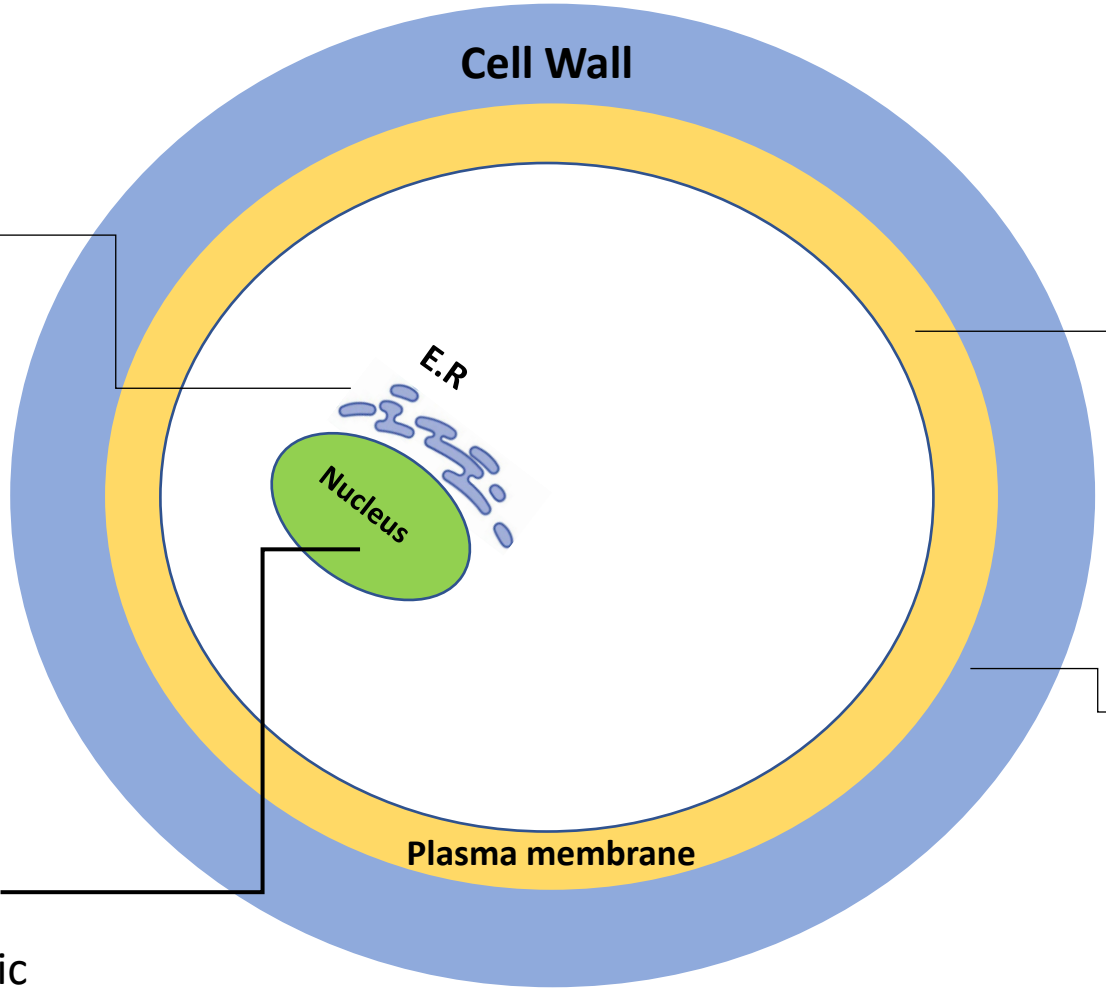
Invasive Mucormycosis



Invasive Mucormycosis

- Rapidly progressive and destructive infection
- Suspected mucormycosis requires urgent intervention
- Delayed initiation of therapy is associated with increased mortality
- Maximizing survival rates requires rapid diagnostic and therapeutic intervention

Anti-fungal drugs



Azoles
Target ergosterol biosynthesis

Polyenes
Bind to ergosterol, destroys membrane

Echinocandins
Inhibit β(1,3)-D-gulcan synthase & disrupts cell wall

Flucytosine
Inhibits nucleic acid synthesis

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Table 4. 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

d not in severely ill unstable patients, **e** not in patients with previous azole exposure, **f** if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended

Tissot, Haematologica 2017

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Table 5. ECIL-6 recommendations for first-line treatment of candidemia after species identification.

Candida species	Overall population		Hematologic patients	
C. albicans	Echinocandins[a]	A I	Echinocandins	A II
	Fluconazole[b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins[a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins[a]	A II	Echinocandins[a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins[c]	B II	Echinocandins	B III

b not in severely ill patients, **c** if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered

Tissot, Haematologica 2017

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Table 7. ECIL-6 recommendations for 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

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Tissot, Haematologica 2017

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Table 8. ECIL-6 recommendations for salvage therapy of invasive aspergillosis.

	Grade	Comments
Liposomal amphotericin B	B II	No data on voriconazole failure
Amphotericin B lipid complex	B II	No data on voriconazole failure
Caspofungin	B II	No data on voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole[a]	B II	No data on voriconazole failure
Voriconazole[a]	B II	If not used in first-line
Combination	B II	Various studies and conflicting results

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

Tissot, Haematologica 2017

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Table 9. **ECIL-6 recommendations for first-line therapy 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	

CNS: central nervous system.

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a]Both comments apply to the oral solution but may not apply to the solid oral formulation.

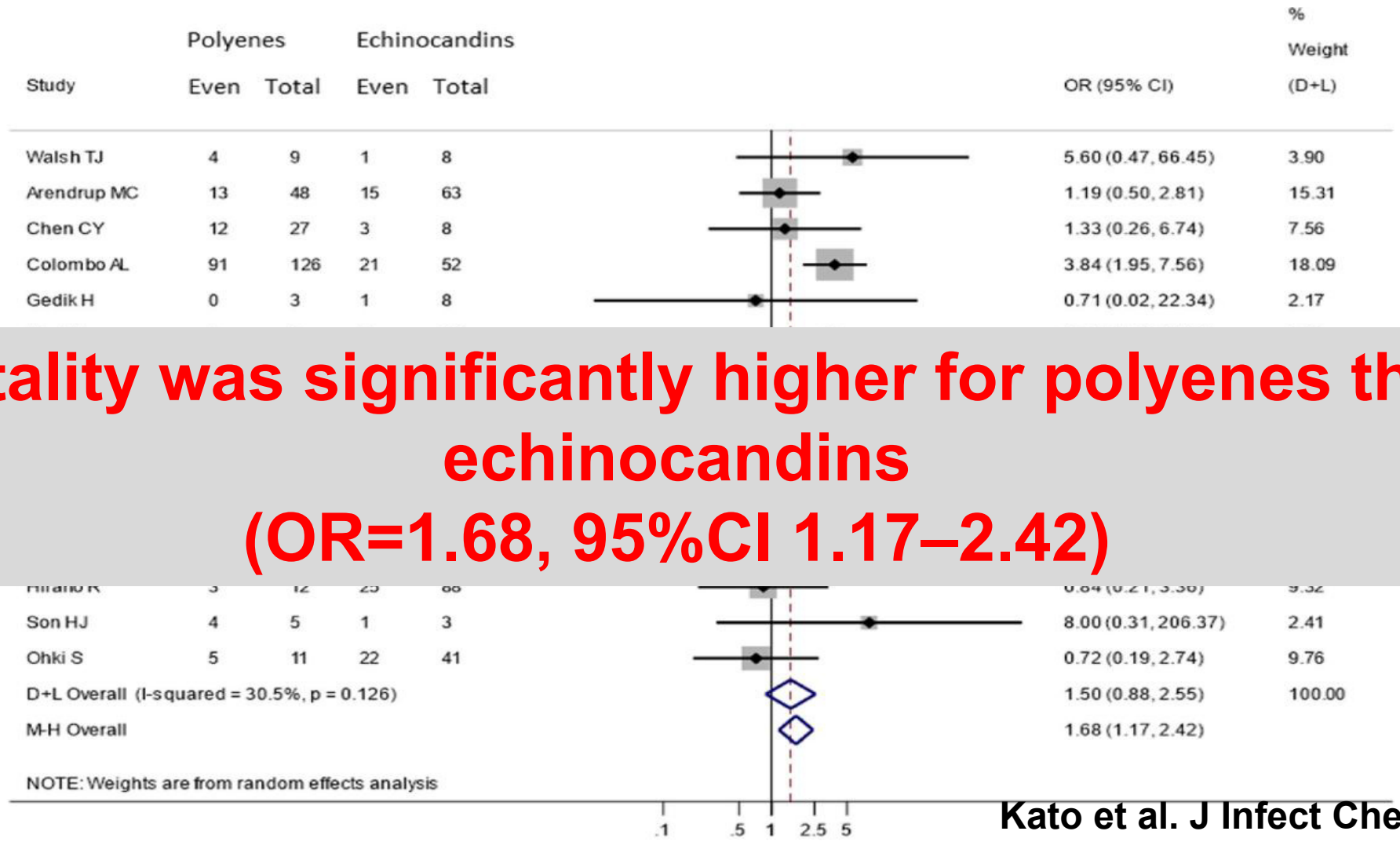
Isavuconazole vs Caspofungin for candidemia/Invasive candidiasis
(ACTIVE trial, n=400, Kullberg 2019)

- **IV Isavuconazole** (199p) vs. **Caspofungin** (201p)
- **Outcome:** Overall response (mycological eradication and clinical cure/improvement at EOIVT)
- **Primary outcome**: Isavuconazole: 120/199 (**60.3%**) vs Caspofungin: 143/201 **(71.1%)** (difference: -10.8%; 95% CI -19.9–-1.8)
- The lower limit of the 95% CI for the treatment difference (-19.9%) was lower than the prespecified noninferiority margin of -15%
- This study **did not demonstrate noninferiority of isavuconazole** relative to caspofungin

Kullberg, CID 2019;68(12):1981–9

Echinocandins vs polyenes for candidemia (meta-analysis, n=854, 15 studies, Kato 2021)

Odd ratios for mortality comparing echinocandins versus polyenes in the initial treatment of candidemia

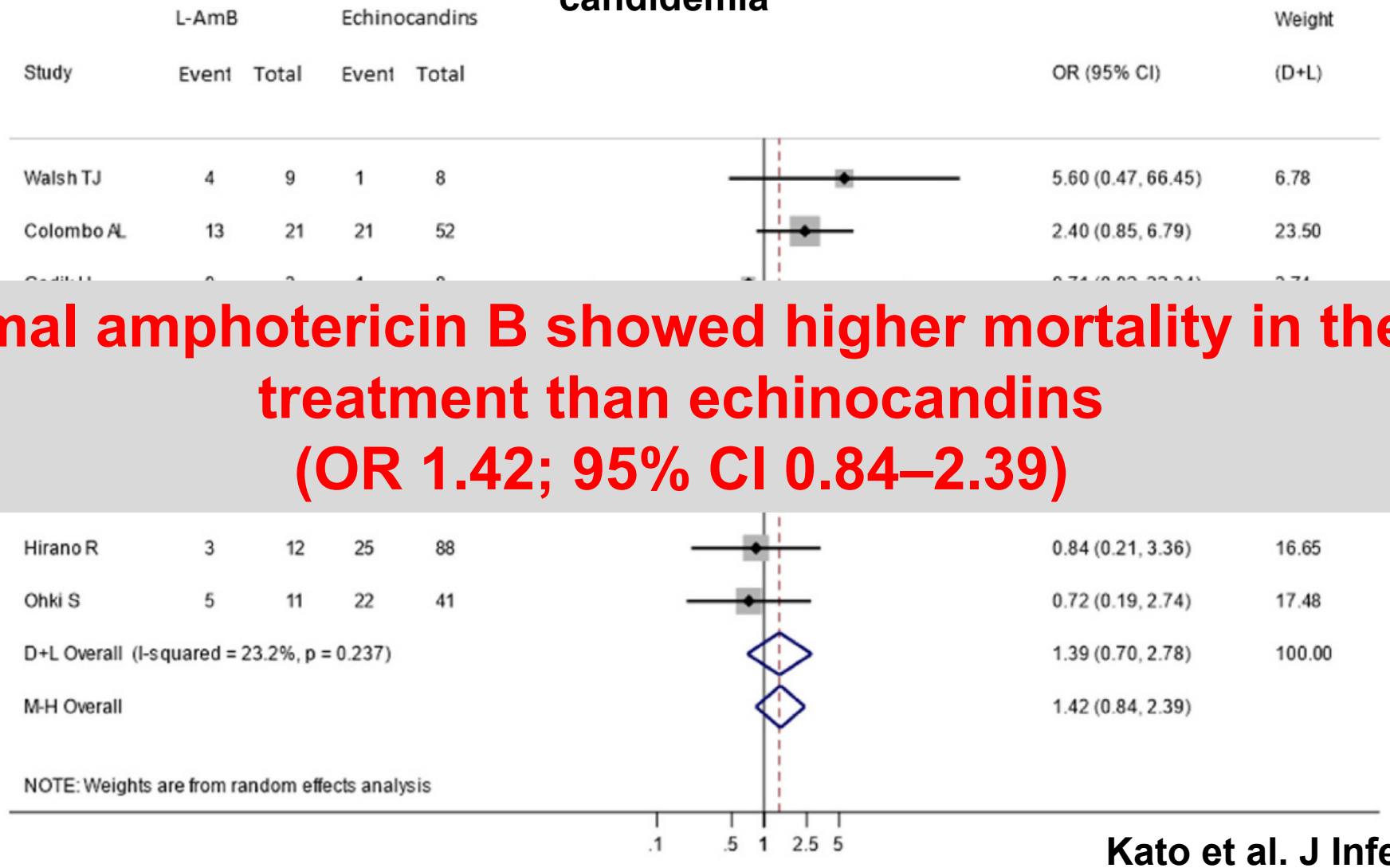


Mortality was significantly higher for polyenes than echinocandins (OR=1.68, 95%CI 1.17–2.42)

Kato et al. J Infect Chemother, 2021

Echinocandins vs polyenes for candidemia (meta-analysis, n=854, 15 studies, Kato 2021)

Odd ratios for mortality comparing echinocandins versus L-AmB in the initial treatment of candidemia



Liposomal amphotericin B showed higher mortality in the initial treatment than echinocandins (OR 1.42; 95% CI 0.84–2.39)

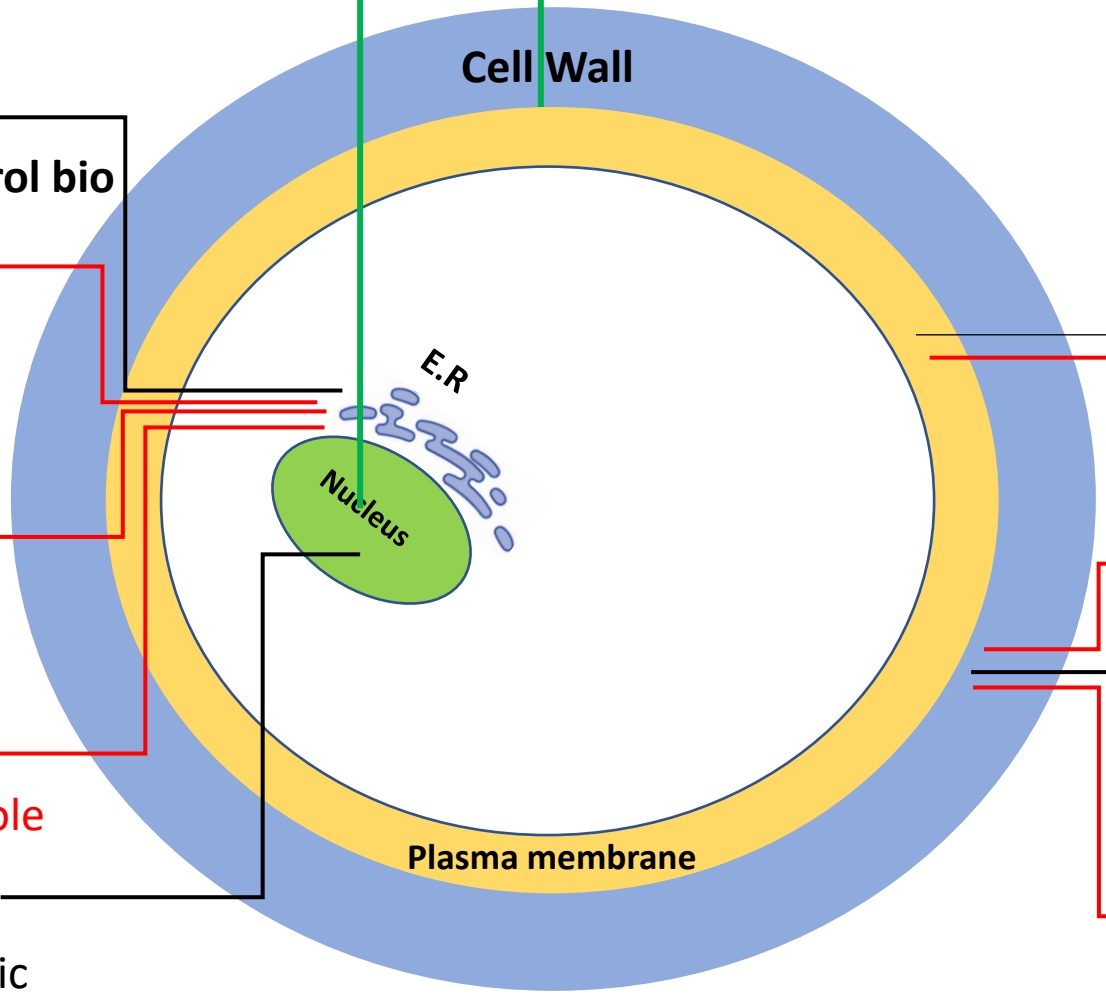
Kato et al. J Infect Chemother,

Amphotericin B vs azoles vs echinocandins in candidemia/IC (Network meta-analysis, 13 RCTs, n=3528, Demir 2021)

- For all forms of invasive candidiasis, echinocandins were associated with the highest rate of treatment success when compared to amphotericin B (OR 1.41, 95% CI 1.04–1.92) and the triazoles (OR 1.82, 95% CI 1.35–2.51)
- Rank probability analysis favored echinocandins as the most effective choice 98% of the time
- Overall survival did not significantly differ between groups

Among patients with invasive candidiasis, echinocandins had the best clinical outcomes and should remain the first-line agents in the treatment of invasive candidiasis

Demir et al. Mycoses, 2021



Fosmanogepix (PO,IV)
Inhibit Gwt1e, inhibits GPI anchored protein important for mannoprotein binding in cell wall

Olorofim (PO, IV)
Inhibit pyrimidine synthesis

Azoles
Target ergosterol bio

Oteseconazole (PO)
More specific for fungal CYP51

Opelconazole (INH)

PC945
inhaled triazole

Flucytosine
Inhibits nucleic acid synthesis

Polyenes
Bind to ergosterol, destroys membrane

Encochleat ampho B (PO)
Targeted delivery into macrophages, REC

Ibrexafungerp (PO, IV)
Inhibit BDG at different site

Echinocandins
Inhibit β(1,3)-D-gulcan synthase & disrupts cell wall

Rezafungin (IV)
Modified anidulafungin long h/f (Q week)

Rezafungin (CD101)

- Next generation echinocandin “Modified anidulafungin”
- IV administration
- Long half-life (130 h) -> **once weekly** administration
- Large volume of distribution, with prolonged accumulation in tissues, but **poor CNS, Eye** and **urinary** penetration
- Elimination – biliary

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
Rezafungin	Except *C. parapsilosis* (higher MIC)		Fungistatic				
Ibrexafungerp							
Olorofim						Activity against *F. oxysporum* >> *F. solani*	
Manogepix	Except *C. krusei* (higher MIC)					Some resistant isolates (*F. oxysporum*, *F. verticilloides*)	Few resistant isolates (*S. apiospermum*)

Activity against most isolates

Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

No *in vitro* activity on

- Non-Aspergillus molds
- *Cryptococcus spp.*
- Endemic fungi
- Rare non-Candida opportunistic yeasts (e.g. *Trichosporon spp., Rhodotorula spp., Saprochaete spp.*)

Ibrexafungerp

- Triterpenoid
- **Oral** formulation (IV in development) – bioavailability 35-50%, improved with low gastric pH and food
- 1,3,b-D-Glucan synthase inhibitor (partial overlap with echinocandins) -> limited cross resistance (active against FKS harboring isolates)
- Large volume of distribution (including good bone penetration)
- **Poor CNS and urinary** penetration
- Elimination – biliary

Ibrexafungerp: Spectrum of *in vitro* activity

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
Rezafungin	Except *C. parapsilosis* (higher MIC)		Fungistatic				
Ibrexafungerp			Fungistatic				
Olorofim						Activity against *F. oxysporum* >> *F. solani*	
Manogepix	Except *C. krusei* (higher MIC)					Some resistant isolates (*F. oxysporum*, *F. verticilloides*)	Few resistant isolates (*S. apiospermum*)

Activity against most isolates

Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

in vitro activity on

- **Candida:**

- Potent fungicidal activity for most pathogenic *Candida spp*., including:
- *C.parapsilosis*
- *C.auris*
- Echinocandin-resistant *C.albicans/C.glabrata* harboring FKS mutations

- **Aspergillus:**
- **Fungistatic** effect; synergistic with triazoles and ampB

No *in vitro* activity

- **Not** active in vitro against:
  - ✓*Mucorales spp.*
  - ✓*Fusarium spp.*
- **Marginal** fungistatic activity:
  - ✓*Scedosporium spp.*
  - ✓*Lomentospora prolificans*
- Effective for PCP prophylaxis in mouse model

AE, interactions

- Coadministration of strong CYP3A inducers should be avoided as ibrexafungerp might not reach sufficient drug concentrations
- Coadministration of CYP3A inhibitors requires a dose reduction of ibrexafungerp
- The most common AEs are mild to moderate and due to **gastrointestinal** tract symptoms, including nausea, diarrhea, abdominal pain, and vomiting, that may be dose limiting

Hoenigl et al. Drugs, 2021

Ibrexafungerp – clinical trials

- FDA approved for the treatment of **vulvovaginal candidiasis** following results of recent phase III studies
- Assessment for the treatment of **IFI** is currently ongoing

Ibrexafungerp – vulvovaginal candidiasis **(VANISH 303 study)**

- Female pts age ≥12 yrs with acute VVC, VSS score ≥4
- PO Ibrexafungerp 300 mg X 2 for 1 day (188 pts) or placebo (94 pts)
- **Outcomes:** clinical cure (VSS = 0) at the test-of-cure visit (day 11 ± 3)
- Clinical cure: 51% vs 29%; P=0.001
- Mycological eradication 50% vs 19%; P < 0.001
- Overall success 36 % vs 13%, p<0.001
- Cure at late F/U (day 25±4) 60% vs 45%, p=0.009

Schwebke et al, Clin Infect Dis. 2021

Ibrexafungerp – vulvovaginal candidiasis **(VANISH 306 study)**

- Female patients aged ≥12 years with acute VVC, VSS score ≥4
- PO Ibrexafungerp 300 mg X 2 for 1 day (188 pts) or placebo (84 pts)
- Outcomes: clinical cure (VSS = 0) at the test-of-cure visit (day 11 ± 3)
- Clinical cure 63% vs 44.0%; P =0.007, mycological eradication 58.5% vs 29.8%; P < 0.001, overall success - 46.1% vs 28.4%; P = 0.022, clinical improvement - 72.3% vs 54.8%; P = 0.01
- Cure at late F/U (day 25±4) 73.9% vs 52.4%
- Superiority over placebo

Sobel et al, BJOG. 2022

Ibrexafungerp step down following initial echinocandins in non neutropenic IC

Phase II, randomized, open label

Invasive candidiasis Non-neutropenic adults

Oral step down following **initial echinocandin** with either:

- Ibrexafungerp 1000 mg (day 1) then 500 mg qd (**7 pts**)
- Ibrexafungerp 1250 mg (day 1) then 750 mg qd (**7 pts**)
- SOC: Fluconazole or Micafungin (**8p**)

Response: 86% ibrexafungerp 750 mg, 71% ibrexa 500mg; 71% SOC

Dose estimated to achieve the target exposure was 750 mg daily, the dose was well tolerated

Spec et al, JAC. 2019

Ibrexafungerp: Ongoing trials

- ***NCT03672292 (SCYNERGIA)*: Ibrexa + voriconazole vs voriconazole** for **IPA**
- ***NCT03059992 (FURI)*: Ibrexa single arm** for **intolerant/refractory IFI**
- **NCT03363841 (CARES) Ibrexa single** arm for ***Candida auris*** invasive infection
- **NCT05178862 (MARIO)** A Phase 3, Randomized, Double-blind Study for Patients With **Invasive Candidiasis** Treated With **IV Echinocandin Followed by Either Ibrexa or Oral Fluconazole**

Summary

- Alternative for azole resistant and echinocandin resistant candida infections
- Oral step-down option when azole not tolerated (or resistant)
- Combination for molds after additional studies

Olorofim

- Both intravenously and orally
- Bioavailability 45-82%
- Orotomide class - inhibits fungal dihydroorotate dehydrogenase (DHODH), a key enzyme in pyrimidine biosynthesis
- Large volume of distribution: Therapeutic concentrations in lung, **brain**, liver and kidney
- Elimination: biliary

Spectrum of *in vitro* activity

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
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Activity against most isolates

Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

Spectrum of *in vitro* activity

Aspergillus:

- Highly active with uniformly low MICs (≤0.25 µg/ml) against all pathogenic *Aspergillus spp* (including cryptic species and azole-resistant *A.fumigatus*)

Scedosporium and Lomentospora:

- Potent *in vitro* activity (MIC ≤0.5 µg/ml) against *Scedosporium apiospermum* complex and *Lomentospora prolificans*

Fusarium:

- Effect is species-specific: *F.oxysporum* complex > *F.solani* complex

Dimorphic fungi

- Potent *in vitro* activity against *Coccidioides immitis*, *Coccidioides posadasii*, and *Talaromyces marneffei*

Not active against

- Yeasts (Candida and *Cryptococcus spp.*)
- Mucorales spp.

Clinical trials

- Ongoing: NCT03583164 (FORMULA-OLS)
- Phase II, open label, non-comparator, single arm
- Olorofim max. 300 mg qd (dose adjusted according to TDM)
- Invasive mold infections with limited alternative therapeutic options

- Limited data on promising clinical data for the treatment of L. prolificans infections and coccidioidomycosis

- Phase 3 - F2G – olorofim vs amibisom

Olorofim indication summary

- Option for azole resistant *aspergillus*
- Option for other mold infections: *F.oxysporum*, *scedosporium*, *lomentospora*
- *Coccidioidomycosis*

Fosmanogepix

- **Intravenous and oral routes**, bioavailability >90%
- Prodrug, converted by systemic phosphatases to the active moiety **manogepix**
- Inhibits Gwt1, an enzyme in the glycosylphosphatidylinositol (GPI) biosynthesis pathway, loss of anchoring of mannoproteins, **compromises cell wall integrity**
- Large volume of distribution: **brain, eyes and intra-abdominal abscesses**

Spectrum of *in vitro* activity

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
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Activity against most isolates

Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

Spectrum of *in vitro* activity

- **Candida:**
  - ✓Highly active against **most** pathogenic Candida spp., including *C.auris*
  - ✓Majority of echinocandin and azole-resistant Candida spp

- **Cryptococcus neoformans**

Spectrum of *in vitro* activity

- **Aspergillus:**
- Potent antifungal activity against Aspergillus spp. Including: Azole-resistant *A.fumigatus* and cryptic species

- **Fusarium:**
- Active against most *Fusarium spp*., in particular *F.solani* and *F.oxysporum* complexes

- **Scedosporium and Lentospora:**
- Highly active against most *Scedosporium spp.* and *L.prolificans*

Not active against

- Candida:
- **C. krusei and C. kefyr** (10-fold higher MIC due to mutation in the target gene (Gwt1) or from efflux pumps activity)

- Mucorales
- in vitro antifungal activity of manogepix against most Mucorales is limited (MEC90 4 – 16 µg/ml),

Adverse events, interactions

- Well-tolerated across all doses with no clinically significant adverse events observed and no dose limiting toxicities

- Most of the AEs were mild, transient and required no treatment

Clinical trials

- NCT03604705 Phase II, open label, **non-comparator**, single arm, fosmanogepix for **candidemia** in non-neutropenic adults (20 pts)
- Treatment success 16/20 (80%), mortality 5/21 (23.81%)

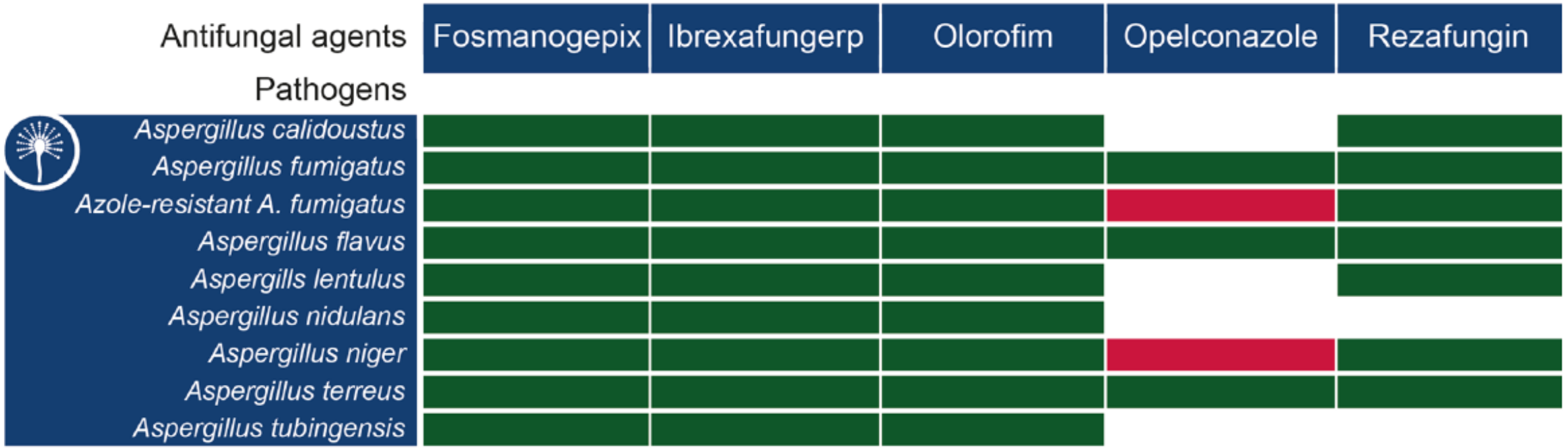
- NCT04148287 (APEX) - Phase II, open label, non-comparator, **IC** of **candida auris**

- NCT04240886 (AEGIS) - Phase II, open label, non-comparator, single arm, for invasive **mold** infections

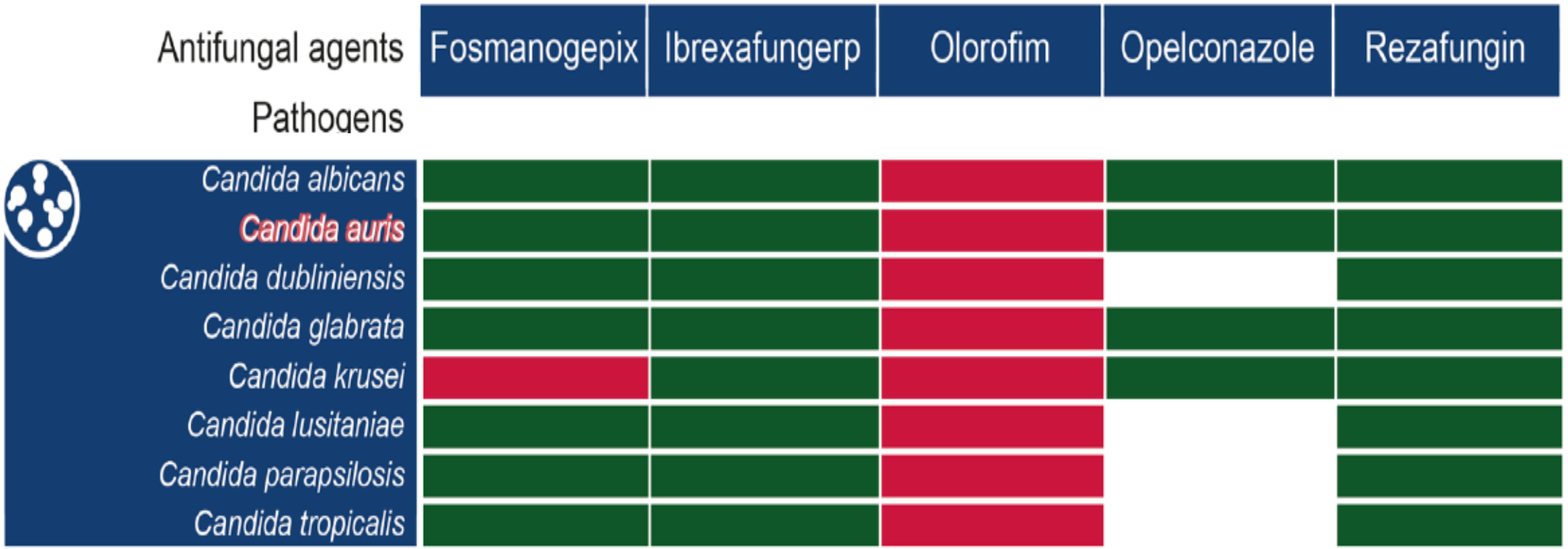
Indications summary

- Very wide spectrum of coverage
- Candida infection (besides krusei)
- Mold infections (besides Mucorales)

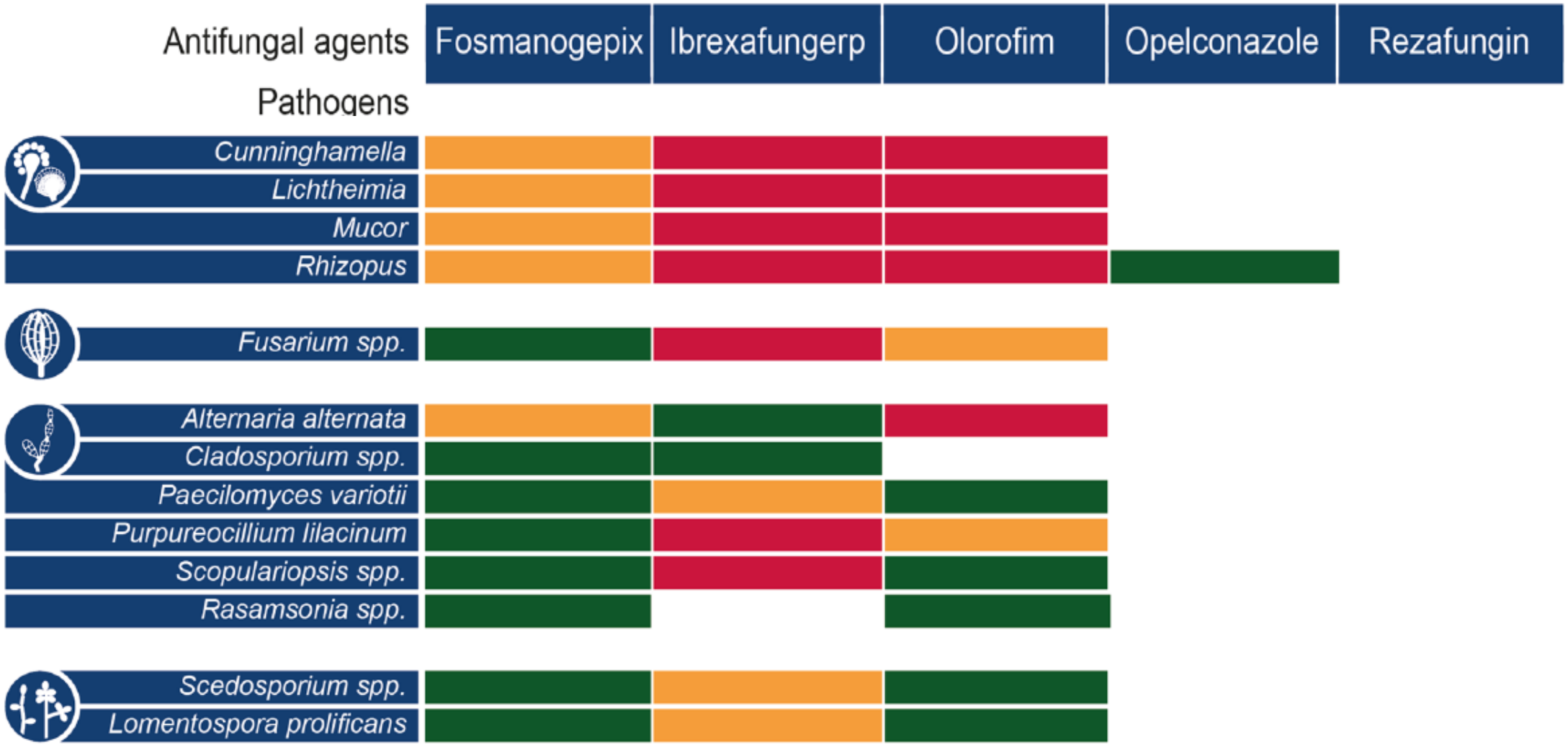
Aspergillus spp



Candida spp


Antifungal agents
Pathogens
Fosmanogepix
Ibrexafungerp
Olorofim
Opelconazole
Rezafungin
Candida albicans
Candida auris
Candida dubliniensis
Candida glabrata
Candida krusei
Candida lusitaniae
Candida parapsilosis
Candida tropicalis

Rare molds spp



Other fungi


Antifungal agents
Fosmanogepix
Ibrexafungerp
Olorofim
Opelconazole
Rezafungin
Cryptococcus gattii
Cryptococcus neoformans
Trichosporon asahii
Exophiala dermatitidis
Malassezia furfur
Pneumocystis jirovecii
Blastomyces dermatitidis
Coccidioides immitis
Histoplasma capsulatum
Fonsecaea pedrosoi
Madurella mycetomatis
Talaromyces marneffei
Phialophora verrucosa
Legend
Potent activity
!!!
Variable activity
!?
No activity
x
Unknow / currently investigated
?