Impact of invasive fungal diseases and antifungal drug resistance on human health

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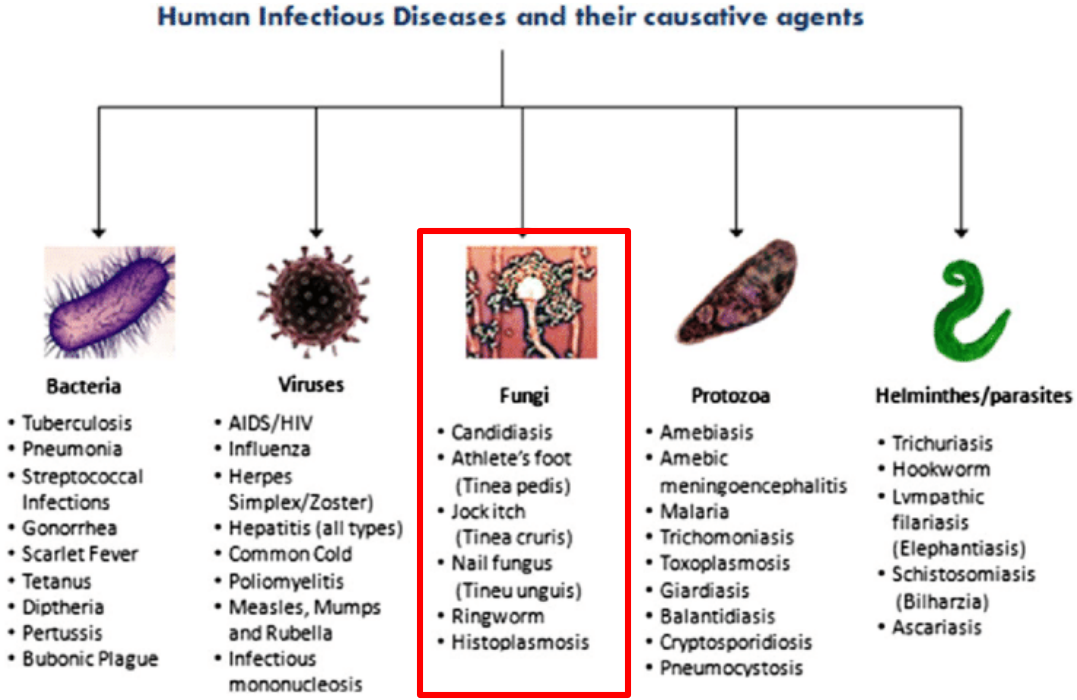
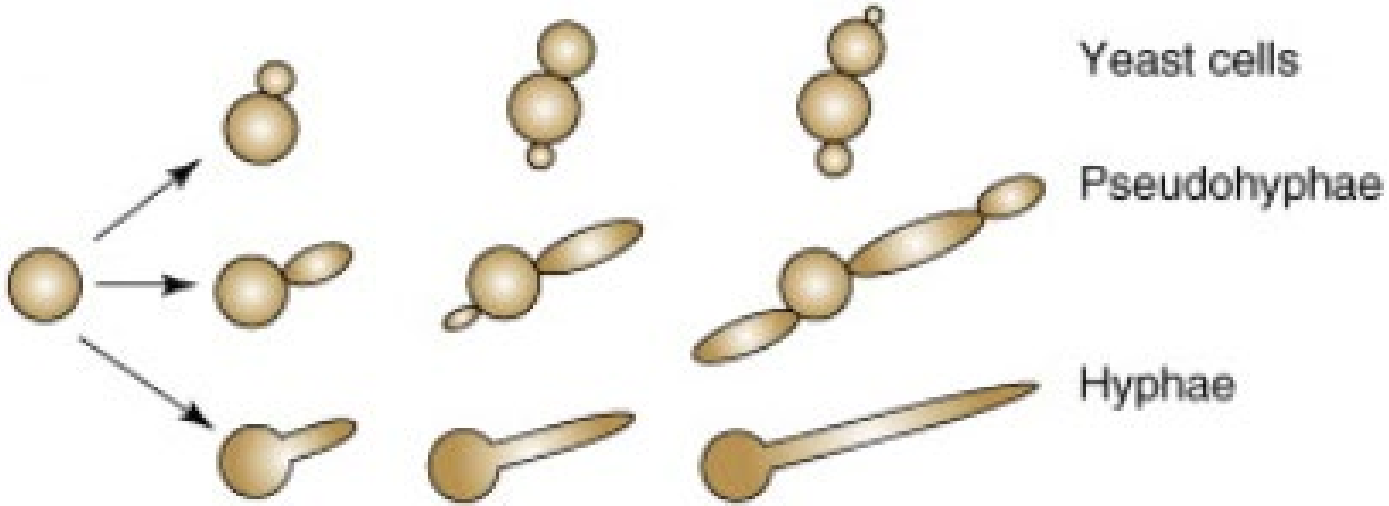
NATIONAL LEADERS IN MEDICINE

WUMG

Classification of human infections

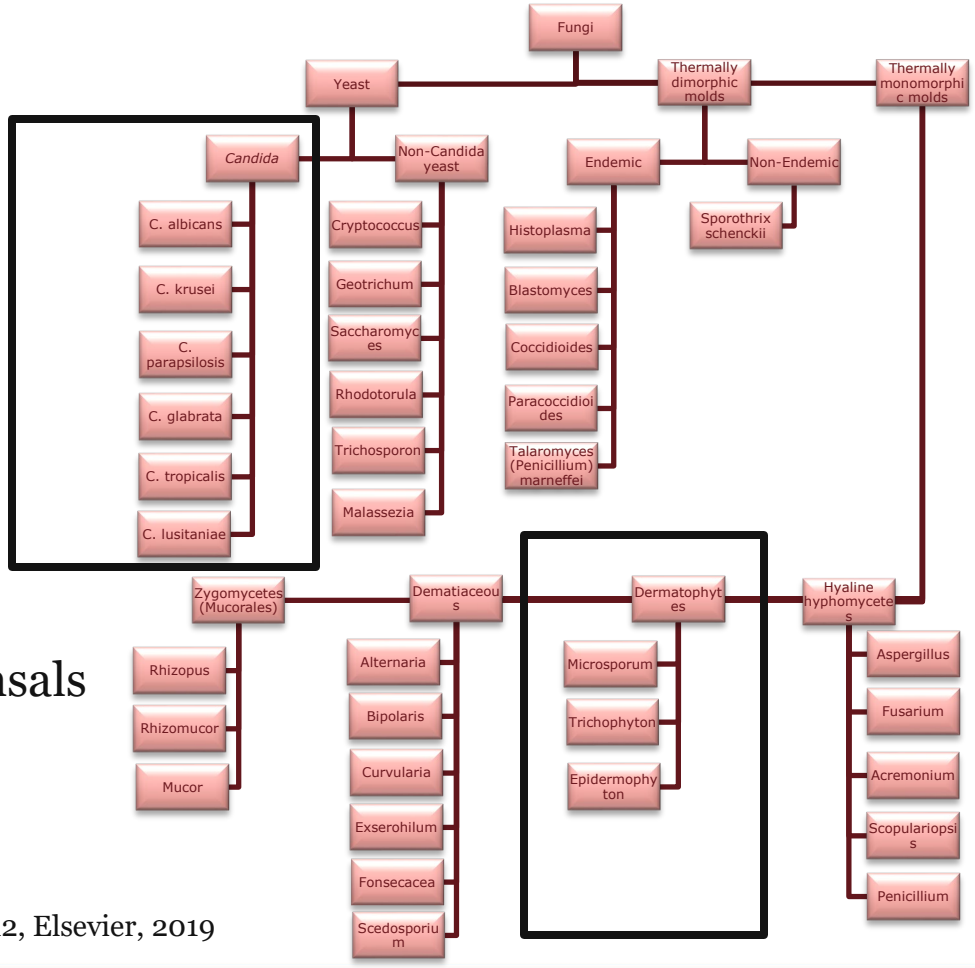


Fungal morphology



Spec, Comprehensive Review of Infectious Disease, Ch2, Elsevier, 2019

Medical Classification of Fungi



▭ =Part of microbiome/commensals

Spec, Comprehensive Review of Infectious Disease, Ch2, Elsevier, 2019

Two main varieties of infection

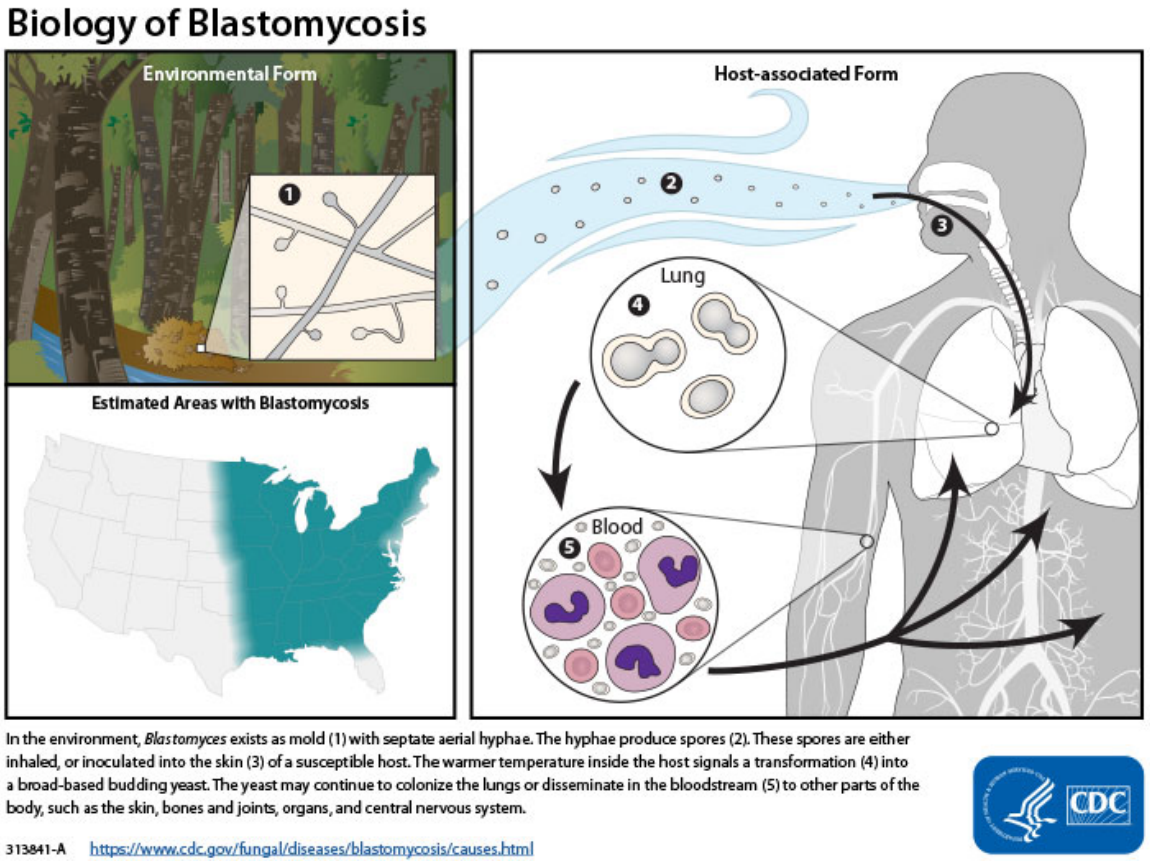
Commensals

- Candida and skin disease
- Part of microbiome, cause disease when there is:
  - Too much of them
  - End up in wrong place

Environmental

- "Everything" else
- Majority of lifecycle is spent in environment
- Spores/Conidia are formed and patient inhales the fungus
- Infection starts as pneumonia, and may or may not disseminate
- Where they disseminate, and how often they do varies widely
- Rare exception of direct inoculation

Example of spread of environmental fungus

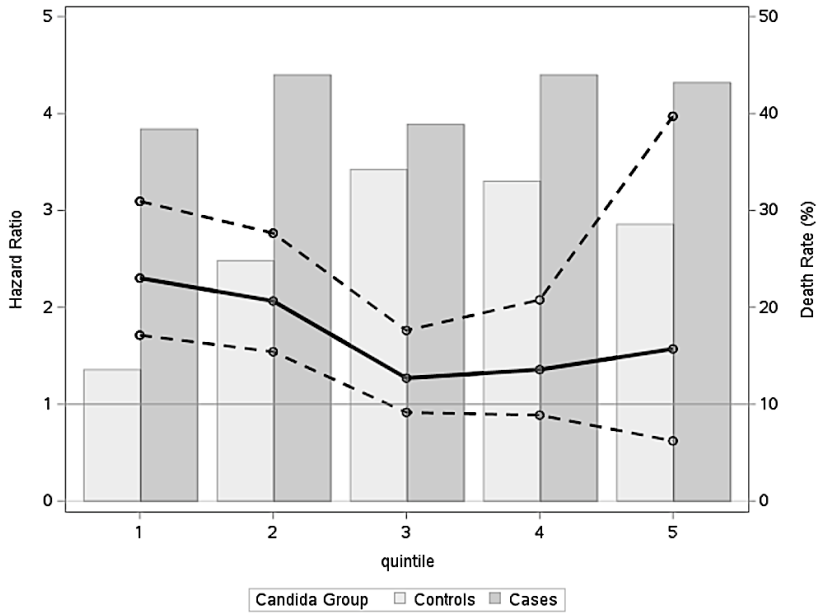


Global burden of fungal infections

- Fungi are the most common rare disease we have
- Combined, responsible for ~1.5 million deaths a year
- ~300,000 of cryptococcal meningitis in Sub-Saharan Africa alone
- Aspergillus is experiencing a 4.4%~ increase in incidence yearly
- Economic Cost: $7.2 billion dollars in direct healthcare costs in 2017, total cost of $11.5 billion, if assessed at "value of statistical life" total cost is >$48 billion

ASM Blog: Invasive Fungal Infections: A Creeping Public Health Threat
Open Forum Infectious Diseases, Volume 9, Issue 4, April 2022, ofac097

Outcomes-Candida

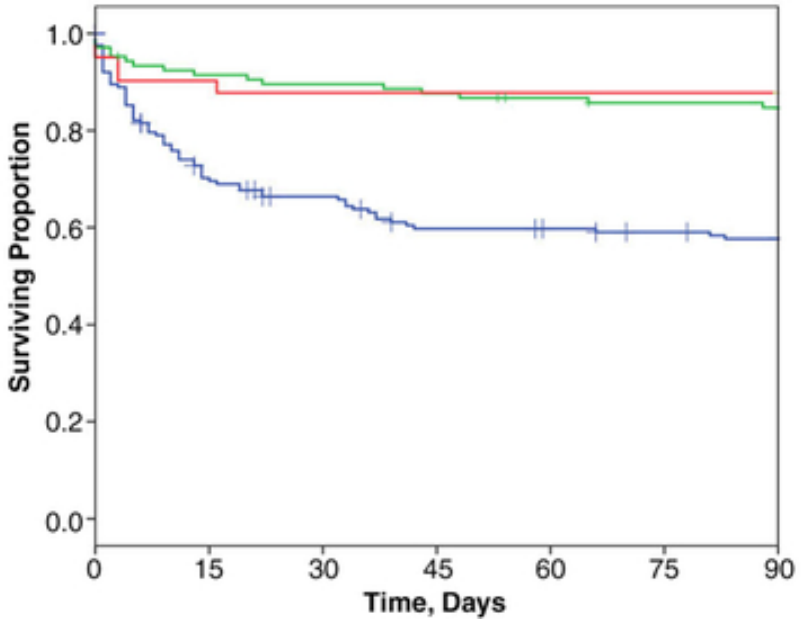


- Mortality around 45%
- 10-25% attributable mortality
- Attributable mortality worse in those less sick

Clinical Infectious Diseases, ciac004, https://doi.org/10.1093/cid/ciac004

Mortality- Cryptococcus

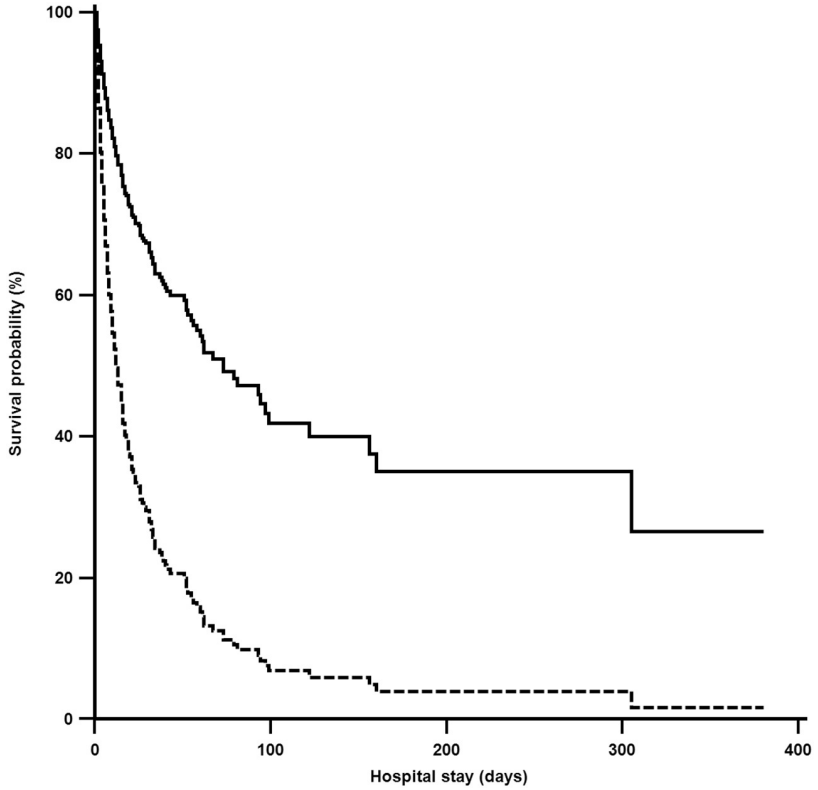
- In patients living with HIV and transplants, mortality is ~15% but 40% in those without
- The latter group is growing



Am J Med. 2019 Aug;132(8):977-983.e1.

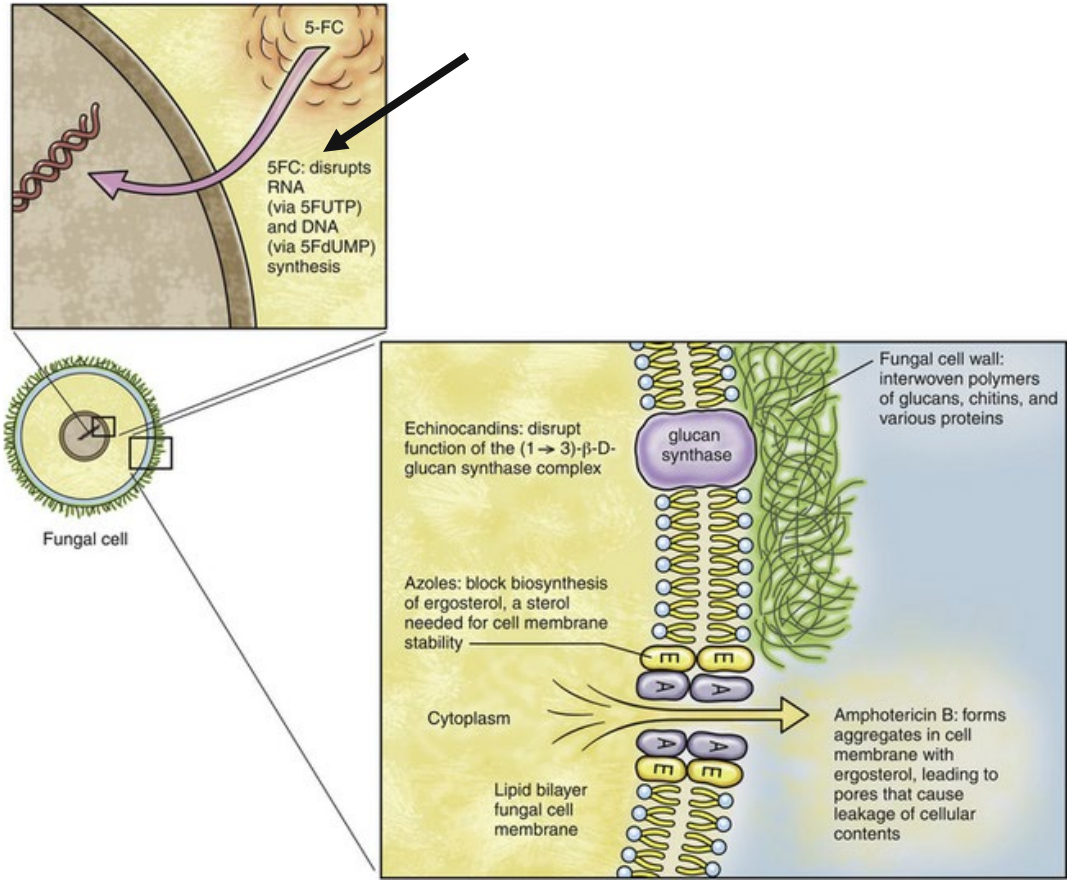
Outcomes-Mucor

- Mortality ~100% if surgery not combined with antifungal therapy
- 70% if combined
- Many survivors are permanently disfigured



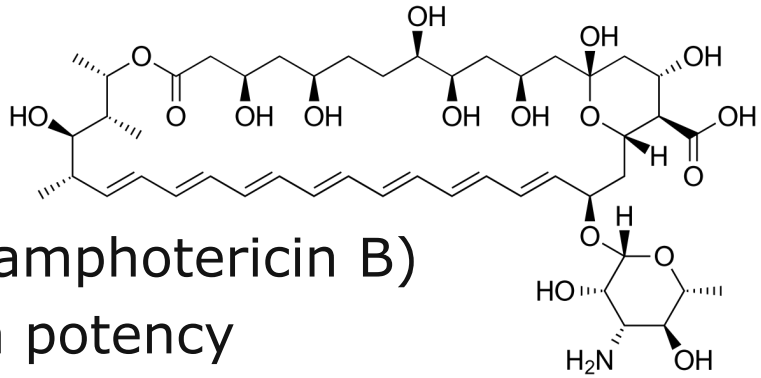
Clinical Microbiology and Infection 2020 26944.e9-944.e15DOI: (10.1016/j.cmi.2019.11.021)

Treatment



Stevens DA. Systemic antifungal agents. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases, 7 ed. Philadelphia, PA: Churchill Livingstone Elsevier 2011:549-563.

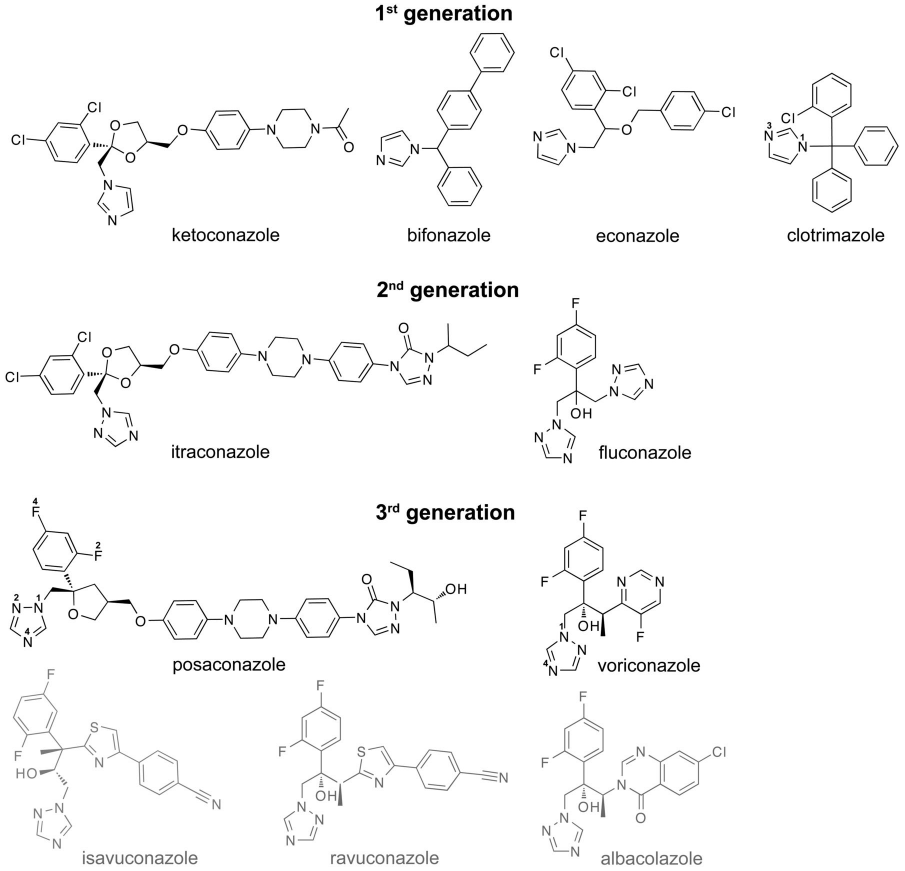
Class 1: Polyenes



- Only one systemic medication (amphotericin B)
- Broad spectrum of activity, high potency
- Unfortunately an IV only therapy
- Probably the most potent antifungal ever made, but….
- Also a very good "antihuman"
  - Extreme renal toxicity, not a matter of if, just a matter of when
  - Electrolyte wasting (Potassium and Magnesium)
  - Infusion reactions

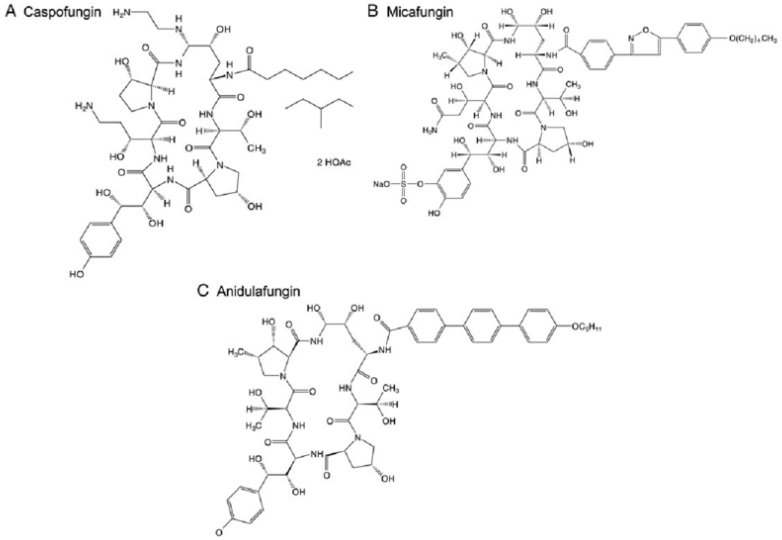
Class 2: Azoles

- Most diverse class of antifungals
- Varying levels of broadness of activity
- Only PO class
- Significant issues:
  - Most have difficult absorption
  - Difficult Drug-Drug interactions
  - Idiosyncratic side effects
  - Liver toxicity
  - Narrow therapeutic index



Class 3: Echinocanins

- The “good” antifungal
- Very well tolerated
- However:
  - IV only
  - Narrow spectrum of activity



Impact of resistance: Intrinsic resistance

- Poor/no PO options
  - *Candida krusei*
  - *C. glabrata*
  - Azole resistant *Aspergillus*
- Intrinsic resistance to all antifungals (at least in some isolates)
  - *Scapulariopsis brumptii*
  - *Lomentospora prolificans*
  - *Scetosporium apiospermum/Pseudoalascheria boydeii*
  - *C. auris* (4%)
  - *Fusarium,* especially *F. solani*

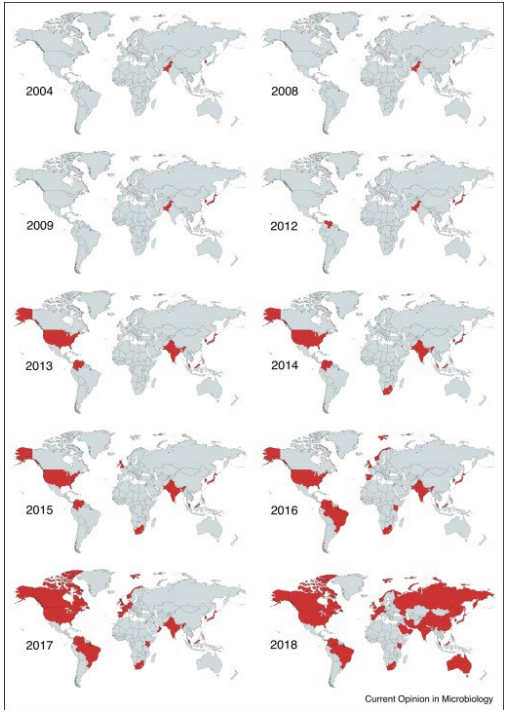
Impact of resistance: Rise of resistance; Candida

- Echinocandin resistance of *C. glabrata* in Duke (2001-2010) increase from 4.9% to 12.3%
- New emergence and spread of fluconazole resistance in *Candida parapsislosis*

Clin Infect Dis. 2013 Jun;56(12):1724-32
Antimicrob Agents Chemother. 2015 Oct; 59(10): 6581–6587.

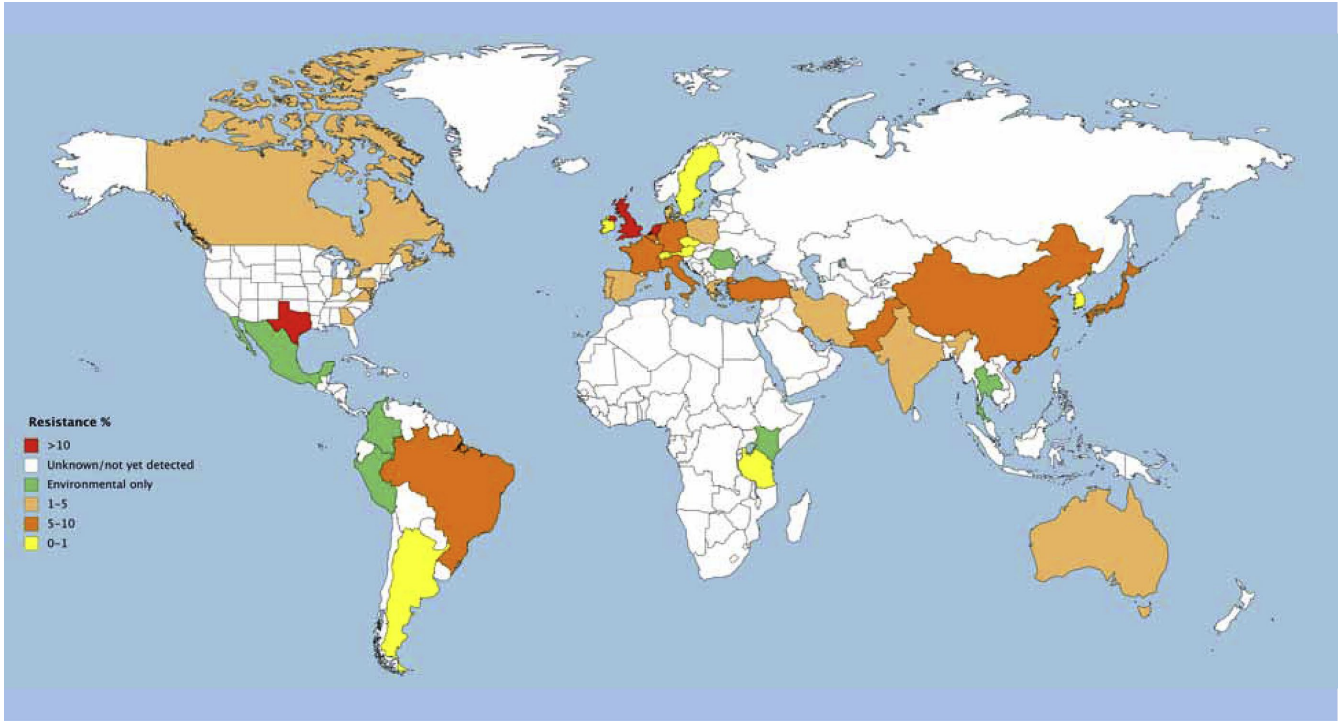
Impact of resistance: Emergence of *C. auris*

- From 2004 to now, explosive growth of a novel, highly resistant species of *Candida*
  - *90% resistant to fluconazole*
  - *30% resistant to amphotericin B*
  - *10% resistant to Echinocanins*
  - *4% to all three*
- In some places, it is now a significant portion of new cases



Current Opinion in Microbiology Volume 52, December 2019, Pages 84-89

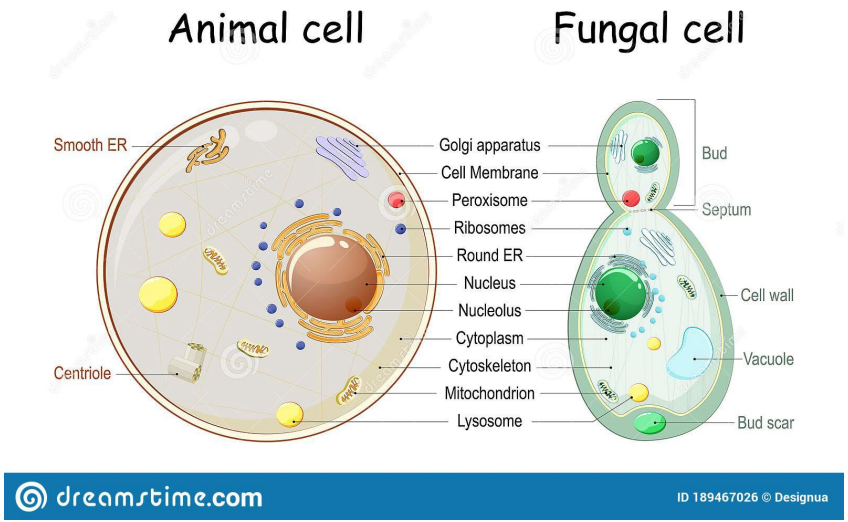
Impact of resistance: Rise of resistance; aspergillus

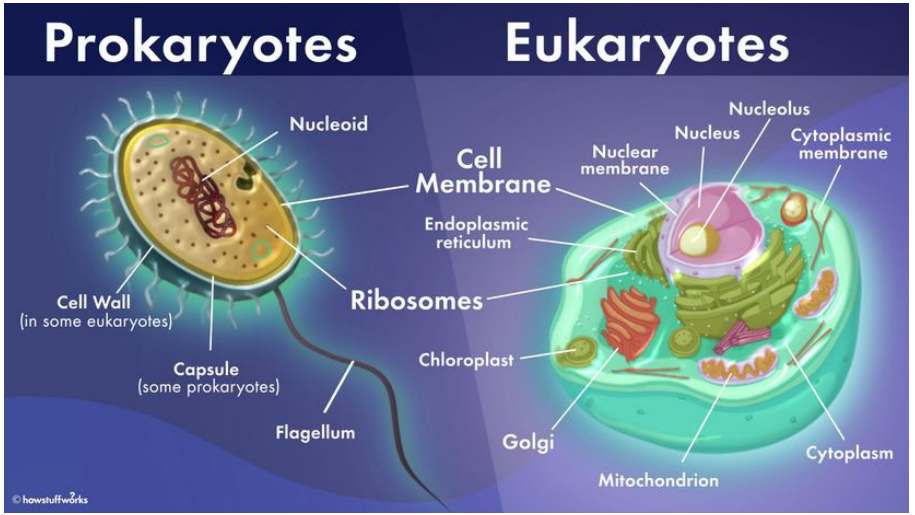


Clinical Microbiology and Infection 2019 25799-806

SOLUTION: JUST MAKE NEW DRUGS

Why are antifungals hard to develop?





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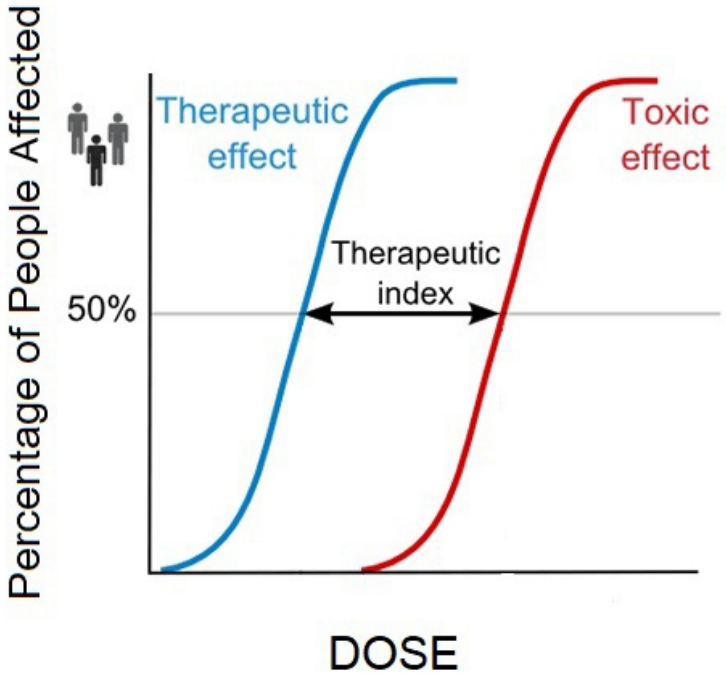
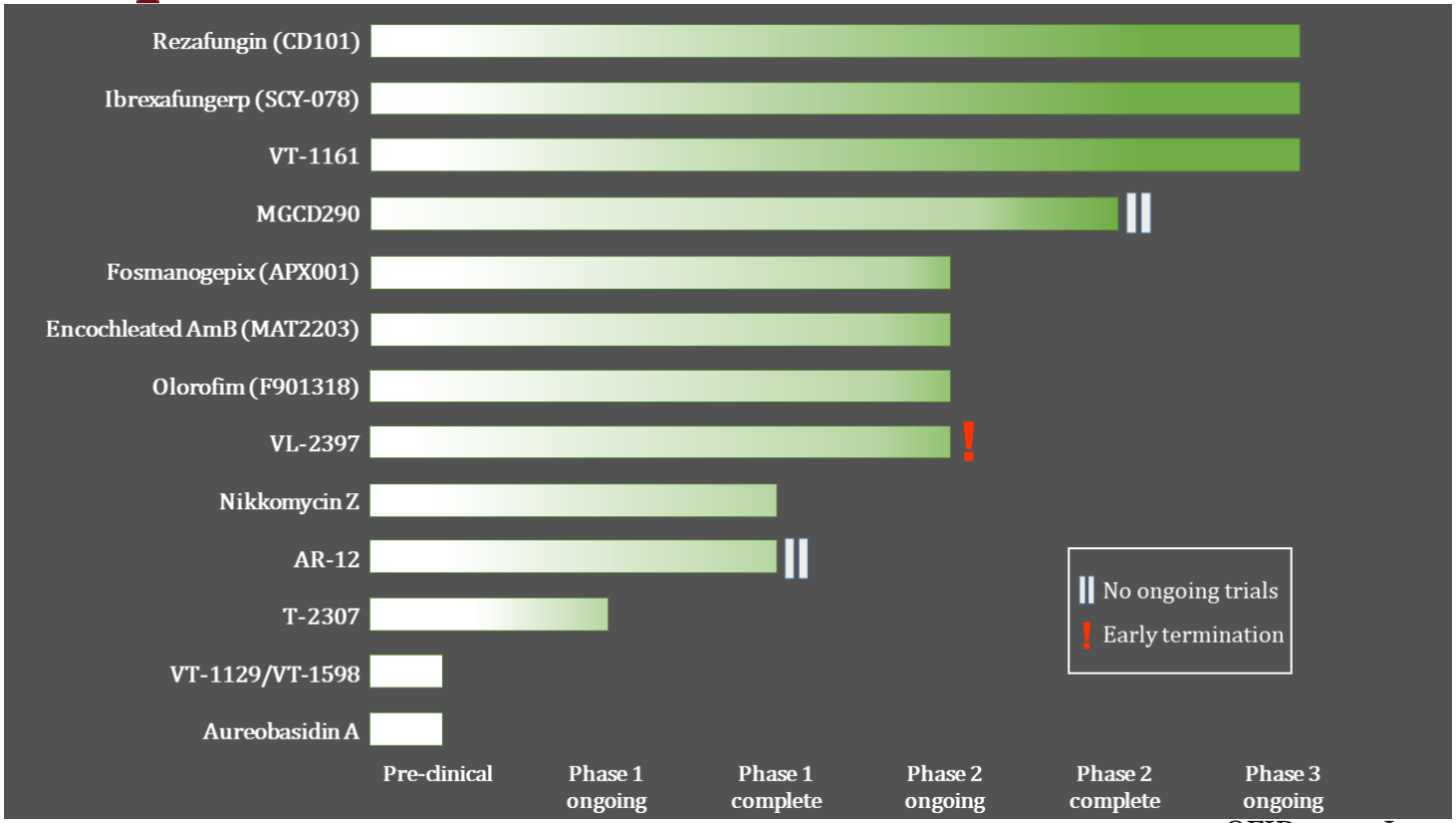


Antifungal Effect

Antihuman effect

The Pipeline



OFID 2020 Jan 12;7(2):ofaa016.

Conclusions

- Fungi are a complicated set of diseases
- The outcomes are far from good
- The current armamentarium is limited, and far from perfect
- There is some hope for future compounds, but much less so than bacteria, and they are much harder to develop
- It is important that we protect our drugs, because the outcomes are much worse without therapy, and second line therapy is often very inferior