Sabato
11.05.2024

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INFETTIVOLOGIA
IERI, OGGI E DOMANI:
UNA DISCIPLINA SEMPRE AL PASSO CON I TEMPI

Attualità in terapia antifungina:
Non più la cenerentola!

Francesco Cristini

FUNGAL DISEASES FROM A GLOBAL PERSPECTIVE

- **Fungal infections are silent killers, and cause misery to millions. Annually, over 150 million severe cases of fungal infections occur worldwide, resulting in approximately 1.7 million deaths per year.**
- **More die of fungal diseases than either TB (1.5 million deaths per year) or malaria (405,000 deaths per year).**
- **After headaches and rotten teeth, skin fungal infections are the commonest diseases on Earth.**

- **Only 30 species of fungi regularly cause disease of the 600 species that have ever caused infection in humans. All these fungi can grow at body temperature, unlike most environmental fungi.**
- **The common fungi causing infection are *Trichophyton*, *Candida* and *Aspergillus*.**

Fungal infections can be separated into five groups with some overlap:

•**Invasive fungal infections**, which are often fatal (esp. cryptococcal meningitis, Pneumocystis pneumonia, disseminated histoplasmosis, invasive aspergillosis, Candida bloodstream infection).

•**Skin, hair and nail infection**, (esp. ringworm, tinea capitis, athlete's foot, onychomycosis).

•**Mucosal infection**, (esp. oral and oesophageal candidiasis, Candida vaginitis (thrush))

•**Allergic fungal disease**, (esp. allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS))

•**Chronic lung or deep tissue infection**, (esp. chronic pulmonary aspergillosis, endemic mycoses)

Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision

F Bongomin, W. Denning et al - J. Fungi 2017, 3, 57

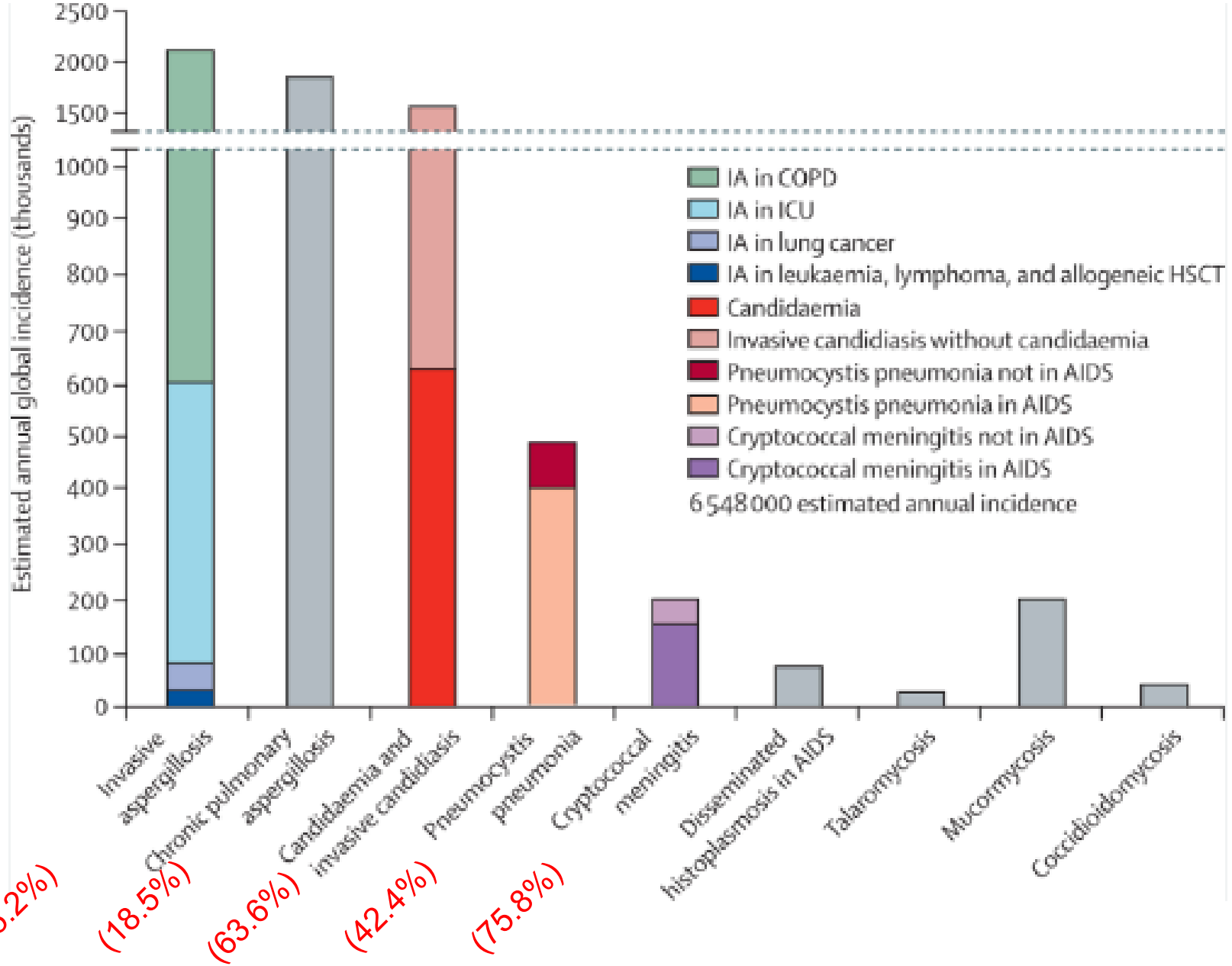
Burden of fungal diseases

Fungal Disease		Annual Incidence	Global Burden	Comments
Superficial			~1,100,000,000	

Global incidence and mortality of severe fungal disease

W. Denning – Lancet Infect Dis 2024 Jan 12:S1473-3099(23)00692-8.

All severe fungal infections:
- Annual incidence: 6.5 million
- Crude annual mortality: 3.8 million
- *2.5 million deaths directly attributable*



Corresponde:

Global incidence and mortality of severe fungal disease

Kevin S Ikuta, Tomislav Meštrović, Mohsen Naghavi - Lancet infect dis 2024 May;24(5):e268.

???????

Author’s reply:

Global incidence and mortality of severe fungal disease - Author's reply

W. Denning - Lancet Infect Dis. 2024 May;24(5):e269.

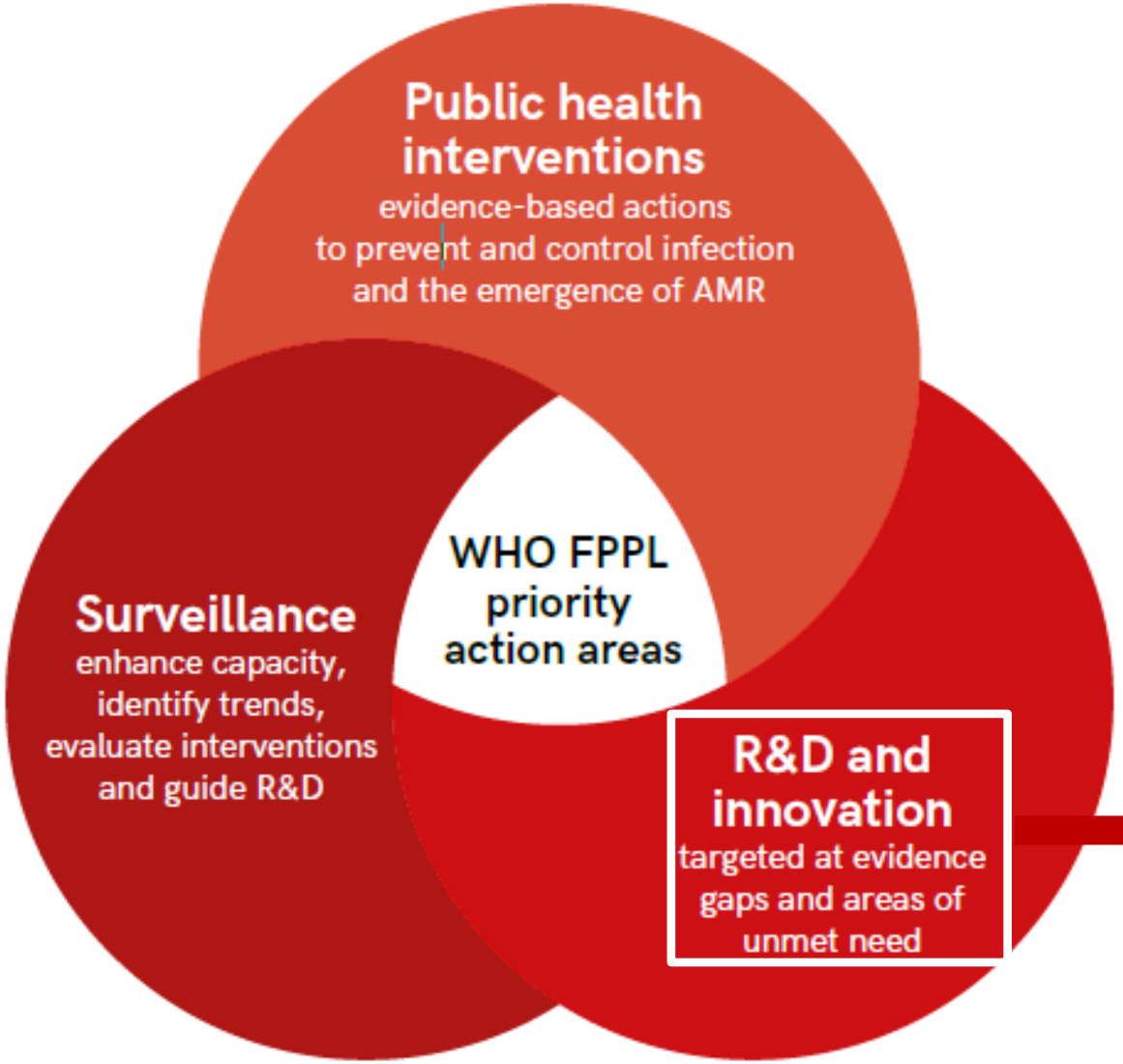
!!!!!!!!

WHO fungal priority pathogens list to guide research, development and public health action

25 October 2022 | Report

Priority areas for action

WHO fungal priority pathogens list to guide research, development and public health action



Focus R&D investments on **innovative antifungal agents** (i.e. **no cross-resistance to other antimicrobial classes, new chemical class, new target, and new mode of action-no or minimal drug-drug interaction**) effective against priority pathogens.

Improve existing therapies and generate new knowledge on their optimal use, including pharmacokinetics/ pharmacodynamics and therapeutic antifungal monitoring. Optimize combination therapies to **prevent further resistance, enhance efficacy and minimise toxicity**.

WHO fungal priority pathogens list to guide research, development and public health action

Critical group


Cryptococcus neoformans


Candida auris


Aspergillus fumigatus


Candida albicans

High group


Nakaseomyces glabrata (Candida glabrata)


Histoplasma spp.


Eumycetoma causative agents


Mucorales


Fusarium spp.


Candida tropicalis


Candida parapsilosis

Medium group


Scedosporium spp.


Lomentospora prolificans


Coccidioides spp.

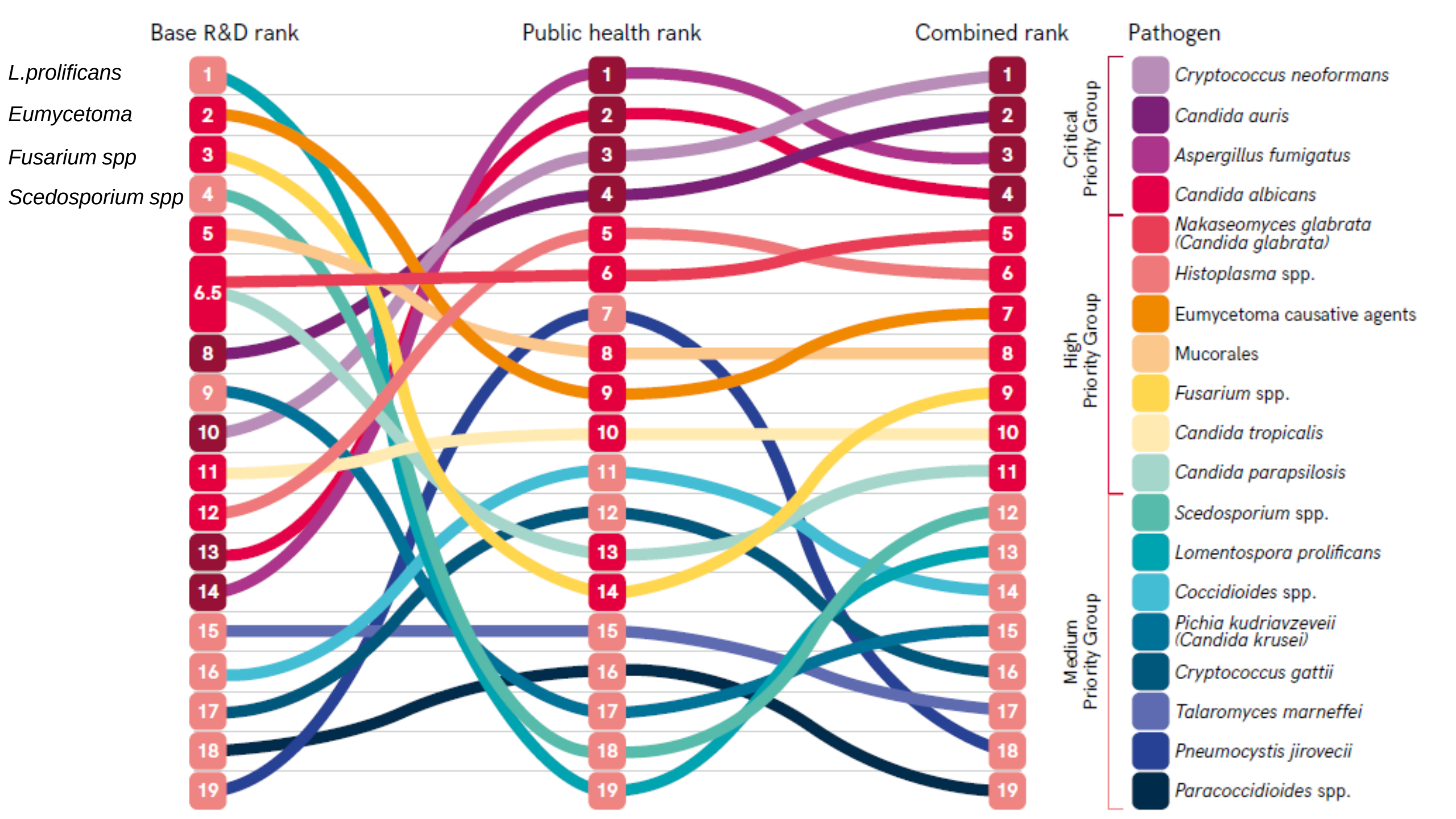

Pichia kudriavzeveii (Candida krusei)


Cryptococcus gattii


Talaromyces marneffei


Pneumocystis jirovecii


Paracoccidioides spp.


Base R&D rank
Public health rank
Combined rank
Pathogen
L.prolificans
Eumycetoma
Fusarium spp
Scedosporium spp
1
2
3
4
5
6.5
8
9
10
11
12
13
14
15
16
17
18
19
Critical Priority Group
High Priority Group
Medium Priority Group
Cryptococcus neoformans
Candida auris
Aspergillus fumigatus
Candida albicans
Nakaseomyces glabrata (Candida glabrata)
Histoplasma spp.
Eumycetoma causative agents
Mucorales
Fusarium spp.
Candida tropicalis
Candida parapsilosis
Scedosporium spp.
Lomentospora prolificans
Coccidioides spp.
Pichia kudriavzeveii (Candida krusei)
Cryptococcus gattii
Talaromyces marneffei
Pneumocystis jirovecii
Paracoccidioides spp.

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

Numero di isolamenti di Candide da emocolture (Paz degenti)

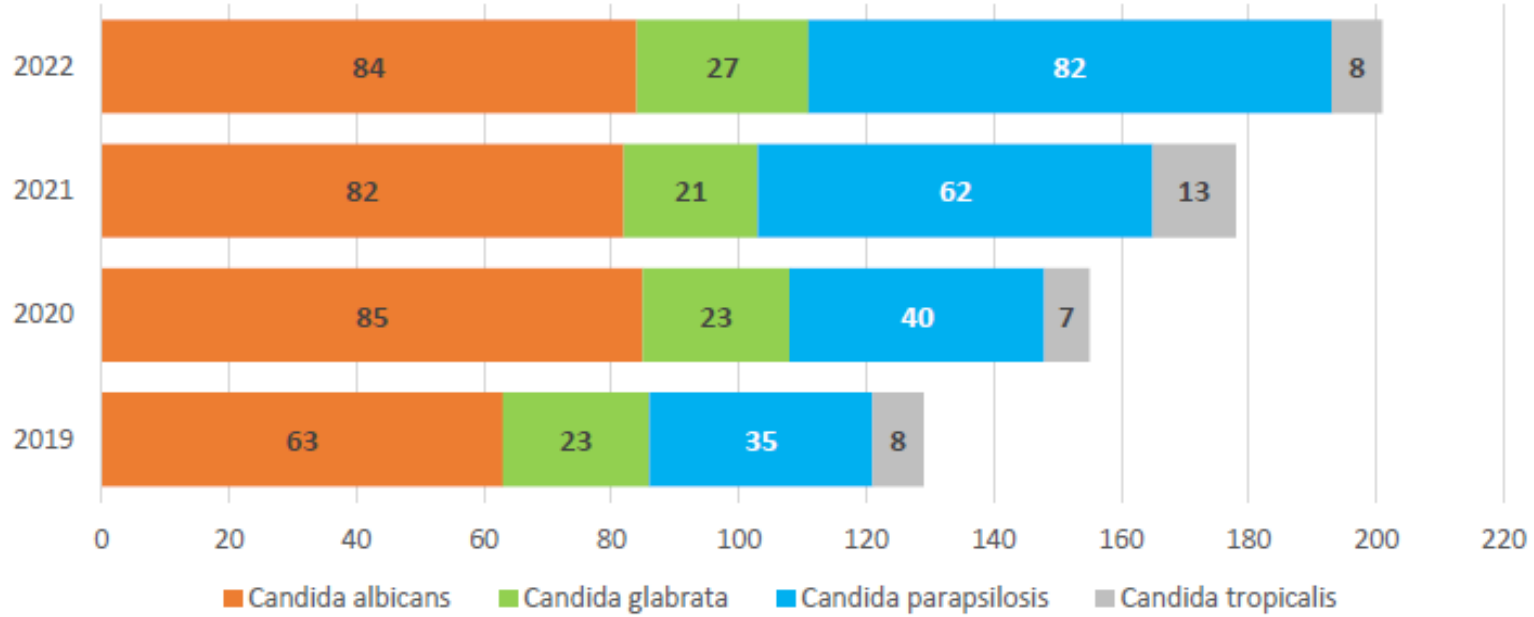
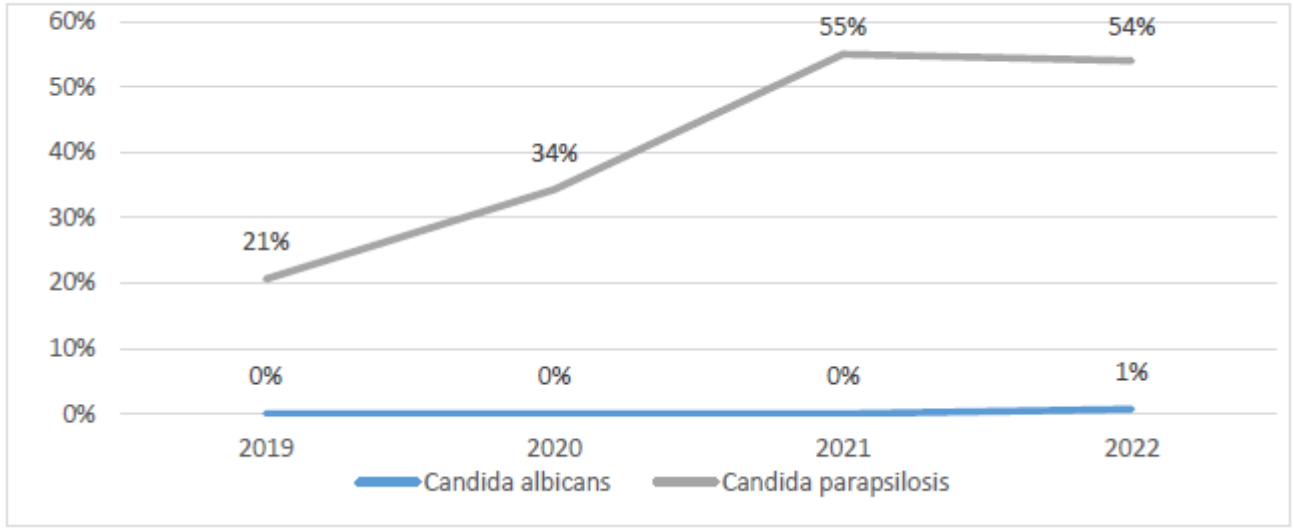


Fig 62- % ceppi I/R a Fluconazolo

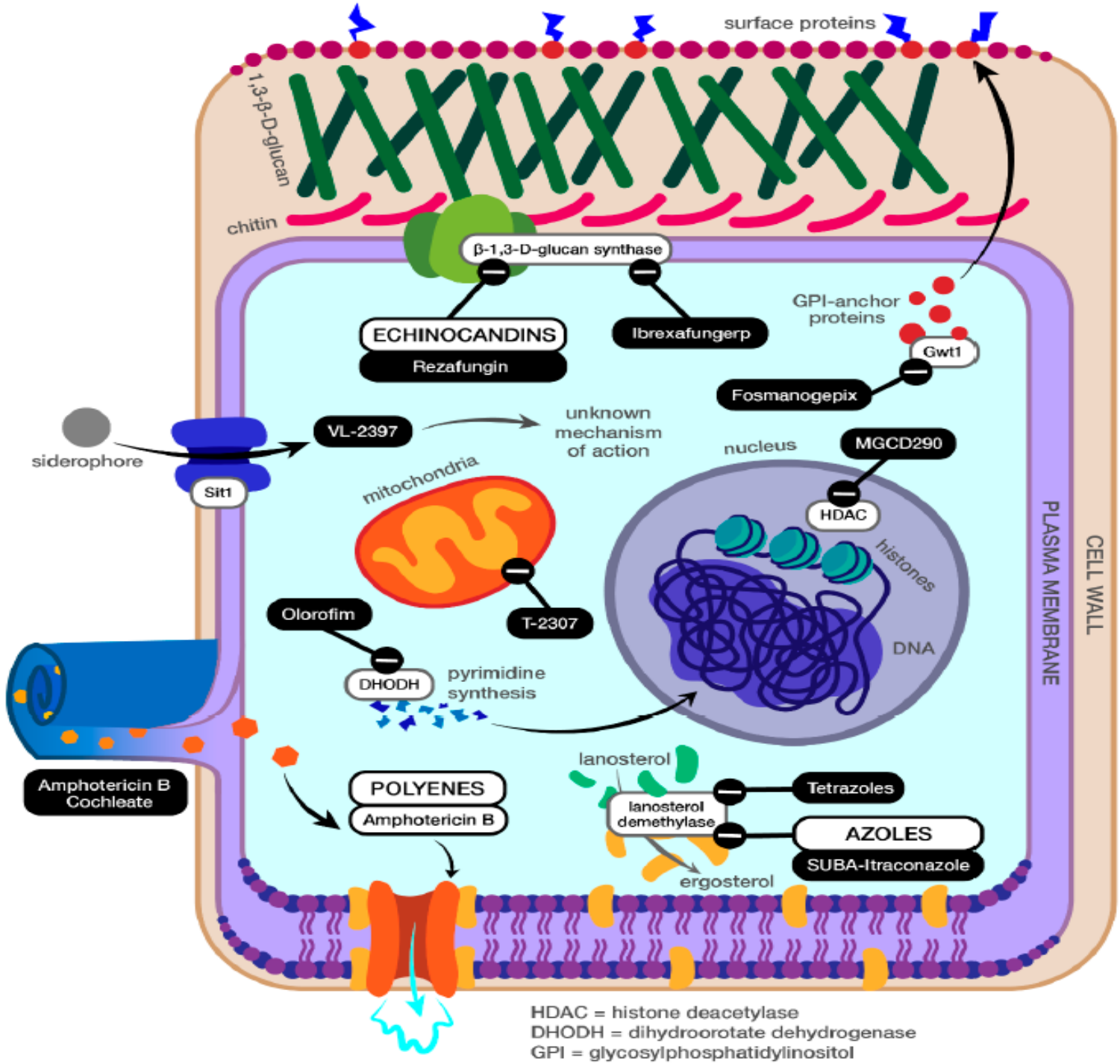


CURRENT ANTIFUNGAL ARMAMENTARIUM

Three classes used in the treatment of most systemic mycoses:

- **polyenes (amphotericin B)**
  - → it binds to ergosterol of the cell membrane
- **azoles (fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazole)**
  - → inhibition of fungal cytochrome P450 → synthesis of ergosterol
- **echinocandins (caspofungin, micafungin and anidulafungin)**
  - → inhibition of beta-(1,3)-D-glucan synthase

	Azoles: FluCONAZOLE	VoriCONAZOLE	IsavuCONAZOLE	Echinocandins: MicaFUNGIN CaspoFUNGIN AnidulaFUNGIN	Amphotericin
Yeast					
Candida albicans	+	+	+	+	+
Candida tropicalis	+	+	+	+	+
Candida dubliniensis	+	+	+	+	+
Candida kefyr	+	+	+	+	+
Candida auris	+	+	+	+	+
Candida glabrata	-	+	+	+	+
Candida parapsilosis	+	+	+	+/-	+
Candida krusei	-	+	+	+	+
Candida guilliermondii	+	+/-	+	+/-	-
Candida lusitaniae	+	+	+	+	-
Cryptococcus spp.	+	+	+	-	+
Mold					
Aspergillus fumigatus	-	+ ?	+	+/-	+
Aspergillus nidulans	-	+	+	+/-	+
Aspergillus flavus	-	+	+	+/-	-
Aspergillus terreus	-	+	+	+/-	-
Aspergillus niger	-	-	+/-	+/-	+
Aspergillus lentulus	-	-	+	+/-	+
Mucorales					
Rhizopus spp.	-	-	+	-	+
Mucor spp.	-	-	+	-	+
Lichtheimia spp.	-	-	+	-	+
Fusarium spp.	-	+	+	-	+
Scedosporium spp.	-	+	+		+


surface proteins
1,3-β-D-glucan
chitin
β-1,3-D-glucan synthase
ECHINOCANDINS
Rezafungin
Ibrexafungerp
GPI-anchor proteins
Gwt1
Fosmanogepix
siderophore
VL-2397
Sit1
unknown mechanism of action
nucleus
MGCD290
HDAC
histones
DNA
mitochondria
T-2307
Olorofim
DHODH
pyrimidine synthesis
Amphotericin B Cochleate
POLYENES
Amphotericin B
lanosterol
lanosterol demethylase
Tetrazoles
AZOLES
SUBA-Itraconazole
ergosterol
PLASMA MEMBRANE
CELL WALL
HDAC = histone deacetylase
DHODH = dihydroorotate dehydrogenase
GPI = glycosylphosphatidylinositol

Emerging Diagnostics and Therapeutics for Invasive Fungal Infections

Friedman DZP, Schwartz IS. Infect Dis Clin North Am. 2023 Sep;37(3):593-616

NEW DRUGS, OLD CLASSES

OTESECONAZOLE

Tetrazoles

Oteseconazole is highly specific for the fungal cytochrome P450 51 (CYP51, lanosterol 14-a-demethylase). This high specificity results in **2 unique characteristics**: oteseconazole is associated with considerably **less toxicity** and **drug–drug interactions** that arise from inhibition of human CYP enzymes.

Food and Drug Administration (FDA) approval in July 2022 for the treatment of recurrent vulvovaginal candidiasis in women who are not of childbearing potential (concern about teratogenicity in animal studies).

It has an extraordinarily long half-life (138 days)

It may well become a valuable option in the treatment of recurrent yeast and dermatophyte infections in select patient populations.

Maybe no other uses on the horizon.

OPELCONAZOLE

Triazoles

INHALED triazole

Favorable activity against most Aspergillus species (NOT A niger)

Activity against Candida and Cryptococcus spp., NOT active against most Mucorales, except moderate activity against Rhizopus oryzae

It reaches adequate drug levels within pulmonary tissues and has minimal systemic absorption

It is currently being investigated in a **phase 2 study for prophylaxis against aspergillosis in lung transplant recipients**

Treatment studies are not yet on the horizon

REZAFUNGIN

Echinocandin

A new echinocandin that retains similar activity to others in the class

Prolonged half-life permits **once-weekly dosing**
outpatient treatment without the need for central venous access ??

Once-weekly dosing enables a **high upfront maximum serum concentration**
earlier sterilization of blood and deep-seated infections ??
reduced risk of resistance that can develop during prolonged therapy ??

New forms of administration are in development such as topical and subcutaneous forms (VVC).

In phase 2 and 3 trials of candidemia and invasive candidiasis, weekly rezafungin was non-inferior to daily caspofungin, followed by an oral step down in all-cause mortality, serious adverse reactions, and blood culture clearance.

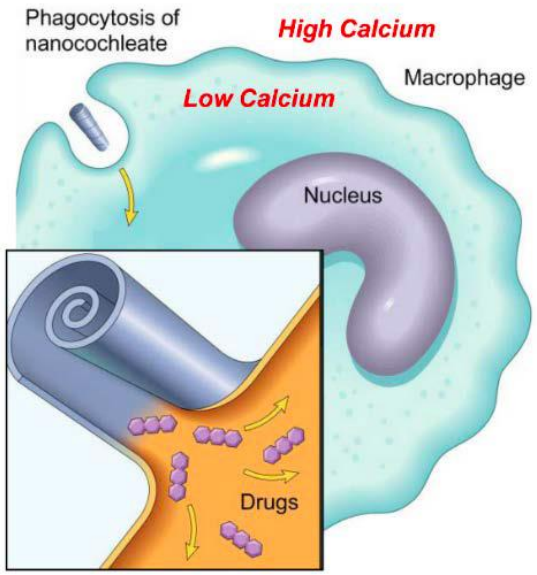
Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial *Thompson GR 3° et al - Lancet. 2023 Jan 7;401(10370):49-59.*

Rezafungin is also being evaluated for prophylaxis against invasive fungal infections and PCP.
Ongoing phase 3 trial (ReSPECT) rezafungin VS fluconazole and trimethoprim–sulfamethoxazole for the prevention of IFI and PJP in recipients of allogeneic stem cell transplants.

ORAL ENCHOLEATED AMPHOTERICIN B (CAMB)

Polyenes

A **murine mouse model**. C. albicans was administered intravenously to mice; the non-cochleate group received intraperitoneal deoxycholate amphotericin or oral liposomal amphotericin, and experienced 100% mortality. The group that received amphotericin B cochleate orally experienced 100% survival at Day 16 post infection



The drug is trapped within a cochleate - a spiral sheet of a lipid bilayer and calcium ions - that protects the drug from gastric degradation and permits the uptake and concentration of AMB within phagocytes, which maintains a low serum concentration to reduce toxicities (especially nephrotoxicity)

ORAL ENCHOLEATED AMPHOTERICIN B (CAMB)

Oral Lipid Nanocrystal Amphotericin B for Cryptococcal Meningitis: A Randomized Clinical Trial

Boulware et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

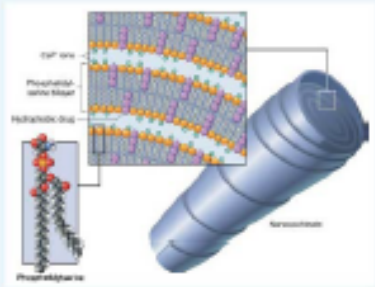
BACKGROUND: We conducted a randomized clinical trial to evaluate the antifungal efficacy of oral lipid nanocrystal (LNC) amphotericin (MAT2203) with flucytosine (5FC) in the treatment of cryptococcal meningitis.

PARTICIPANTS: We recruited adults with HIV diagnosed with cryptococcal meningitis from three hospitals in Uganda.

METHODS

Study participants had a positive CSF CrAg, Glasgow Coma Scale score = 15, and had to be able to tolerate oral medication. Participants were randomized to either the IV amphotericin control arm or to an interventional arm.

	ARM 1: 7 doses of IV Amphotericin + 5FC	ARM 2: 2 doses of IV Amphotericin + MAT2203 + 5FC	ARM 3: Oral MAT2203 + 5FC
	N=41	N=40	N=40
18-week Survival	85%	90%	85%
2-week CSF Sterility	67.6%	62.2%	63.6%
Grade 3-4 Hgb AEs	43.9%	20%	22.5%
Grade 3-4 K+ AEs	17%	5.1%	5%



Clinical antifungal activity did not differ between oral LNC-amphotericin and IV amphotericin

CONCLUSION: Oral LNC-amphotericin B with 5FC demonstrated similar antifungal activity, similar survival, and less toxicity than IV amphotericin and 5FC. Oral LNC-amphotericin B appears to be a promising antifungal candidate to be moved forward in future clinical trials for the treatment of severe fungal infections.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad440

FIRST-IN-CLASS DRUGS

OLOROFIM (F901318)

Orotomides

orphan drug designation from FDA end EMA for the treatment of coccidioidomycosis, scedosporiosis (including lomentosporiosis), invasive scopulariopsis, and invasive aspergillosis

A new antifungal class with a novel mechanism of activity

→ The class inhibits dihydroorotate dehydrogenase, a key enzyme in **pyrimidine biosynthesis**.

The inhibition of pyrimidine production negatively affects fungal nucleic acid, cell wall, and phospholipid synthesis, as well as cell regulation and protein production

Olorofim can be administered **orally** **and** **intravenously**, although the oral formulation has been the primary target of most studies (highly bioavailable, large volume of distribution, high concentrations within the lungs, kidneys, and plasma)

Strong activity has been established against common Aspergillus spp. (A. fumigatus, A. nidulans, A. terreus, and A. niger) as well as cryptic species (A. lentulus and A. calidoustus). Olorofim was **effective against multi-drug resistant Aspergillus strains**, indicating a **lack of cross resistance** due to its novel mechanism of activity

It displays activity against **uncommon moulds**, including **Lomentospora prolificans** (for which there is currently no other effective therapeutic alternative) and **Scedosporium** spp

Minimal or no activity against Candida spp., Mucorales spp., and Cryptococcus neoformans, with variable and often species-specific results against Fusarium spp

OLOROFIM (F901318)

Ongoing studies:

Phase 2 trial: **Evaluate F901318 Treatment of Invasive Fungal Infections in Patients Lacking Treatment Options (FORMULA-OLS)**
specifically studied the efficacy of olorofim for patients with invasive mold infections who lacked suitable alternative therapy options

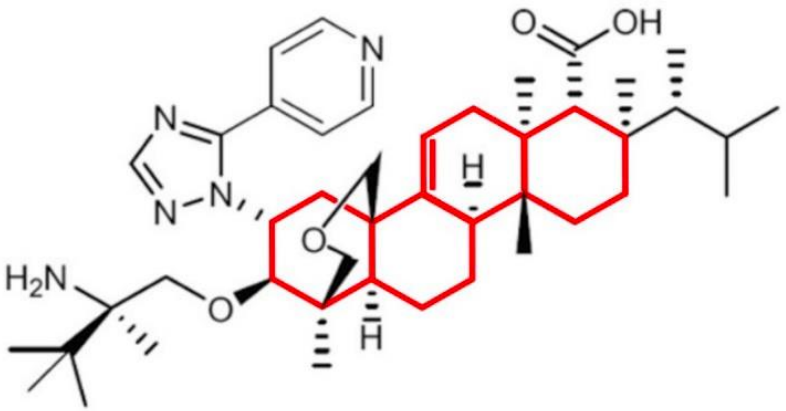
The primary infections included those caused by Aspergillus spp., Lomentospora prolificans, and Scedosporium spp.

Phase 3 trial: **Olorofim Aspergillus Infection Study (OASIS)**
comparing olorofim versus liposomal AMB followed by standard of care for proven/probable invasive aspergillosis (OASIS)

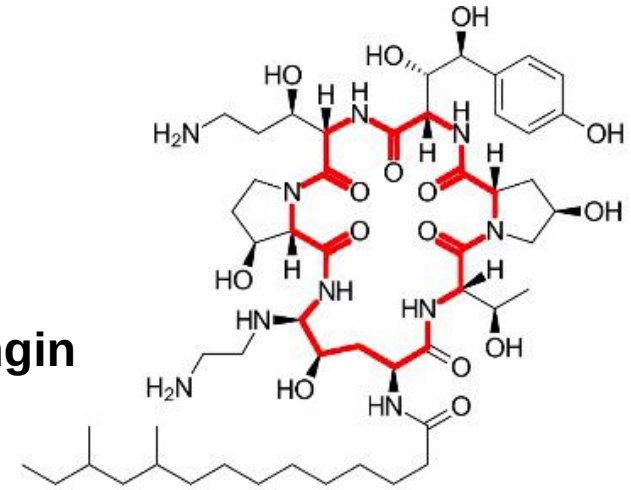
IBREXAFUNGERP (SCY-078)

Terpenoid

Inhibits 1,3-B-d-glucan synthesis to achieve antifungal effect, like echinocandins. However, as a triterpenoid enfumafungin derivative, ibrexafungerp is structurally unique from the echinocandin class



Ibrexafungerp



Caspofungin

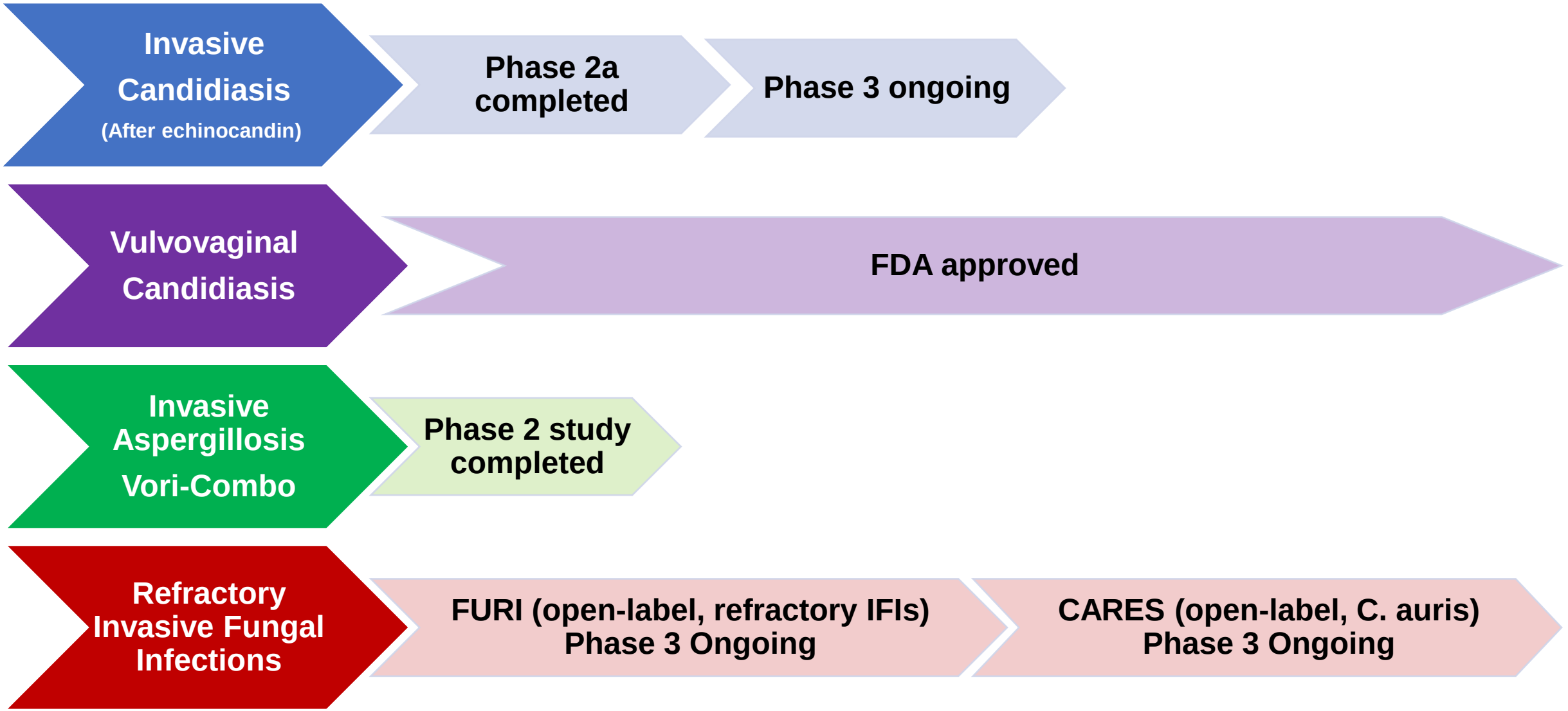
Characteristics:

- Activity against:
  - Candida spp.
  - Aspergillus spp.
  - Pneumocystis spp.
- Active against azole and most echinocandin-resistant strains
- **Oral**
- Favorable safety profile > 500 exposed
- Low risk of drug-drug Interactions
- Extensive tissue distribution •(Vdss> 8 L/kg)

IBREXAFUNGERP (SCY-078)

National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov



FOSMANOGEPIX (APX001)

orphan drug designation from FDA for the treatment of invasive candidiasis, invasive aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis and coccidioidomycosis. From EMA for invasive candidiasis

Glycosylphosphatidylinositol-inhibitor
Prodrug of manogepix

Mechanism of Action: manogepix **impedes** the fungal glycosylphosphatidyl-inositol anchor synthesis pathway, which is a critical process for the **production of cell wall mannoproteins**. As a result, the fungal cell is affected by **cell wall fragility, reduced germ tube and hyphal formation**, endoplasmic reticulum stress, and **decreased potential for biofilm formation**

Low affinity for human GPI anchor proteins, little toxicity in human studies thus far

Clinical Advantages: Broad spectrum, intravenous and oral formulation >90% bioavailability

- Spectrum of Activity:
  - Candida spp. including C. auris
  - Not active against C. krusei
  - Cryptococcus neoformans and gattii
  - Coccidioides
  - Low minimal inhibitory concentrations (MICs) for Aspergillus and DTT hyaline moulds
  - Mucorales

FOSMANOGEPIX (APX001)

Favorable outcomes in **animal studies**: C auris infections, Candida endophthalmitis and meningoencephalitis, Cryptococcal meningitis, pulmonary scedosporiosis, disseminated fusariosis, pulmonary mucormycosis

Synergistic with liposomal AMB in improving survival in animals with aspergillosis, mucormycosis, and fusariosis

Fosmanogepix has been evaluated in **3 human studies + 1 planned:**

NCT03604705: An Efficacy and Safety Study of APX001 in Non-Neutropenic Patients With Candidemia. Phase 2. **PUBLISHED results**

NCT04148287: An Open-label Study of APX001 for Treatment of Patients With Candidemia/Invasive Candidiasis Caused by Candida Auris (APEX). Phase 2. **PUBLISHED results**

NCT04240886: Open-label Study of APX001 for Treatment of Patients With Invasive Mold Infections Caused by Aspergillus or Rare Molds (AEGIS). Phase 2. **TERMINATED** in favour of a future phase 3 study in the same subject

NCT05421858: An interventional efficacy and safety phase 3 double-blind, 2-arm study to investigate iv followed by oral fosmanogepix (pf-07842805) compared with iv caspofungin followed by oral fluconazole in adult participants with candidemia and/or invasive candidiasis. **PLANNED not yet recruiting**

NEW DRUGS, OLD CLASSES

FIRST-IN-CLASS DRUGS

Drug	Pharmacology	Spectrum of Activity: Candida	Cryptococcus	Aspergillus	Mucorales	Dimorphic Fungi[a]	Others	Phase of Development and Anticipated Indications	Notes
Oteseconazole	Class: tetrazole MOA: Inhibition of lanosterol 14-α-demethylase ROA: oral	+	+	-	- (variable activity against *Rhizopus*)	+ Includes Coccidioides, Histoplasma, and Blastomyces species.	*Trichophyton*	FDA-approved for r/r VVC in women without childbearing potential Anticipated use: treatment of r/r VVC, r/r dermatophytosis	Extremely long half-life (138 d) Once-weekly dosing Teratogenic in animal studies; absolutely contraindicated in women with reproductive potential
Opelconazole	Class: triazole MOA: Inhibition of lanosterol 14-α-demethylase ROA: inhaled	+	+	+	- (some activity against *Rhizopus*)	ND		Phase 2 trials Anticipated use: Prophylaxis of IPA	Limited systemic absorption
Rezafungin	Class: echinocandin MOA: Inhibition of β-D-glucan synthase ROA: intravenous	+ (variable against *C parapsilosis*)	-	+	-	ND	*Fusarium* *Pneumocystis*	Phase 3 trials Anticipated use: IC (including *C auris*)	Once-weekly dosing
Encochleated amphotericin B	Class: polyene MOA: Binding of ergosterol and formation of pores within the cell membrane ROA: oral	+	+	+	+	+		Phase 2 trials Anticipated use: Induction therapy for cryptococcosis and endemic mycosis, r/r mold infections	Minimal nephrotoxicity
Ibrexafungerp	Class: triterpenoid MOA: Inhibition of β-D-glucan synthase ROA: oral	+	ND	+	-	+	*L prolificans* *P variotii* *Pneumocystis*	FDA-approved for r/r VVC, phase 3 trials Anticipated use: Oral step down for IC (including *C auris*)	Active against most echinocandin-resistant *Candida* Anti-biofilm
Fosmanogepix	Class: GPI inhibitor MOA: Inhibition of Gwt1 ROA: oral, intravenous	+ (except *C krusei*)	+	+	+/–	+	*Fusarium* *L prolificans* *Scedosporium* *Trichophyton*	Phase 3 trials Anticipated use: r/r mold infections	High barrier to resistance Anti-biofilm
Olorofim	Class: orotomide MOA: Inhibition of DHODH ROA: oral, intravenous	-	-	+	-	+	*F oxysporum* *L prolificans* *Scedosporium* *T marneffei* *Trichophyton*	Phase 3 trials Anticipated use: r/r aspergillosis and mold infections	-

CONCLUSIONS

INNOVATIONS OF NEW/FUTURE antifungals:

Long half-life
No cross resistance
Low drug-drug interactions
Better tolerability
Efficacy for PDR rare fungi
Better PK/PD properties
Oral formulations

… and it's not over:

-Other compounds (preclinical, phases 1&2)
-Some drugs only for sinergistic mechanisms
-No antifungals agents, repurposed for in vitro antifungal activity
-Natural products, plant and marine-based antifungals
-human anti-candida monoclonal antibodies
-Phage Therapy