Podiplomski tečaj protimikrobnega zdravljenja

Protiglivna zdravila

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Ljubljana, 4.6.2025

1

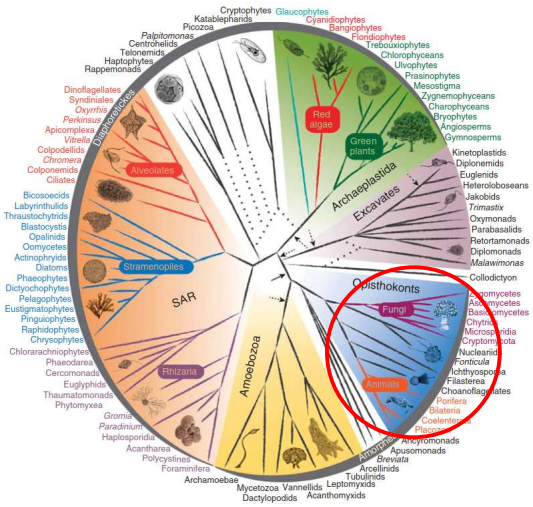
Kaj so glive?

- Evkarionti
- Heterotrofi
- Glavni razkrojevalci v ekosistemu

https://en.wikipedia.org/wiki/Fungus#/media/File:Fungi_collage.jpg

2

Glive so v sorodu z nami



- Filogenetika
- Kraljestvi živali in gliv sta tesno povezani
- Izziv za zdravljenje in razvoj cepiv
- Ključni razliki
  - ergosterol
  - celična stena (glukan)

Burki F et al. Cold Spring Harb Perspect Biol 2014

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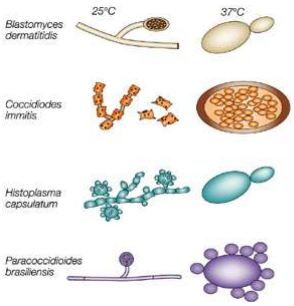
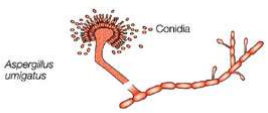
Kraljestvo gliv

<u>Kvasovke</u>
Cryptococcus
Saccharomyces
C. glabrata



<u>Dimorfne glive</u>
Blastomyces
(Para)Coccidioides
Histoplasma
C. albicans



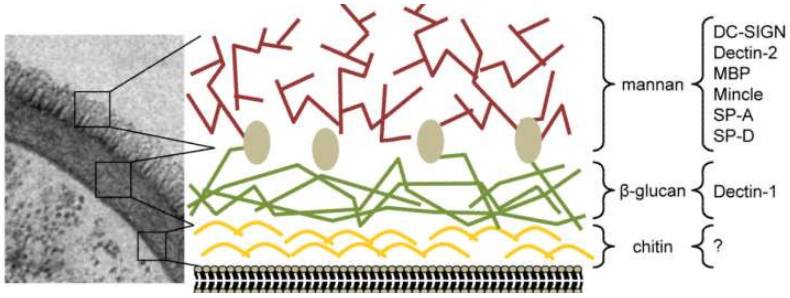
<u>Plesni</u>
Aspergillus
Zygomycetes

4

Imunski odziv na okužbo

- Štiri družine PRR: Toll-like (TLR), Nod-like (NLR), RIG-I like (RLR) in CLR (*C-type lectin receptors)*

Vežejo se na celice gliv. Prepoznajo ogljikohidratne strukture v celični steni gliv: β-glukan in manan.



Hardison SE. Nat Immunol 2012

5

Če ni prepoznave glivne celične stene

The NEW ENGLAND JOURNAL of MEDICINE

Deep Dermatophytosis and Inherited CARD9 Deficiency

Authors: Fanny Lanternier, M.D., Saad Pathan, Ph.D., Quentin B. Vincent, M.D., Luyan Liu, M.Sc., Sophie Cypowyj, Ph.D., Carolina Prando, M.D., Ph.D., Mélanie Migaud, B.S., +25, and Anne Puel, Ph.D. Author Info & Affiliations

Published October 31, 2013 | N Engl J Med 2013;369:1704-1714 | DOI: 10.1056/NEJMoa1208487
VOL. 369 NO. 18 | Copyright © 2013

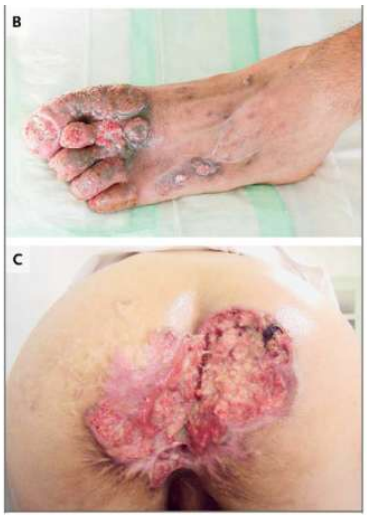
BRIEF REPORT

Human Dectin-1 Deficiency and Mucocutaneous Fungal Infections

N ENGL J MED 361;18 NEJM.ORG OCTOBER 29, 2009

Science AAAS

Chronic Mucocutaneous Candidiasis in Humans with Inborn Errors of Interleukin-17 Immunity
Anne Puel *et al.*
Science **332**, 65 (2011);
DOI: 10.1126/science.1200439



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Breme glivnih okužb - globalno

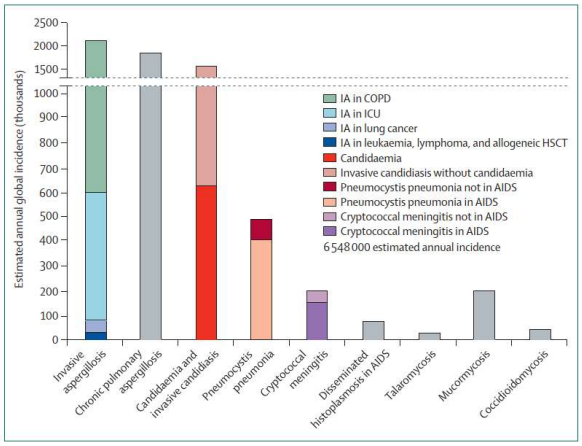

Figure 1: **Estimated annual incidence of life-threatening invasive mycoses, together with chronic pulmonary aspergillosis**

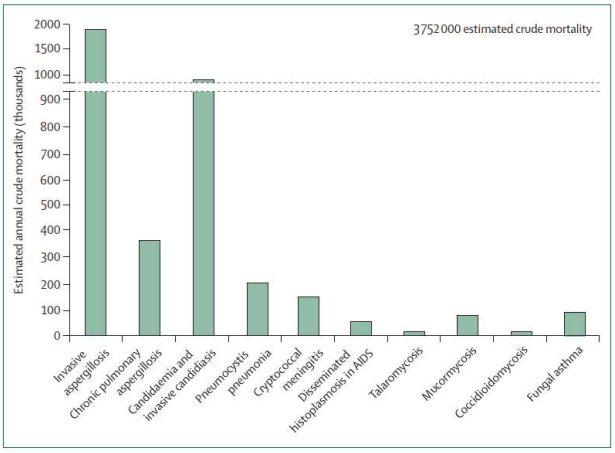

Figure 2: **Estimated crude mortality of severe fungal disease, worldwide**

Denning D et al. Lancet Inf Dis 2024

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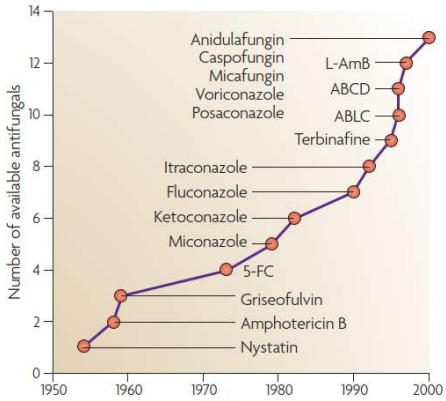
Razvoj sistemskih antimikotikov



- Amfotericin B: 4 preparati
- Azoli: 6 zdravil
- Ehinokandini: 3 zdravila
- Zaviralec skvalen epoksida: terbinafin
- Analog pirimidina: 5-flucitozin

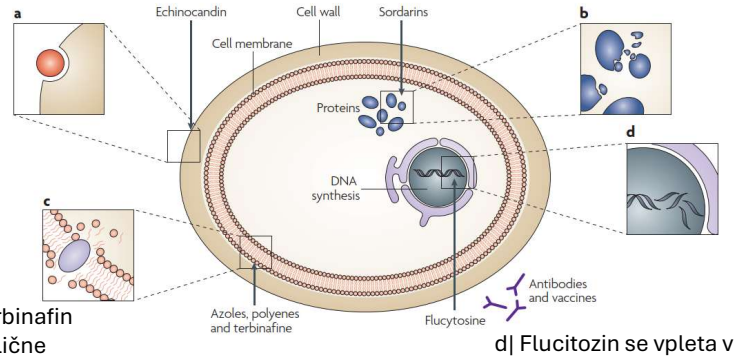
Ostrosky-Zeichner L et al. Nat Rev Drug Discov 2010

8

Ključni mehanizmi delovanja protiglivnih zdravil

a| Ehinokandini in nikomicin Z zavirajo tvorbo celične stene.

b| Sordarini se vpletajo v sestavljanje beljakovin.



c| Azoli, polieni in terbinafin motijo integriteto celične membrane.

d| Flucitozin se vpleta v sintezo DNK. Protitelesa in cepiva preprečujejo okužbo ali blokirajo in/ali uničujejo glivne celice.

Ostrosky-Zeichner L et al. Nat Rev Drug Discov 2010

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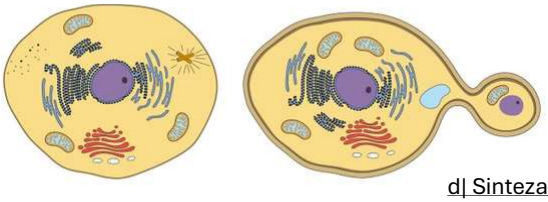
Razlika med človeško in glivno celico

a| Celična stena
Mi: je nimamo
Glive: kompleksni OH

b| Sinteza beljakovin
Mi *vs* glive: velika podobnost

Človeška celica

Glivna celica



c| Integriteta membran
Mi: holesterol
Glive: ergosterol

d| Sinteza DNK
Mi *vs* glive: velika podobnost

https://www.shutterstock.com/search/fungus-cell-structure

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Amfotericin

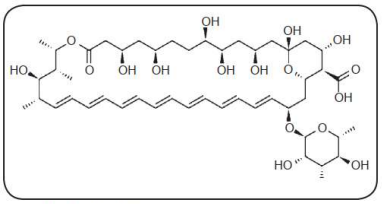

FIGURE 1 - Chemical structure of amphotericin B.

- 1958: amfotericin
- 1995: lipidne oblike
- Vezava na ergosterol in tvorba por v celični membrani
- Povzroči iztok K in citoplazemske vsebine
- Odpornost: zmanjšanje sinteze ergosterola
- Slaba biološka uporabnost (samo IV), dobra razporeditev (razen CŽS, oko)
- Pozor pri okužbi z *A. terreus, Scedosporuim* spp*, C. lusitanie*

Chávez-Fumagalli MA et al. Revista Da Sociedade Brasileira De Medicina Tropical 2015

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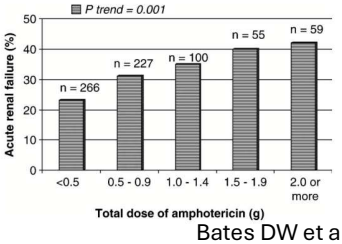
Amfotericin - neželeni učinki

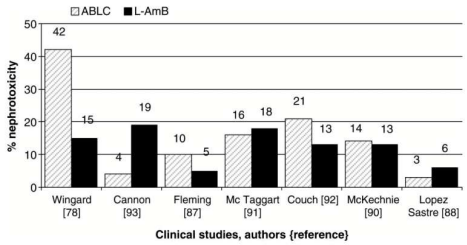
- Izguba kalija
- Okvara ledvic
- Povišana temperatura



Bates DW et al. Clin Inf Dis 2001

Lipidne oblike amfotericina

- Boljša toleranca
- Manj ALO



Saliba F et al. Med mycol 2008

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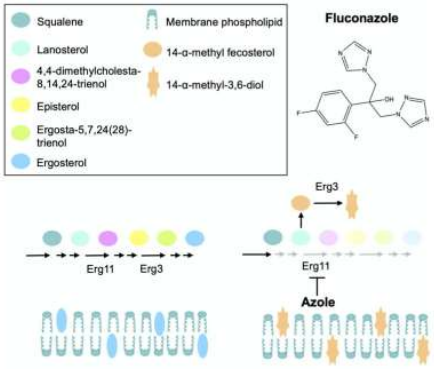
Azoli

- 1982: ketokonazol
- Zavirajo C-14α demetilacijo lanosterola (prekurzor ergosterola)
- Posledica je manj ergosterola in nestabilnost membrane, ki jo povzročijo toksične prekurzorji
- ! Pozor *C. krusei* intrinzično odporna
- Posebnosti

Vorikonazol: kožni rak, periostitis,

Posakonazol: počasno doseganje th nivoja

Izavukonazol: podobno kot flukonazol



Puumala E et al. Antimicrob agent Chemother 2024

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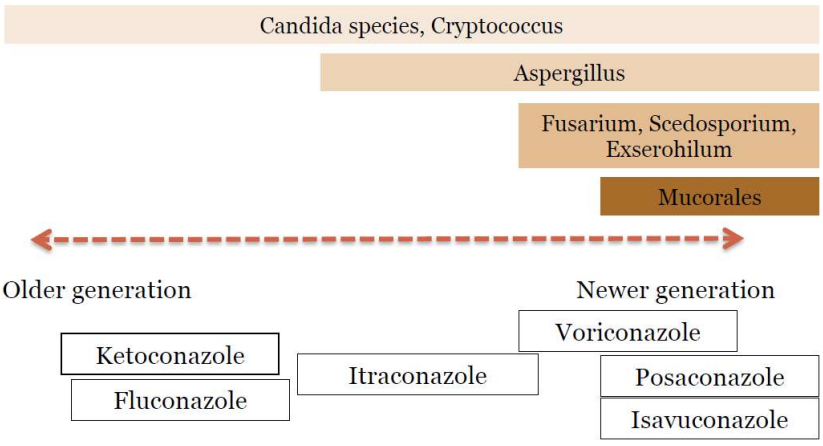
Azoli – protiglivni spekter učinkovitosti



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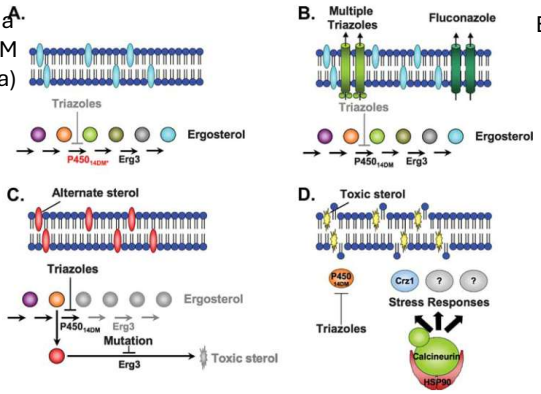
Azoli – mehanizmi odpornosti

A| Mutacija ali upregulacija tarče - citokrom P45014DM (lanosterol 14 –demetilaza)



B| Povečana tvorba izlivnih črpalk

C| Mutacija Erg3, zaradi česar se ne kopičijo toksične predstopnje sterola

D| Hsp90 stabilizira kalcinevrin in posreduje stresne odzive, ki so potrebni za toleranco azolov

Cowen LE et al. Eukaryotic Cell 2008

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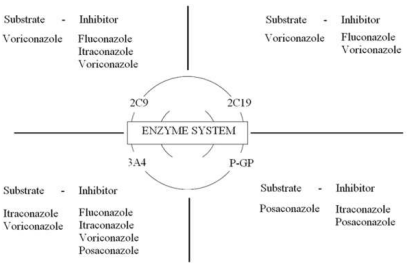
Azoli – interakcije z drugimi zdravili

- Večina NU zaradi inhibicije sistema citokrom P450
- Veliko součinkovanj

Sprememba nivoja ob azolu
- statini
- benzodiazepini
- kalcinevrin zaviralci
- ritonavir
- kumadini
- anti-psihotiki



Zmanjšan nivo azola
- rifampin
- anti-epileptiki

Brüggemann RJM et al. Clini Inf Dis 2009

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Azoli višjih generacij

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

N ENGL J MED 356;4 WWW.NEJM.ORG JANUARY 25, 2007

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Aspergillus rate:
1% *vs* 5,9%

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Aspegillus - vorikonazol vs amfotericin

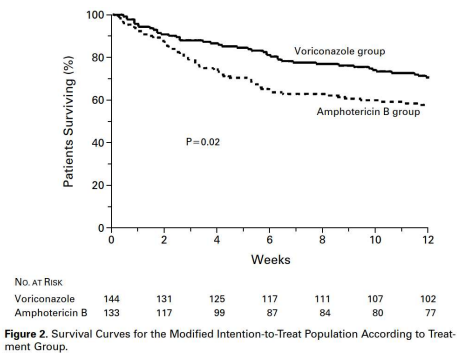


Figure 2. Survival Curves for the Modified Intention-to-Treat Population According to Treatment Group.

- Ugoden klinični izid
  - vorikonazol 53%

  popolni odziv 21% + delni odziv 32%
  - amfo B deoksiholat 31,6%

  popolni odziv 16,5% + delni odziv 15%

- Preživetje
  - vorikonazol 70,8%
  - amfo B deoksiholat 57,9%

Herbrecht R et al. NEJM 2002

18

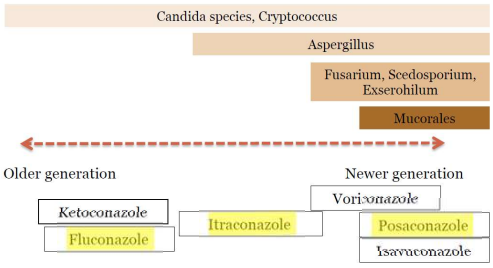
Posakonazol vs fluko/itrakonazol -AML

- Bolniki z AML in prolongirano Ne-penijo (n=602)

- posakonazol (n=304)

- flukonazol (n=240) ali itrakonazol (n=58)

- Spremljanje invazivnih glivnih okužb



Cornely OA et al. NEJM 2007

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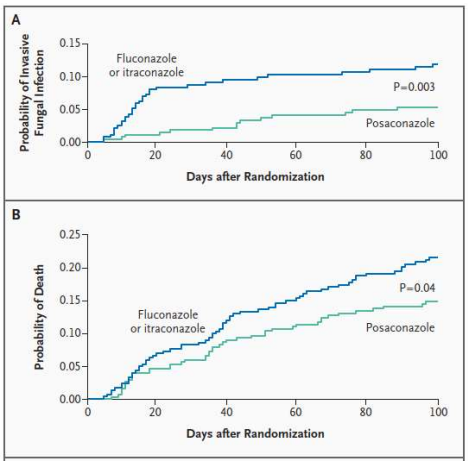
Posakonazol vs fluko/itrakonazol - AML



- Manj IA v skupini s posa
  - posa 1%
  - fluko/itra 7%
- Manjša smrtnost
  - posa 16%
  - fluko/itra 22%
- Več resnih neželenih sopojavov
  - posa 6%
  - fluko/itra 2%

Cornely OA et al. NEJM 2007

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Izavukonazol

- Odličen varnostni profil
- Skrajšuje qTc
- IV in peroralna oblika
- Brez ciklodekstrina kot pri vorikonazolu
- Raziskavi VITAL in SECURE

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Izavukonazol - SECURE

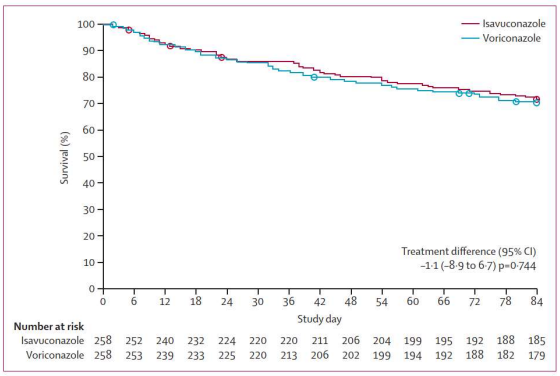

Figure 2: Survival from first dose of study drug to day 84

- Alo PKMC
  - izavukonazol (n=258)
  - vorikonazol (n=256)
- Smrtnost do dneva 42
  - izavu 19%
  - voriko 20%
  - 1,0% (95% CI −7,8 do 5,7)... izavu ne-inferioren
- Neželenih sopojavov
  - izavu 42%
  - voriko 60%; *p*<0,001

Maertens JA et al. Lancet 2016

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Najpogostejši neželeni sopojavi azolov

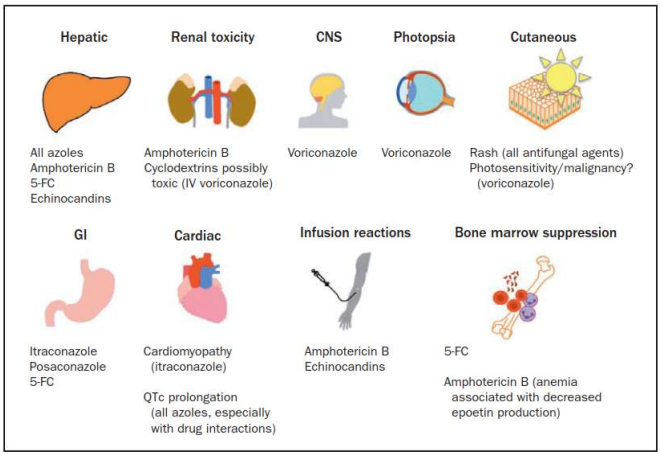

FIGURE 4. Common toxicities of antifungal agents. CNS = central nervous system; 5-FC = flucytosine; GI = gastrointestinal; IV = intravenous; QTc = corrected QT interval.

Lewis LE. Mayo Clin Proc 2011

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Glavni sopojavi vorikonazola

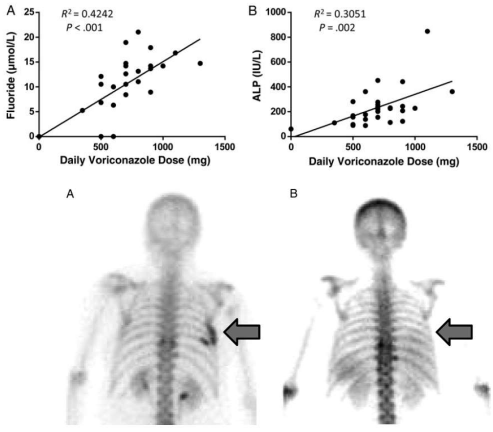

Figure 4. Posterior view of the whole-body bone scan, before and after voriconazole discontinuation. This patient had evidence of right rib periostitis approximately 5 months after beginning voriconazole (*A*). Approximately 11 months after discontinuation of voriconazole, a repeat bone scan shows no evidence of periostitis (*B*).

Moon WJ et al. Clin Inf Dis 2014

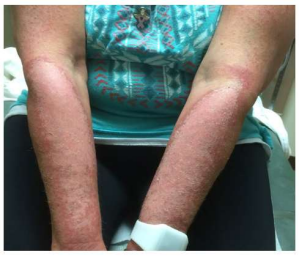

FIGURE 1 Voriconazole-associated phototoxicity presenting on the arms

Levine MT et al. Clin Trasplant 2016

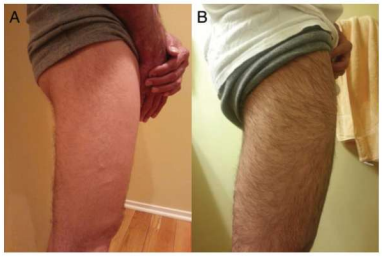

Figure 1. *A*, Voriconazole-associated alopecia is shown on the right leg of a 47-year-old man who had an epidural abscess associated with contaminated methylprednisolone injection. *B*, Three months after discontinuation of voriconazole, the alopecia had resolved.

Malani AN et al. Clin Inf Dis 2014

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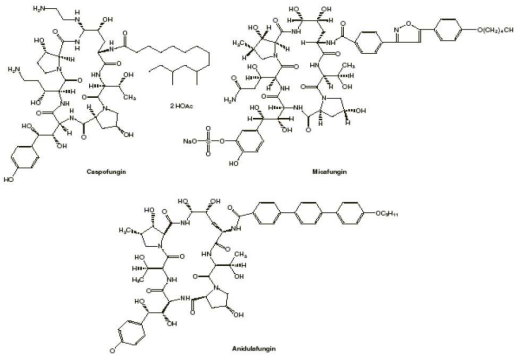
Ehinokandi

- Zavirajo glukan sintazo
- Manj β-1-3-D-glukana
- Nekoliko učinkoviti tudi proti plesnim
- Fungicidni za kandido
- Fungistatični za aspergilus
- ! Pozor: *Cryptococcus neoformans* ni odvisen od β-1-3-D-glukana

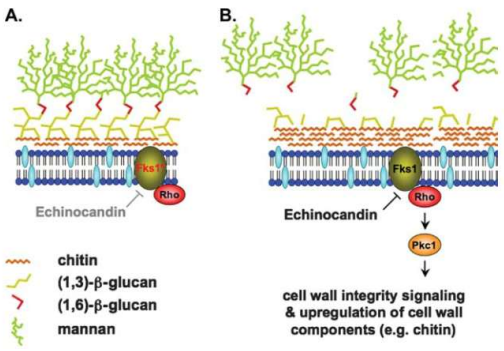


Eschenauer G. Ther Clin Risk Man 2007

25

Ehinokandini – mehanizmi odpornosti

A. Mutacija 1, 3-β-D-glukan sinhaze, ki je tarča ehinokandinov



B. Rho1 posreduje stresne odzive, tudi aktivacijo poti PKC, ki podpira integriteto membrane in spodbudi sintezo drugih sestavin stene (hitina), kar prispeva k toleranci na ehinokandine

Cowen LE et al. Eukaryotic Cell 2008

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Kaspofungin *vs* amfotericin B

Background Caspofungin is an echinocandin agent with fungicidal activity against candida species. We performed a double-blind trial to compare caspofungin with amphotericin B deoxycholate for the primary treatment of invasive candidiasis.

Methods We enrolled patients who had clinical evidence of infection and a positive culture for candida species from blood or another site. Patients were stratified according to the severity of disease, as indicated by the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and the presence or absence of neutropenia and were randomly assigned to receive either caspofungin or amphotericin B. The study was designed to compare the efficacy of caspofungin with that of amphotericin B in patients with invasive candidiasis and in a subgroup with candidemia.

Conclusions Caspofungin is at least as effective as amphotericin B for the treatment of invasive candidiasis and, more specifically, candidemia. (N Engl J Med 2002;347:2020-9.)

Results Of the 239 patients enrolled, 224 were included in the modified intention-to-treat analysis. Base-line characteristics, including the percentage of patients with neutropenia and the mean APACHE II score, were similar in the two treatment groups. A modified intention-to-treat analysis showed that the efficacy of caspofungin was similar to that of amphotericin B, with successful outcomes in 73.4 percent of the patients treated with caspofungin and in 61.7 percent of those treated with amphotericin B (difference after adjustment for APACHE II score and neutropenic status, 12.7 percentage points; 95.6 percent confidence interval, −0.7 to 26.0). An analysis of patients who met prespecified criteria for evaluation showed that caspofungin was superior, with a favorable response in 80.7 percent of patients, as compared with 64.9 percent of those who received amphotericin B (difference, 15.4 percentage points; 95.6 percent confidence interval, 1.1 to 29.7). Caspofungin was as effective as amphotericin B in patients who had candidemia, with a favorable response in 71.7 percent and 62.8 percent of patients, respectively (difference, 10.0 percentage points; 95.0 percent confidence interval, −4.5 to 24.5). There were significantly fewer drug-related adverse events in the caspofungin group than in the amphotericin B group.

Mora-Duarte J et al. NEJM 2002

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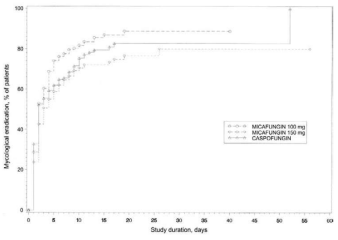
Mikafungin *vs* kaspofungin

Background. Invasive candidiasis is an important cause of morbidity and mortality among patients with health care–associated infection. The echinocandins have potent fungicidal activity against most *Candida* species, but there are few data comparing the safety and efficacy of echinocandins in the treatment of invasive candidiasis.

Methods. This was an international, randomized, double-blind trial comparing micafungin (100 mg daily) and micafungin (150 mg daily) with a standard dosage of caspofungin (70 mg followed by 50 mg daily) in adults with candidemia and other forms of invasive candidiasis. The primary end point was treatment success, defined as clinical and mycological success at the end of blinded intravenous therapy.

Results. A total of 595 patients were randomized to one the treatment groups and received at least 1 dose of study drug. In the modified intent-to-treat population, 191 patients were assigned to the micafungin 100 mg group, 199 to the micafungin 150 mg group, and 188 to the caspofungin group. Demographic characteristics and underlying disorders were comparable across the groups. Approximately 85% of patients had candidemia; the remainder had noncandidemic invasive candidiasis. At the end of blinded intravenous therapy, treatment was considered successful for 76.4% of patients in the micafungin 100 mg group, 71.4% in the micafungin 150 mg group, and 72.3% in the caspofungin group. The median time to culture negativity was 2 days in the micafungin 100 mg group and the caspofungin group, compared with 3 days in the micafungin 150 mg groups. There were no significant differences in mortality, relapsing and emergent infections, or adverse events between the study arms.

Conclusions. Dosages of micafungin 100 mg daily and 150 mg daily were noninferior to a standard dosage of caspofungin for the treatment of candidemia and other forms of invasive candidiasis.



Pappas PG et al. Clin Inf Dis 2007

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Ehinokandini *vs* azoli

- 256 bolnikov z invazivno kandidozo randomiziranih (89% kandidemija)
  - anidula 200 mg, nato 100 mg
  - flukonazol, 800 mg, nato 400 mg
- *Candida* spp
  - *albicans* 62%
  - *glabrata* 18%
  - *parapsilosis* 11%
  - *tropicalis* 10%
  - *C. krusei* izključen

Characteristic	Anidulafungin Group (N=127)	Fluconazole Group (N=118)
Baseline candida pathogen — no. (%)		
Candida albicans	81 (64)	70 (59)
C. glabrata	20 (16)	30 (25)
C. parapsilosis	13 (10)	16 (14)
C. tropicalis	15 (12)	11 (9)
Other candida species	6 (5)	3 (3)

Reboli AC et al. NEJM 2007

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Ehinokandini *vs* azoli

- Učinkovitost
  - anidula 73%
  - flukonazol 61%
- Smrtnost
  - anidula 31%
  - flukonazol 23%
  - *p*=0,013
- Neželeni sopojavi: primerljiva pogostost in spekter

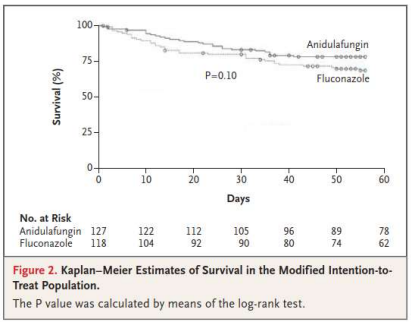

Figure 2. Kaplan–Meier Estimates of Survival in the Modified Intention-to-Treat Population.
The P value was calculated by means of the log-rank test.

CONCLUSIONS

Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive candidiasis. (ClinicalTrials.gov number, NCT00056368).

Reboli AC et al. NEJM 2007

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Ehinokandini *vs* azoli

Odmerjanje ehinokandinov
- Kaspofungin

polnitveni odmerek 70 mg, nato 50 mg
- Mikafungin

150 mg, nato 100 mg
- Anidulafungin

200 mg, nato 100 mg

Neželeni sopojavi
- redki (blag hepatitis)

TABLE 6. DRUG-RELATED ADVERSE EVENTS AND OTHER SAFETY END POINTS.

VARIABLE	CASPOFUNGIN (N=114)	AMPHOTERICIN B (N=125)	P VALUE
	no./total no. (%)		
Clinical events	33/114 (28.9)	73/125 (58.4)	0.002
Chills	6/114 (5.3)	33/125 (26.4)	0.003
Fever	8/114 (7.0)	29/125 (23.2)	0.01
Hypertension	2/114 (1.8)	8/125 (6.4)	
Phlebitis or thrombophlebitis	4/114 (3.5)	6/125 (4.8)	
Tachycardia	2/114 (1.8)	13/125 (10.4)	
Nausea	2/114 (1.8)	7/125 (5.6)	
Vomiting	4/114 (3.5)	10/125 (8.0)	
Tachypnea	0/114	13/125 (10.4)	
Rash	1/114 (0.9)	4/125 (3.2)	
Laboratory abnormalities*	27/111 (24.3)	67/124 (54.0)	0.002
Elevated serum alanine aminotransferase	4/109 (3.7)	10/123 (8.1)	
Elevated serum aspartate aminotransferase	2/108 (1.9)	11/122 (9.0)	
Elevated serum alkaline phosphatase	9/109 (8.3)	19/122 (15.6)	
Elevated total serum bilirubin	3/109 (2.8)	11/124 (8.9)	
Elevated blood urea nitrogen	2/108 (1.9)	19/120 (15.8)	0.02
Elevated serum creatinine	4/109 (3.7)	28/124 (22.6)	0.05
Decreased serum potassium	11/111 (9.9)	29/124 (23.4)	0.04
Decreased hemoglobin	1/111 (0.9)	13/124 (10.5)	
Clinical event or laboratory abnormality	48/114 (42.1)	94/125 (75.2)	0.002
Withdrawal because of adverse event	3/114 (2.6)	29/125 (23.2)	0.003
Infusion-related event	23/114 (20.2)	61/125 (48.8)	0.002
Hypokalemia requiring supplementation within 72 hr after onset	13/114 (11.4)	33/125 (26.4)	0.02
Nephrotoxic effect†	8/95 (8.4)	26/105 (24.8)	0.02

*The denominator for each laboratory abnormality is dependent on the number of patients who had at least one evaluation for that laboratory test following the start of intravenous therapy.

†A nephrotoxic effect was defined as a serum creatinine level that was twice the base-line value or higher, or an increase of at least 1 mg per deciliter (88.4 μmol per liter) in patients with a base-line serum creatinine level above the upper limit of the normal range. Patients with a creatinine clearance of less than 30 ml per minute were excluded from this analysis.

Mora-Duarte J et al. NEJM 2002

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Flucitozin

- Nekompetitivni zaviralec timidilat sintaze
- Moti sintezo RNKA, delno tudi DNK
- Dobro gre v OŽS (kriptokokni mgt)
- ! Pozor: nizek prag za odpornost, zato vedno v kombinaciji
- Prilagajanje odmerkov ledvični funkciji
- Mielotoksičnost

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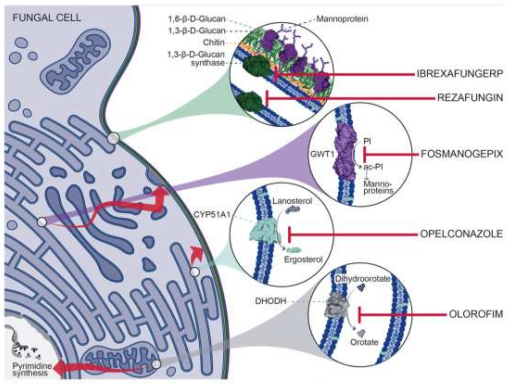
Antifungal agents in clinical and preclinical development

Overview and analysis
April 2025

World Health Organization

Mehanizem delovanja novih antimikotikov
Hoenigl M et al. Drugs 2021



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