Gli antimicotici nella politerapia dell'anziano fragile

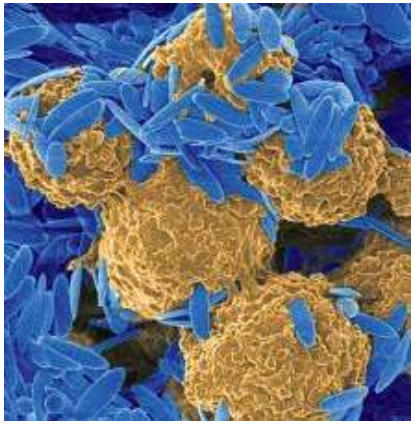
Gaetano Serviddio

Università degli Studi di Foggia

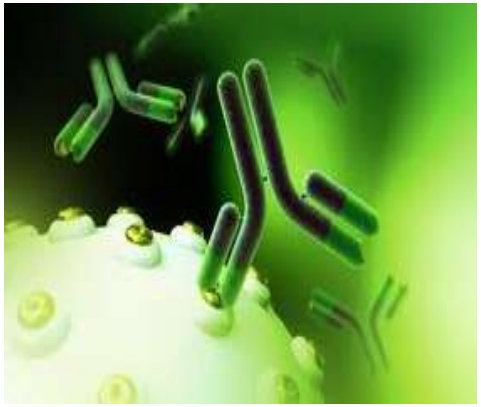
La dimensione del problema

- La peculiarità dell'infezione fungina
- L'interazione fungo – paziente geriatrico
- La sicurezza antimicotici disponibili
- L'interazione antimicotico – paziente geriatrico

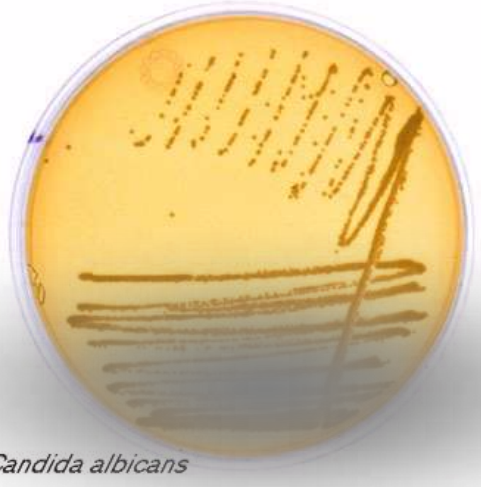
La difesa contro i miceti



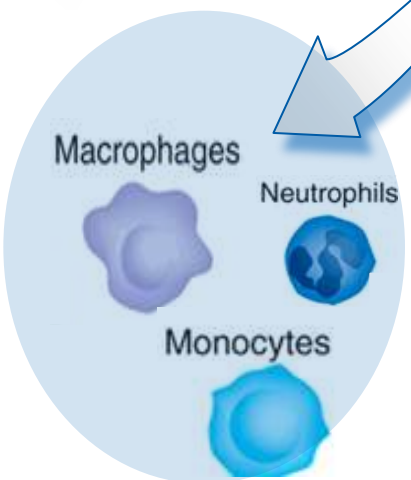
Innata

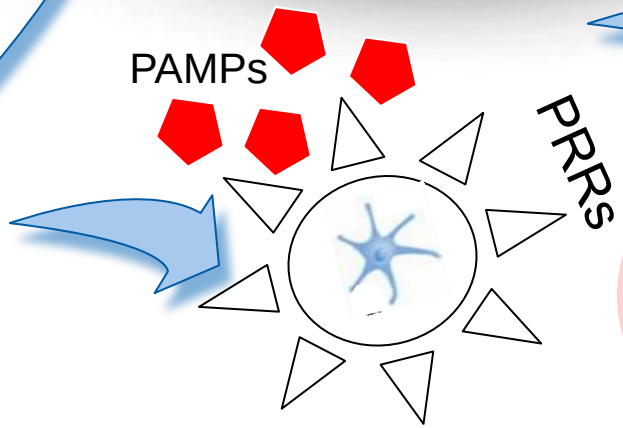


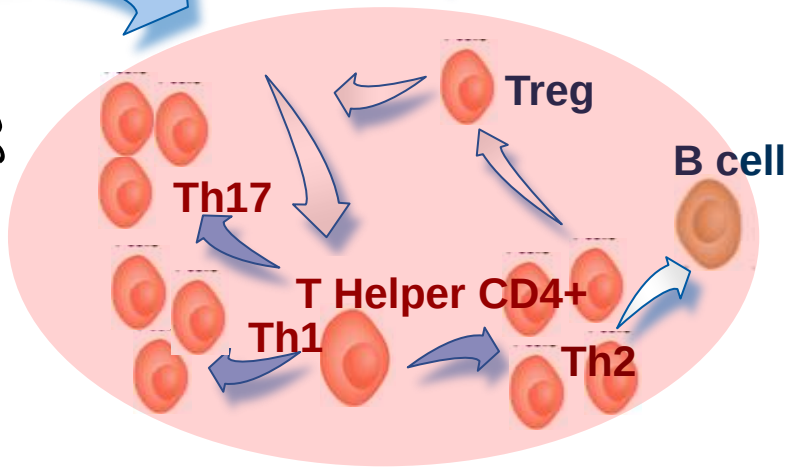
Acquisita



Candida albicans







Alterazioni fisiopatologiche indotte dall'invecchiamento

Table 1 Normal physiological alterations in the elderly

1. Diminished immunological response expressed by decreased phagocytosis
   - Lack of antigen presenting cells (dendritic, naïve T-cells)
   - Decreased memory capacity of mature T-cells
   - Decreased cytokine production
   - Decreased number of B-cells and immunoglobulin production
2. Decreased hepatic function due to decreased liver mass and blood flow, declining phase I metabolism, and decreased bile secretion
3. Decreased renal function (glomerular filtration rate declines on average 1% per year)
4. Hyposalivation
5. *Candida* colonization of dental prostheses
6. *Candida* colonization of the urinary tract, especially after broad spectrum antibiotic use

A. Flevari et al. Treatment of invasive candidiasis in the ederly: a review. Clinical Interventions in Aging 2013:8

Alterazioni fisiologiche dell'anziano e infezioni da candida

Table 2 Physiological effects of aging and their impact on drug metabolism

Hepatic function	Renal function	Body composition	Comorbidities	Alterations in receptor sensitivity
↓ Liver mass ↓ Hepatic blood flow ↓ Phase I metabolism (oxidation by CYP450 enzymes), further inhibited by Fluconazole ↓ Bile secretion Unaffected phase II metabolism	↓ GFR	↓ Total body water ↑ Body fat	Heart failure Hypertension Diabetes Cancer Pain due to various diseases	↓ β-receptor ↓ CYP450

Abbreviations: GFR, glomerular filtration rate; ↓, decrease; ↑, increase.
Note: Data from.[43,48]

L'età avanzata si associa a variazioni fisiologiche e/o vari disordini metabolici che alterano **mucose e barriere mucocutanee** rendendo l'organismo più suscettibile alle infezioni da *Candida*

Flevari A et al. Clin Intervent Aging 2013; 8: 1199

Colonizzazioni del cavo orale da Candida in pazienti anziani ospedalizzati

Characteristic	Day 0 ($n=256$)	Day 4 ($n=178$)	Day 8 ($n=115$)	Day 12 ($n=62$)
Colonization (%)[a*]	67	72	71	71
Nosocomial colonization (%)[a]	–	6·9	6·1	2·7
Heavy carriage of yeasts (%)[b]	51	51	49	45
Association of at least two yeast species: (%)[b]				
Palate	23	27·4	28	26
Tongue	26	27·7	27	28
Gums	27	28·4	29	37
Dental prosthesis	42	39·6	44	41
Candida species: (%)[c]				
C. albicans	59	54·5	52	53
C. glabrata	15	17·5	14·5	24
C. tropicalis	13·5	14	14·5	9
Others	12·5	14	19	14

Fanello S et al. J of Medical Microbiology (2006), 55, 223–228

Fattori di rischio per la candidosi invasiva

Colonizzazione da Candida	Nutrizione parenterale
Antibiotici a largo spettro	Emodialisi
Immunosoppressione	APACHE II score >20
Neutropenia	Catetere venoso centrale
Ustioni (>50%)	Candiduria > 10^5 cfu/ml
Alterazione delle barriere fisiologiche GI	Età estreme
Chirurgia addominale maggiore	Diabete
Chirurgia del tratto urinario con candiduria	Insufficienza renale
Traumatologia maggiore (ISS>20)	Intervento chirurgico recente
Trasfusioni multiple	Catetere urinario
Tossicodipendente per via venosa	Cateteri vascolari
	Prolungata degenza in ICU (>7gg)

Il paziente geriatrico

Angelo Anni 78

Giunge alla nostra osservazione su indicazione dell'urologo

Riscontro di *Candiduria* ricorrente

Non sintomatologia associata

Storia clinica

Papilloma della mucosa vescicale

In passato frequenti episodi di disuria ed ematuria

URINOCOLTURE MULTIPLE:

POSITIVE per "*Candida Glabrata*"

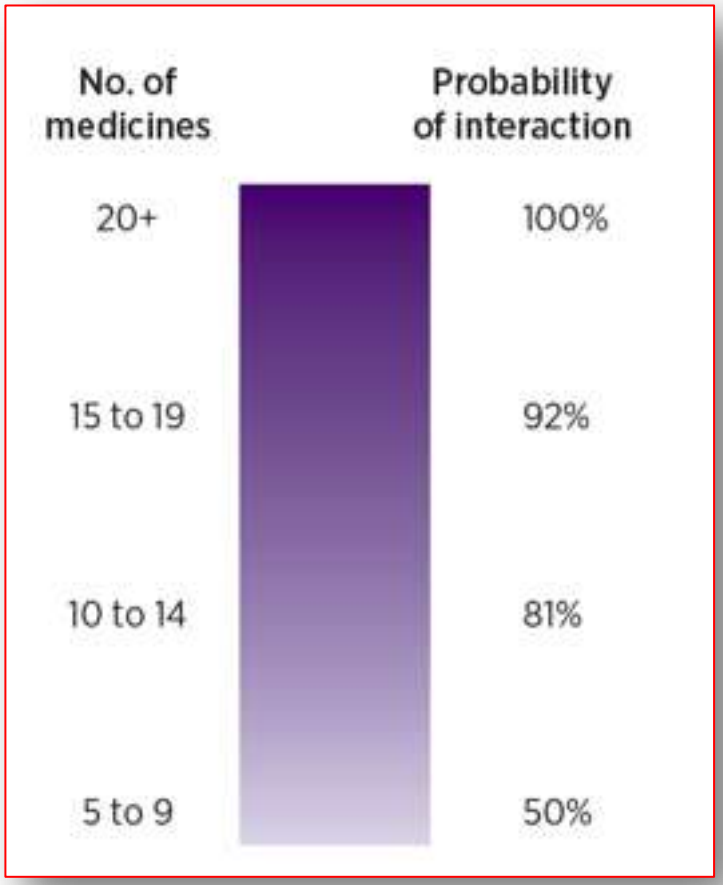
Comorbilità: Diabete mellito di tipo 2, IRC

È stato già sottoposto a trattamento con:

1. **Itraconazolo senza beneficio**
2. **Amfotericina B (lavaggio vescicale)**

La politerapia nel paziente geriatrico

"Concurrent use of five or more different prescription medications"

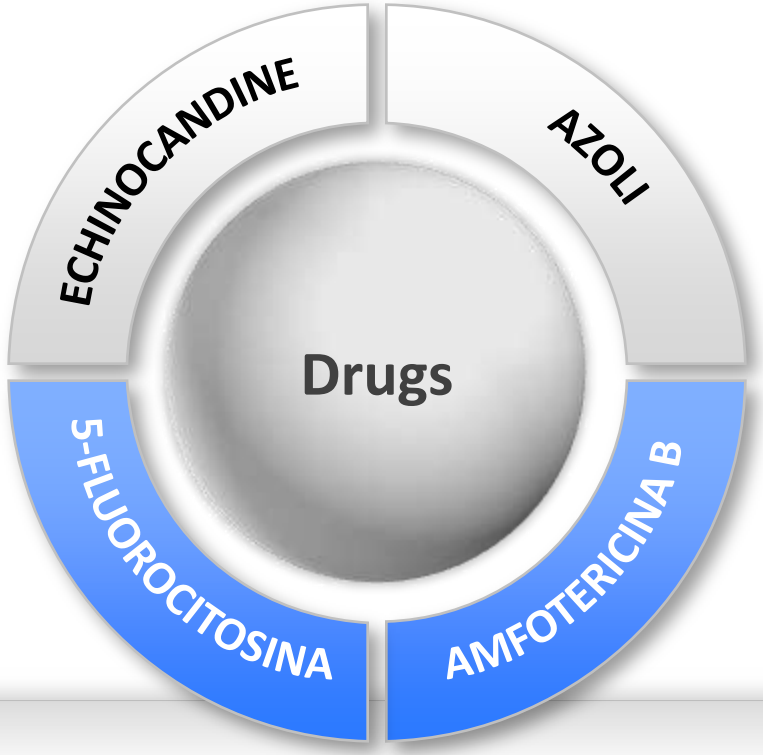


Il 51% degli anziani assume ≥ 6 farmaci

Ferner, BMJ, 2006
Ahmed, PlosOne, 2014
Hajjar, Am J Ger Pharmacol, 2007

Abbiamo 3 classi di antimicotici ed essenzialmente 6 farmaci nel trattamento delle candidiasi invasive

- Caspofungina
- Micafungina
- Anidulafungina



- Fluconazolo
- Voriconazolo
- Posaconazolo
- Itraconazolo

Qual è il più sicuro?

Ci sono dati nell'anziano?

Journal of Antimicrobial Chemotherapy (1999) **44**, 429–437

JAC

Review

The use of fluconazole and itraconazole in the treatment of *Candida albicans* infections: a review

Michael V. Martin*

Department of Clinical Dental Sciences, University of Liverpool, Liverpool L69 3BX, UK

Special patient populations. The volume of distribution and clearance of fluconazole are greater in children than in adults;[19] a relatively high mg/kg dose of fluconazole is therefore necessary in young patients. For those aged greater than 4 weeks, once daily dosing is appropriate. Neonates (aged ≤4 weeks) excrete fluconazole slowly, and less frequent dosing is therefore desirable.[19,20] The pharmacokinetics of fluconazole in the elderly are similar to those in non-elderly adults.[15] Immune status has no effect on the pharmacokinetics of fluconazole in either adultsor children.[7,21,22]

The NEW ENGLAND JOURNAL of MEDICINE

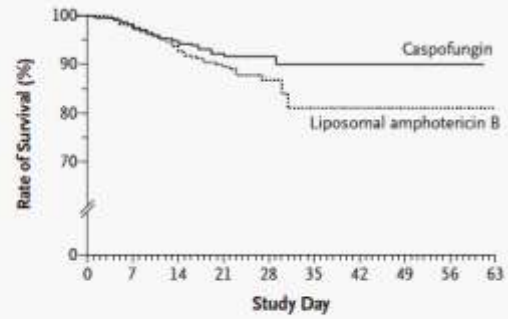
ESTABLISHED IN 1812 SEPTEMBER 30, 2004 VOL. 351 NO. 14

Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

Thomas J. Walsh, M.D., Hedy Teppler, M.D., Gerald R. Donowitz, M.D., Johan A. Maertens, M.D., Lindsey R. Baden, M.D., Anna Dmoszynska, M.D., Ph.D., Oliver A. Cornely, M.D., Michael R. Bourque, M.S., Robert J. Lupinacci, M.S., Carole A. Sable, M.D., and Ben E. dePauw, M.D., Ph.D.

Table 1. Demographic Characteristics of the Patients in the Modified Intention-to-Treat Population.*

Characteristic	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)
Female sex — no. (%)	238 (42.8)	247 (45.8)
Age — yr		
Median	51	49
Range	17–83	16–83
Age group — no. (%)		
≤17 yr	3 (0.5)	8 (1.5)
18–40 yr	158 (28.4)	160 (29.7)
41–65 yr	307 (55.2)	297 (55.1)
>65 yr	88 (15.8)	74 (13.7)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

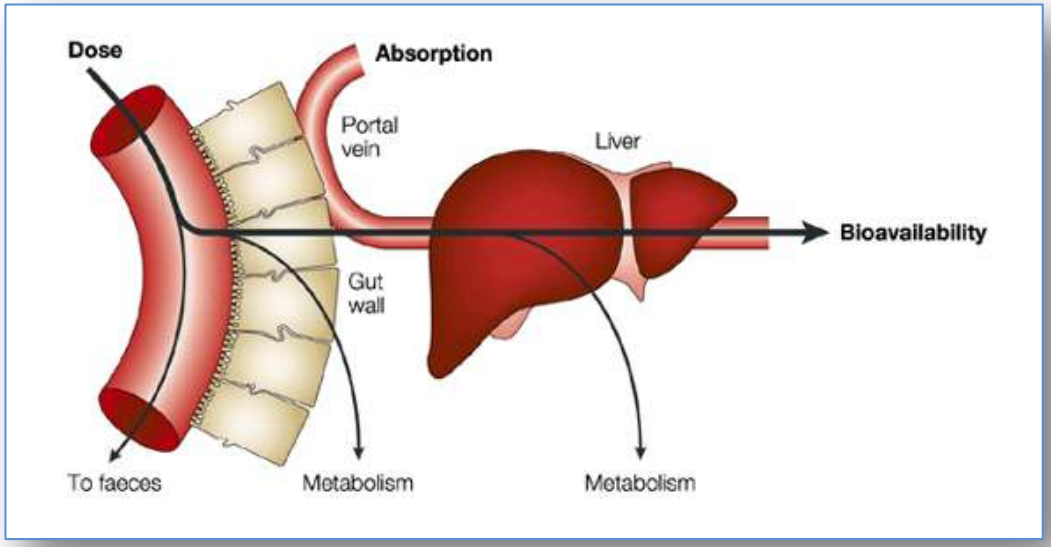
Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

Table 1. Characteristics of the Modified Intention-to-Treat Population.*

Characteristic	Anidulafungin Group (N=127)	Fluconazole Group (N=118)	P Value
Sex — no. (%)			1.00
Male	65 (51)	60 (51)	
Female	62 (49)	58 (49)	
Age — yr			0.29
Mean	57.0±17.0	59.2±16.5	
Range	16–89	24–91	

Il principio dell'ADiME



Assorbimento

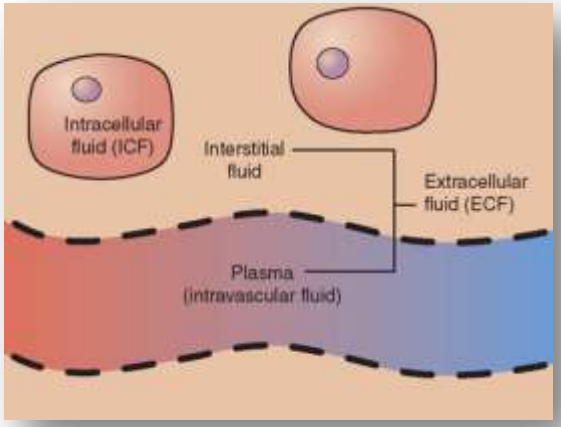
Distribuzione

Metabolismo

Escrezione

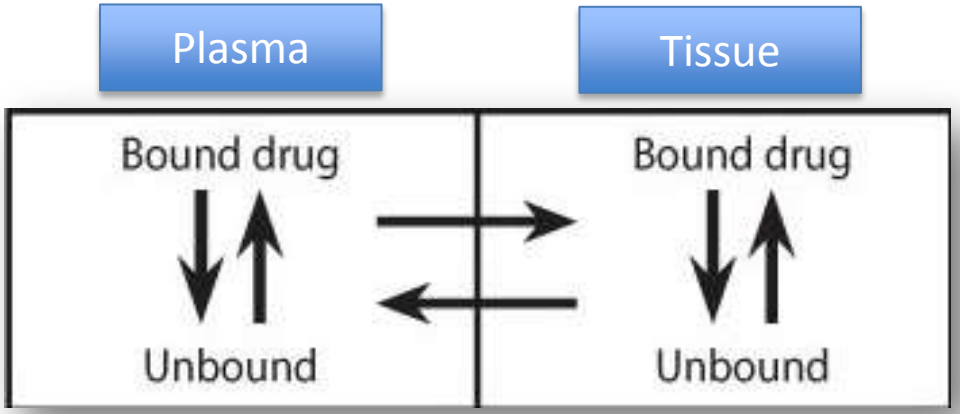
VOLUME DI DISTRIBUZIONE

indica la capacità di penetrazione dei farmaci a livello dei tessuti. È il volume necessario a contenere la quantità totale di farmaco presente nell'organismo alla stessa concentrazione di quella presente nel plasma



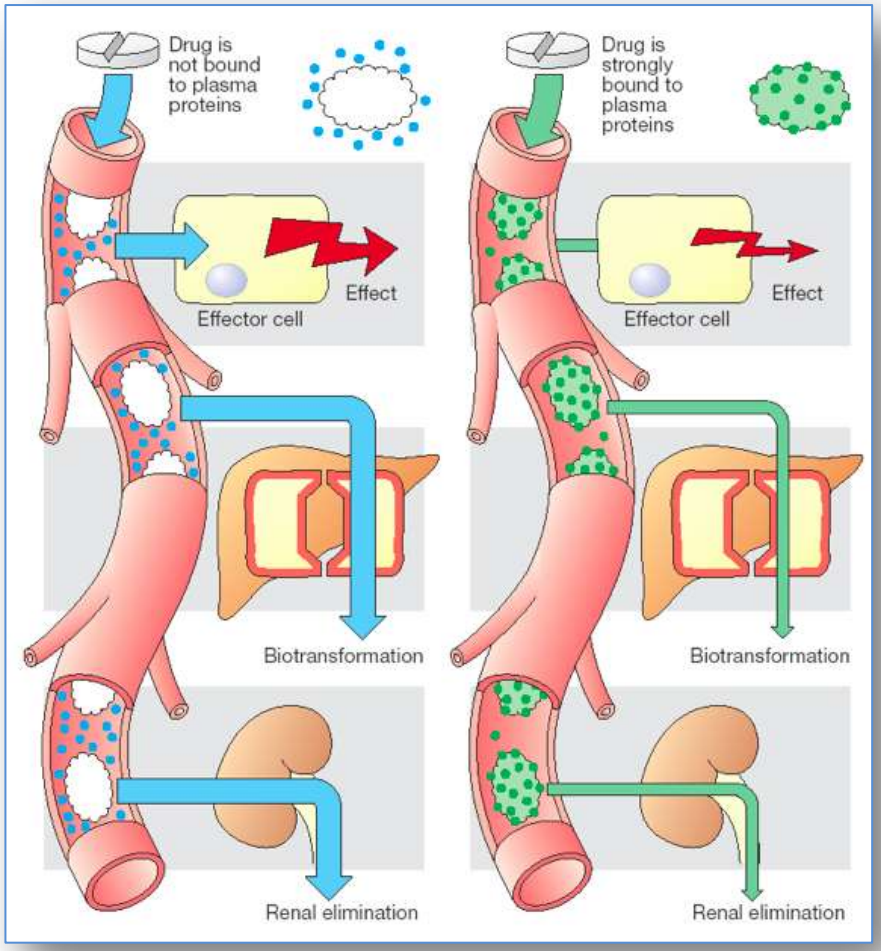
Sostanza	Vd	Compartimento corporeo	Comportamento
Molto polare	3,3 L	Plasma	Non esce dal plasma
Idrosolubile	12 L	Acqua extracellulare	Passa nell'interstizio ma non entra nelle cellule
Liposolubile	42 L	Acqua totale	Passa tutte le membrane cellulari
Molto liposolubile	330 L	Vd apparente	Lega le membrane plasmatiche e si deposita nel tessuto adiposo

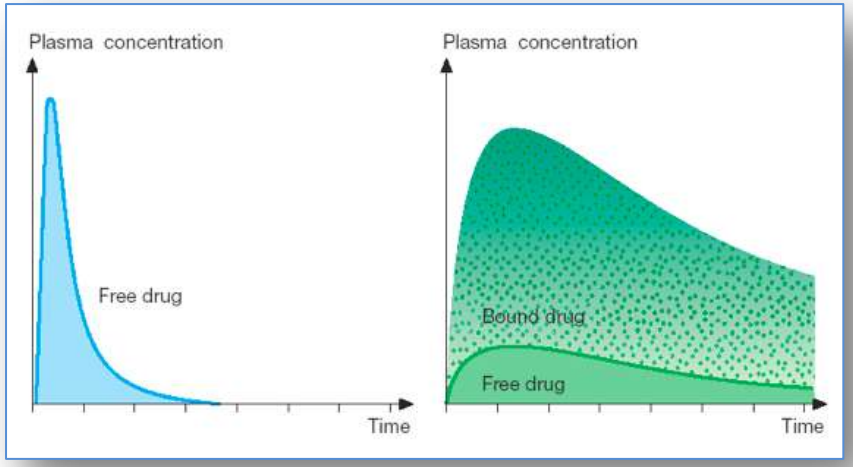
Legame proteina-farmaco



Caratteristiche della molecola	Proteina legata
Farmaci acidi	albumina
Farmaci basici	α1glicoproteina acida
Ormone (es. T3-T4)	Proteina specifica (TBG)

Effetto del legame farmaco-proteine sul metabolismo





Rilevanza farmacocinetica dell'alto legame alle proteine

Blocco nel compartimento ematico

Solo la quota libera esplica il suo effetto ed è metabolizzata

Ad alto legame (>90%)	A medio legame (50-90%)	A basso legame (<50%)
warfarin	ceftriaxone	ampicillina
FANS	fenobarbital	cefotaxime
digossina		aminoglicosidi
teicoplanina		vancomicina

Interazioni

1 FARMACOCINETICHE

- Assorbimento
- Distribuzione
- Biotrasformazione
- Escrezione

2 FARMACODINAMICHE

Conseguenze positive /negative dell'interazione tra farmaci

Effetto terapeutico più intenso e di maggior durata

Riduzione delle dosi e quindi della tossicità dei singoli elementi

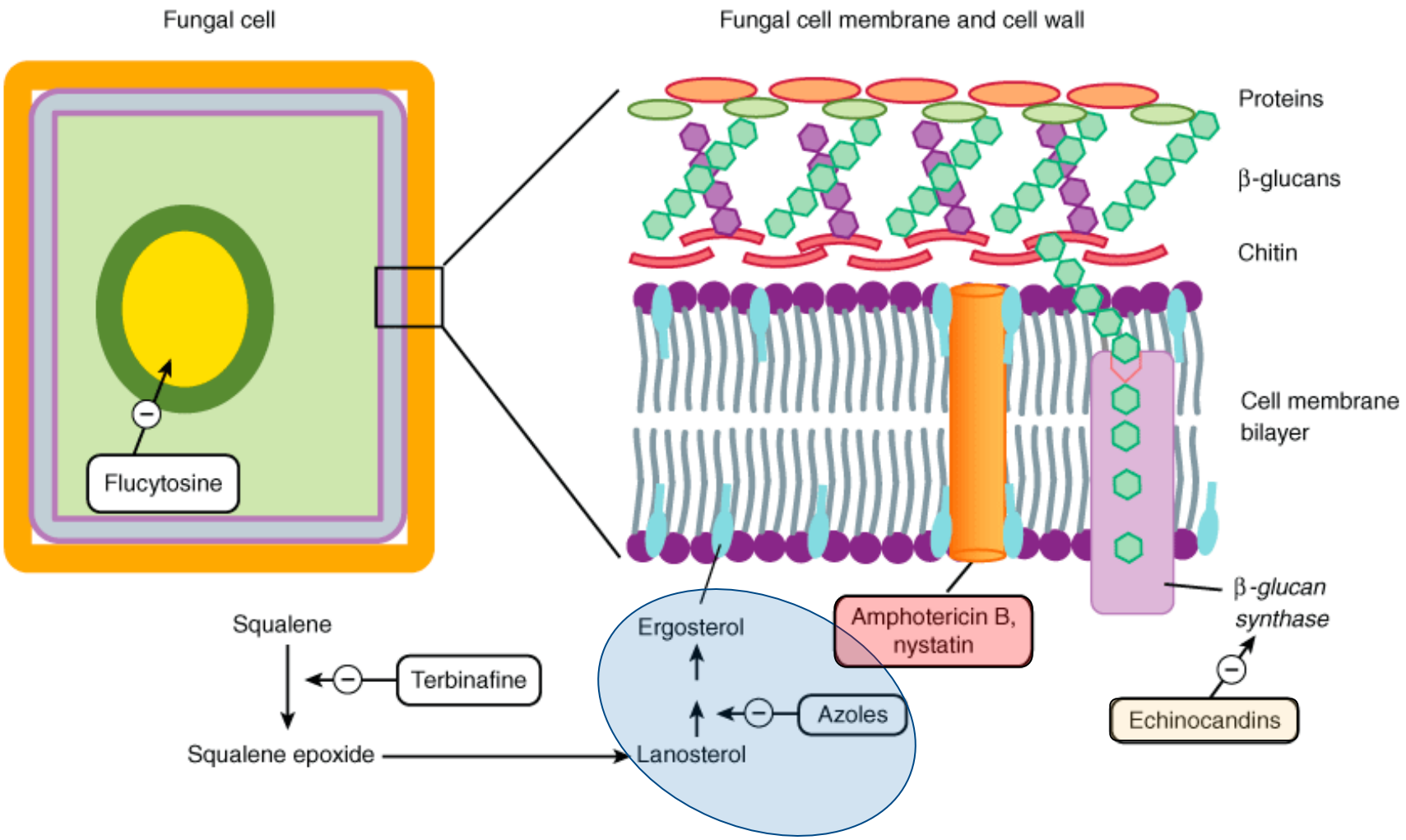
Ritardo nello sviluppo di resistenza (antinfettivi, antitumorali)

Riduzione dell'intensità e della durata degli effetti

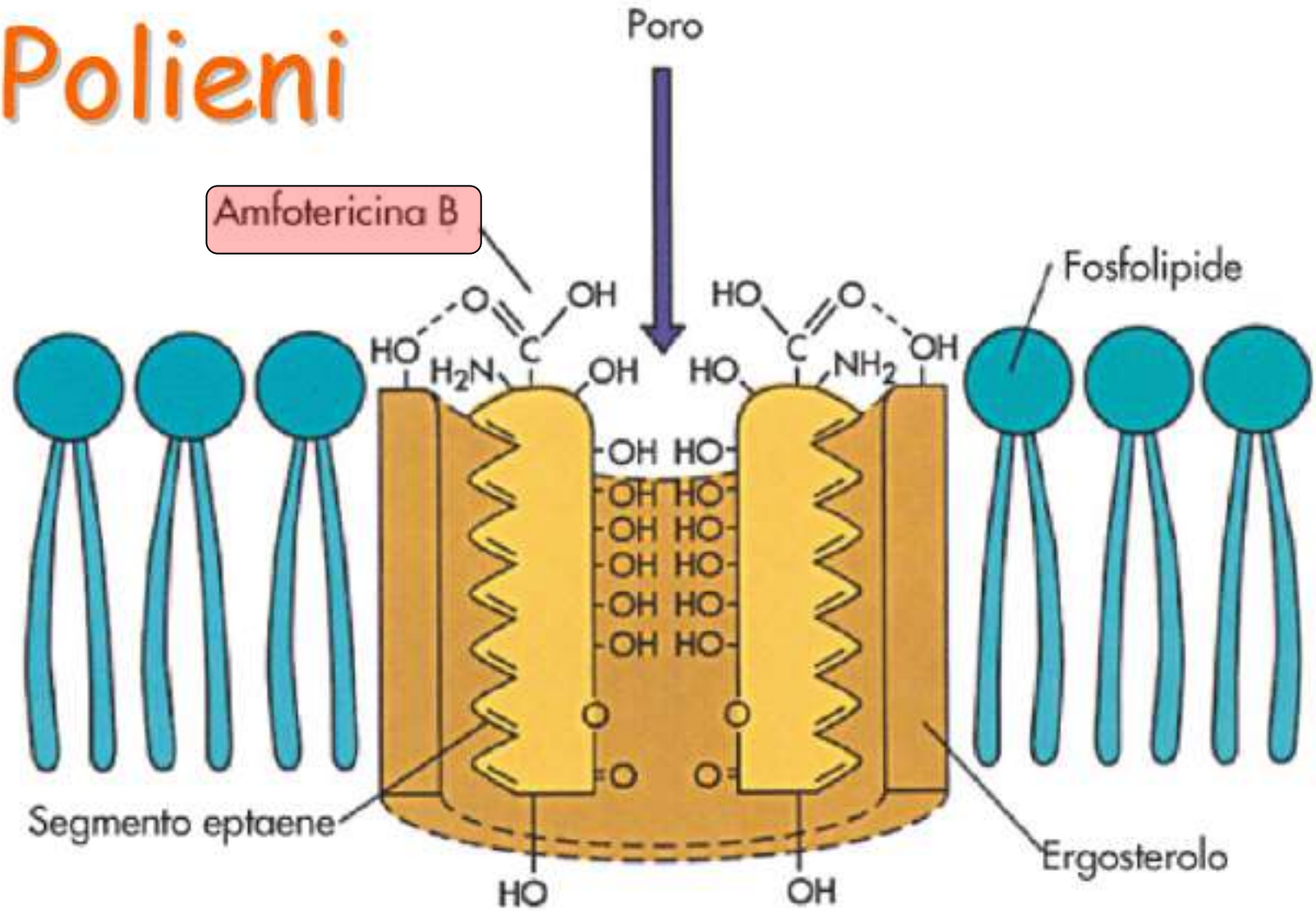
Sommazione degli effetti tossici

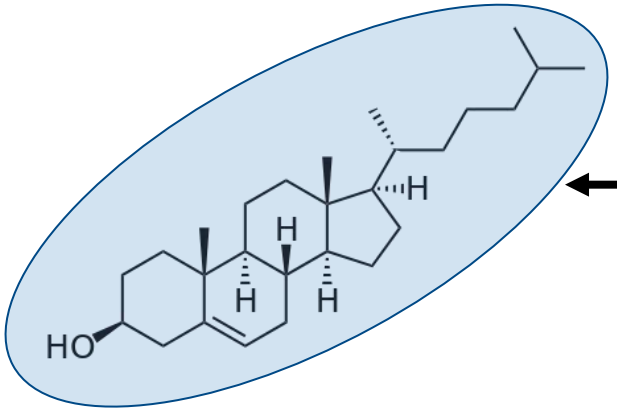
Comparsa di effetti tossici nuovi

Antifungini e tossicità



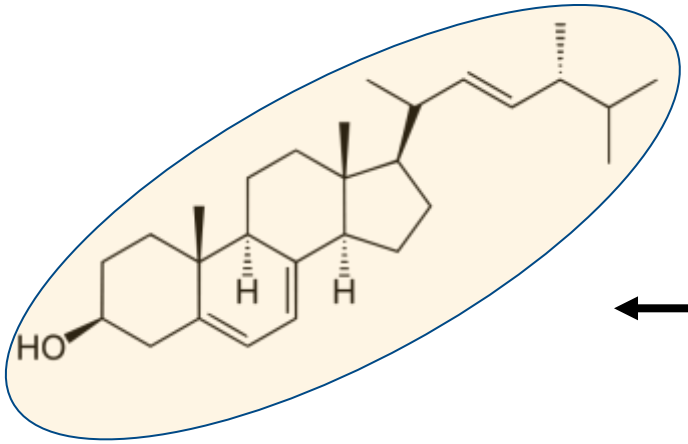
Polieni


Poro
Amfotericina B
Fosfolipide
Segmento eptaene
Ergosterolo

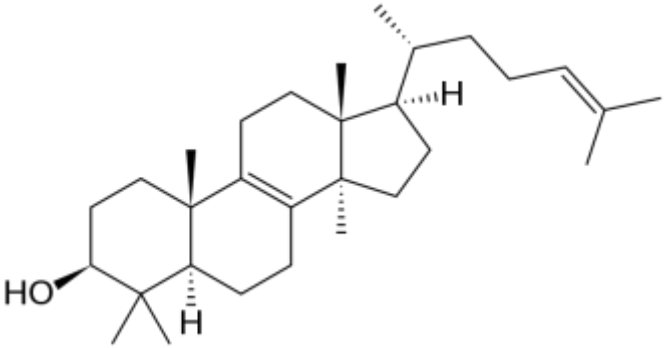


Colesterolo

14-a-Demetilasi

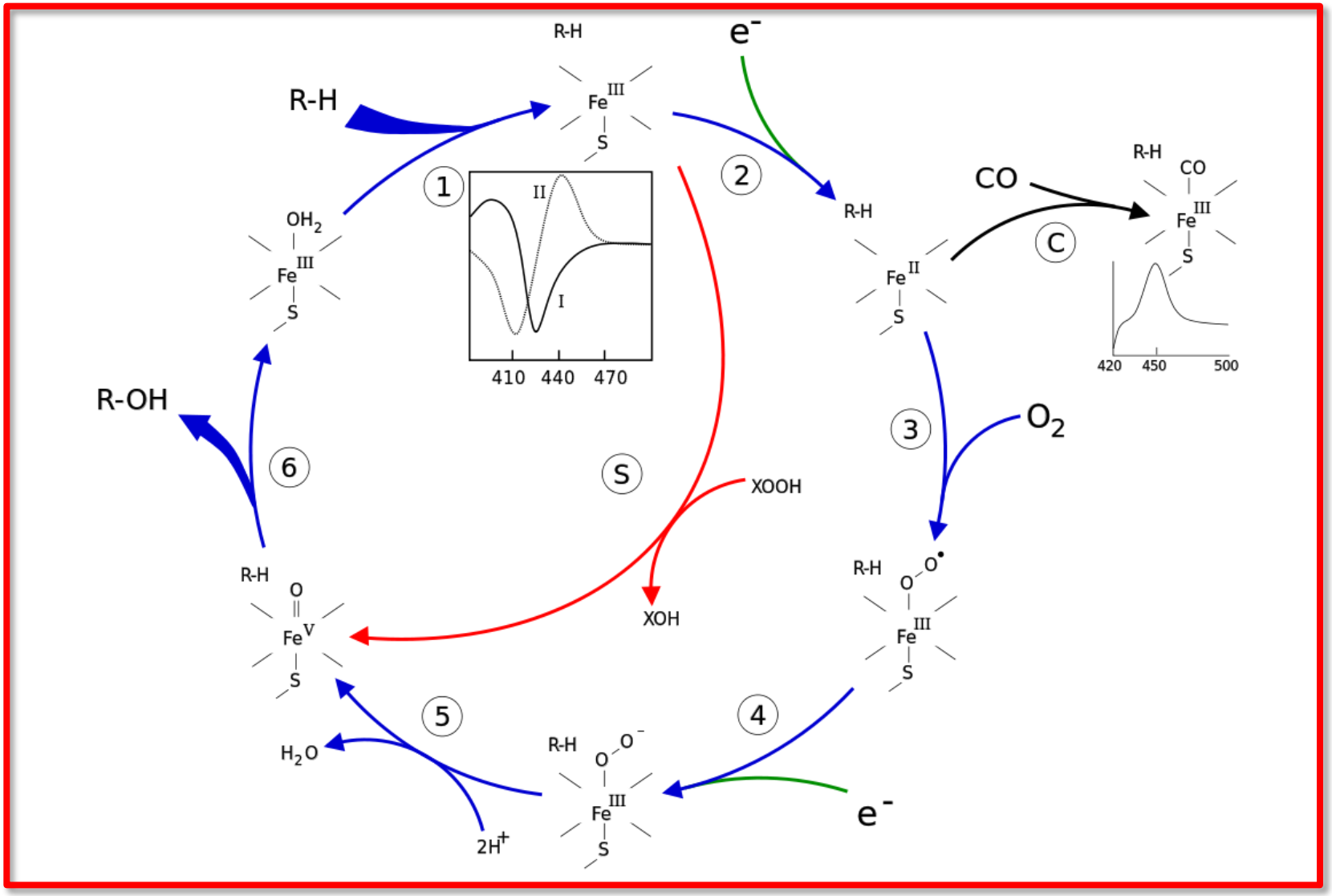


Ergosterolo

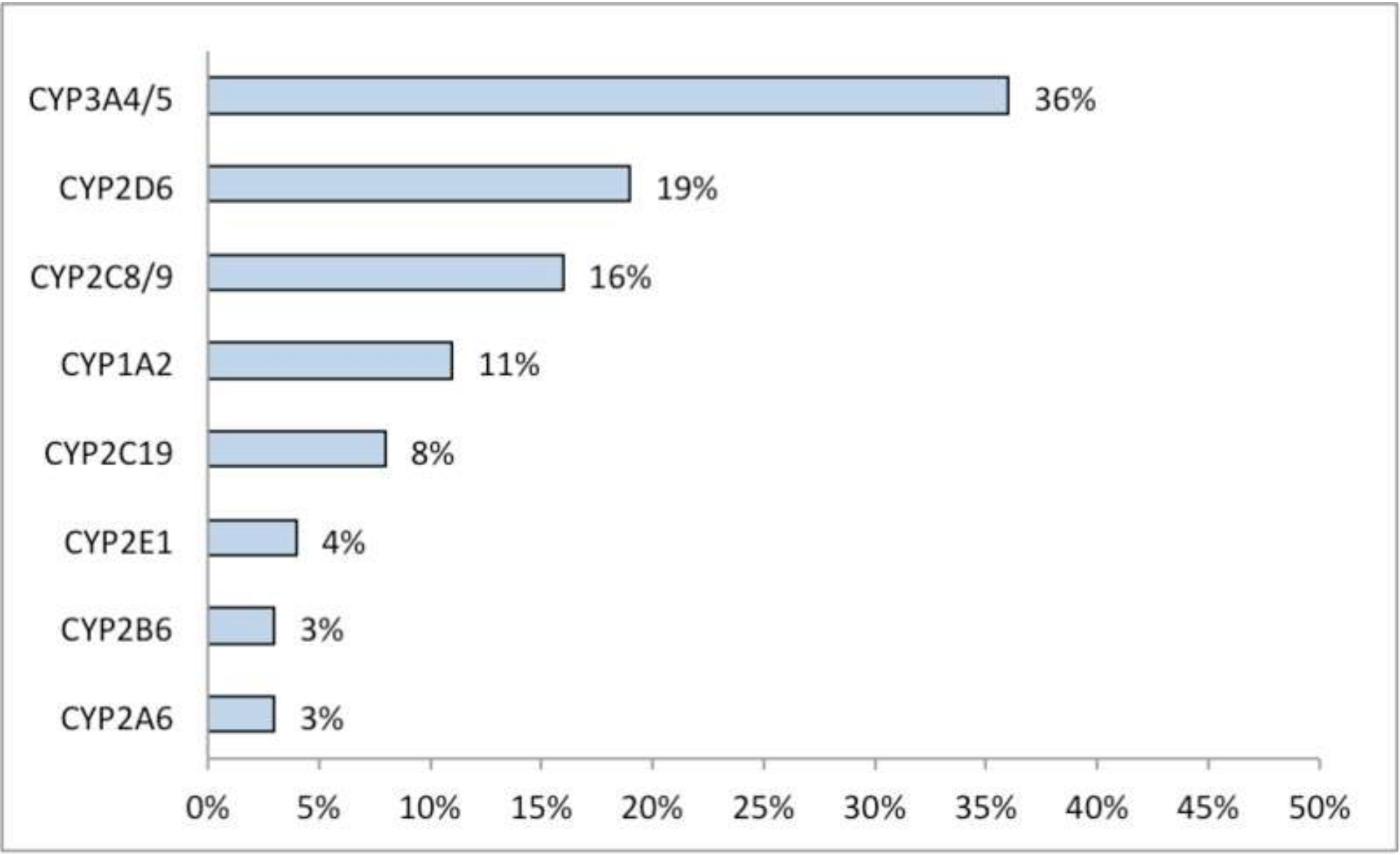


Lanosterolo

Il Citocromo è tutto qui…..

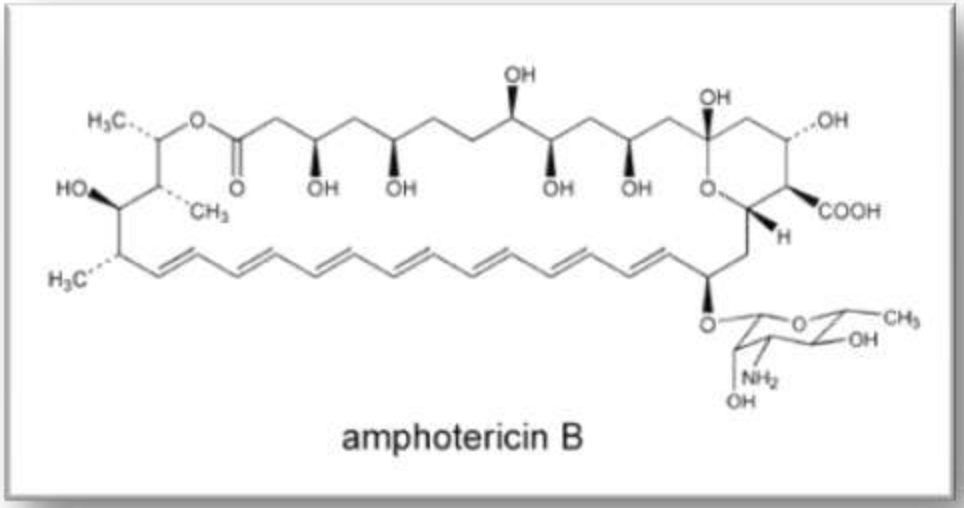


… se lo conosci non lo eviti!



Proportion of antifungal drugs metabolized by different families of CYPs.[15]

L’amfotericina B



Disidratazione
Farmaci nefrotossici
Insufficienza renale

Interagisce
con 186 farmaci

ANEMIA

www.drugs.com
Flevari et al, 2013

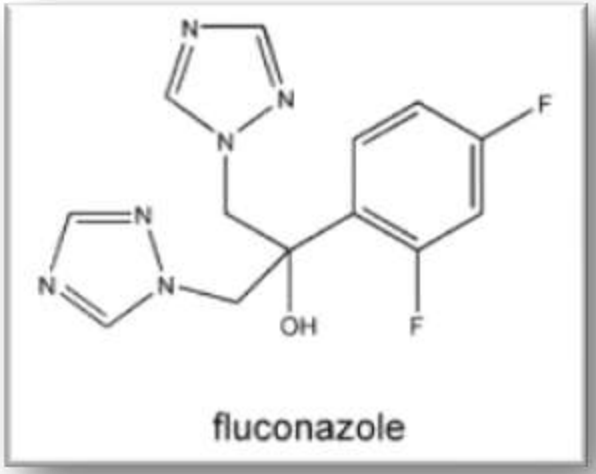
Table 1. Drug interactions caused by amphotericin B formulations.

Drugs	Comments
Cyclosporin Tacrolimus Aminoglycosides	Can cause nephrotoxicity. Monitor Scr, BUN, and electrolytes, and consider renal-sparing AmB formulations or other antifungal agents
Thiazide and loop diuretics Aminoglycosides Corticosteroids	Can cause fluid and electrolyte disturbances (i.e., water retention, hypokalaemia hypomagnesaemia). Monitor Scr, BUN and electrolytes. Supplement electrolytes as needed
Digoxin	Increase cardiac automaticity and inhibition of Na^+-K^+ ATPase pump. Effects secondary to AmB-induced hypokalaemia
5-FC	Can cause myelosuppression. Effect due to diminished renal clearance of 5-FC secondary to AmB-associated nephrotoxicity

AmB: Amphotericin B; BUN: Blood ureanitrogen; 5-FC: 5-Flucytosine; Scr: Serum creatinine.

Expert Opin. Pharmacother. (2005) **6**(13):2231-2243

Gli azoli: il Fluconazolo



fluconazole

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid‡	0.5–0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4–0.7

Interagisce Con 587 farmaci

Inibitore del citocromo P450

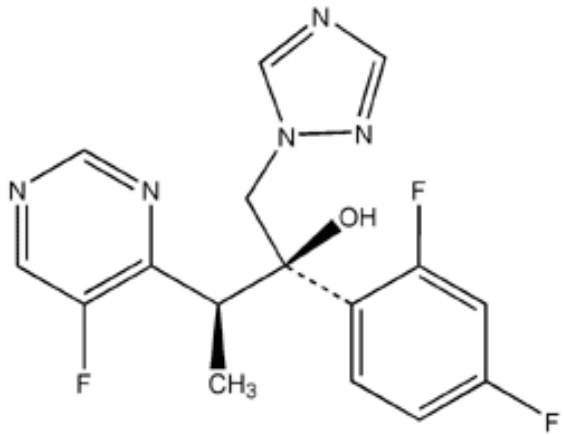
Aumento delle concentrazioni plasmatiche nell'anziano per ridotta clearance renale

Table 3. Fluconazole drug–drug interactions.

Drug	Comments
Benzodiazepines	
Midazolam	↑ Midazolam peak concentration, exposure, $t_{½}$ and bioavailability by ~ twofold. ↓ Midazolam clearance by ~ 51% via the inhibition of hepatic and enteric CYP3A
Triazolam	↑ Triazolam peak concentrations, exposure and $t_{½}$ by ~ 1.25- to 2.5-fold via the inhibition of hepatic and perhaps enteric CYP3A4
Cyclosporin and tacrolimus	
Cyclosporin	↑ Cyclosporin trough concentrations, steady-state concentrations and exposure by ~ 50%, ↓ cyclosporin clearance by ~ 55% via the inhibition of hepatic and perhaps enteric CYP3A
Anticonvulsants	
Phenytoin	↑ Phenytoin trough concentration by ~ 1.25-fold and phenytoin exposure by 75% via dose-dependent inhibition of hepatic CYP3A4
Anticoagulants	
Warfarin	Fluconazole inhibits the primary pathway of warfarin biotransformation by 70% via the inhibition of hepatic CYP2C9
Miscellaneous drugs inhibited by fluconazole	
Alfentanil	↑ Alfentanil exposure and $t_{½}$ by ~ twofold, ↓ alfentanil clearance by ~ 50%, and steady-state volume of distribution by ~ 20% via the inhibition of hepatic CYP3A4
Glyburide	↑ Glyburide serum concentrations via dose-dependent inhibition of hepatic CYP3A4
Saquinavir hard gel capsule	↑ Saquinavir peak concentrations by 56% and exposure by 50% via the inhibition of hepatic CYP3A4
Cyclophosphamide	↓ Cyclophosphamide clearance and ↑ $t_{½}$ via the inhibition of hepatic CYP2C9 and CYP3A4

CYP: Cytochrome P450; $t_{½}$: Half-life.

Gli azoli: il Voriconazolo



voriconazole

Interagisce
Con 636 farmaci

Negli anziani le concentrazioni plasmatiche sono aumentate del 80-90%

Associazioni controindicate: alcaloidi dell'ergot, rifabutina, efavirenz, sirolimus

Ridurre dosaggio FANS, ossicodone, ciclosporina

Table 4. Voriconazole interactions affecting pharmacokinetics/dynamics of other drugs*.

Drug	Comments
Warfarin	Voriconazole inhibits the primary pathway of warfarin biotransformation via the inhibition of hepatic CYP2C9, increases warfarin pharmacodynamic effect by 41% and ↑ partial thromboplastin time by 100%
Cyclosporin and tacrolimus	
Cyclosporin	↑ Cyclosporin trough concentrations by 248%, exposure by 70% via the inhibition of hepatic CYP3A4
Tacrolimus	↑ Tacrolimus trough concentrations via the inhibition of hepatic CYP3A4
Miscellaneous drugs	
Phenytoin	↑ Phenytoin peak concentrations by 70%, exposure by 80% via the inhibition of hepatic CYP2C9 and CYP3A4. The interaction is bidirectional
Omeprazole	↑ Omeprazole peak concentrations by 2.4-fold, $t_{½}$ by 1.15 h and exposure by 3.8-fold via the inhibition of hepatic CYP2C19 and CYP3A4
Prednisolone	↑ Prednisolone exposure by 13 – 30% perhaps via the inhibition of hepatic CYP3A4
Rifabutin	↑ Rifabutin peak concentrations and exposure by twofold via the inhibition of hepatic CYP

*Voriconazole may also increase the plasma concentrations of several drugs, including benzodiazepines, calcium channel blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, vinca alkaloids, sulfonylureas, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, sirolimus, quinidine and pimozide. However, published data describing these possible interactions are lacking.

CYP: Cytochrome P450; $t_{½}$: Half-life.

Le Echinocandine

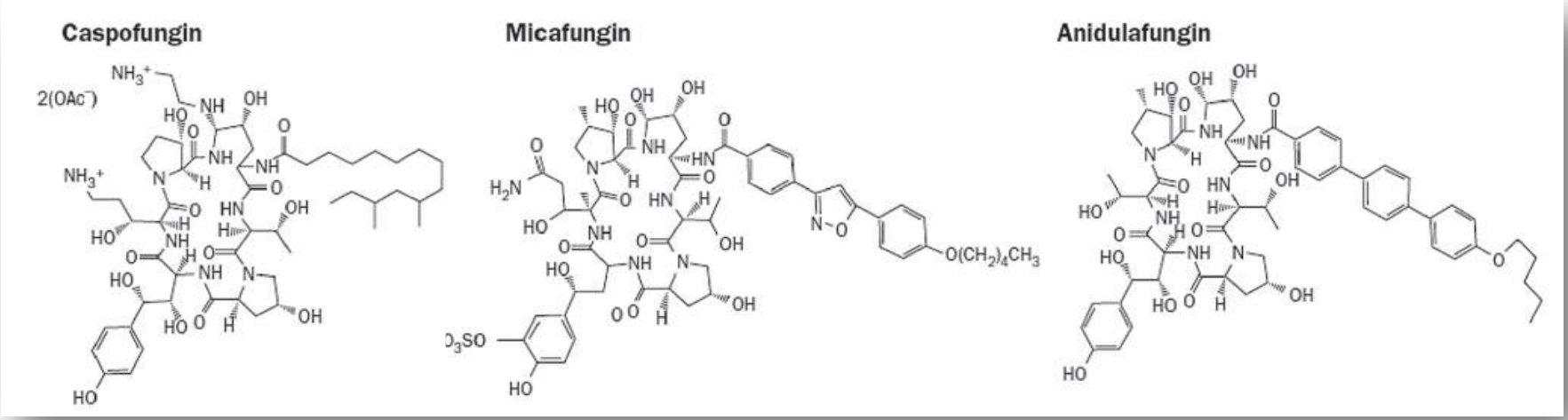


Table 1. Pharmacokinetics of echinocandins for the treatment of Candida infections

Parameter	anidulafungin	caspofungin	micafungin
Mode of administration	IV	IV	IV
Dose linearity	+	+	+
Oral availability [%]	n/a	n/a	n/a
Plasma protein binding [%]	99	97	99
Volume of distribution [L]	30-50	n/a	18
Elimination half-life [h]	24	9-11	10-17
Route of elimination	D, F	D / M U > F	M F > U

E = excretion unchanged; M = drug is metabolised; D = drug is degraded; U = urine; F = faeces

Profilo farmacocinetico: confronto tra echinocandine

Profilo di escrezione[1-5]

ANIDULAFUNGINA

MICAFUNGINA

CASPOFUNGINA

1- ECALTA® Riassunto delle caratteristiche del prodotto.
2- CANCIDAS® Riassunto delle caratteristiche del prodotto.
3- Mycamine for Injection [package insert]. Tokyo, Japan: Astellas Pharma, Inc. June 2006.
4- Balani S.K., Xu X., Arison B.H. et al. Metabolites of caspofungin acetate, a potent antifungal agent, in human plasma and urine. Drug Metab Dispos. 2000;28:1274-1278.
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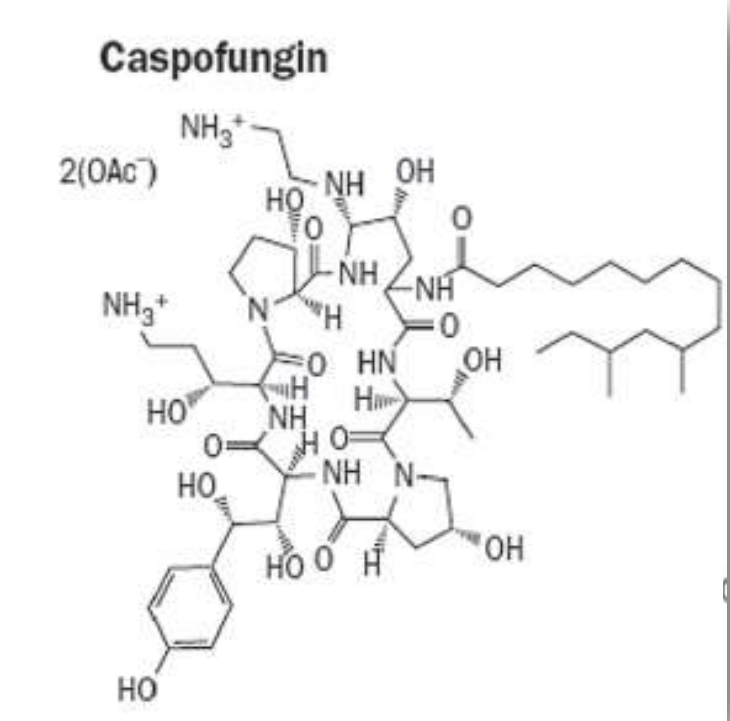
Farmaci antimicotici nell'anziano: caspofungin



Interagisce Con 78 farmaci

La maggior parte Interazione di grado lieve-moderato

Minimo aumento delle concentrazioni plasmatiche nell'anziano

Concentrazioni plasmatiche ridotte da desametasone e rifampicina

Il paziente geriatrico

Angelo Anni 78

Giunge alla nostra osservazione su indicazione dell'urologo

Riscontro di *Candiduria* ricorrente

Non sintomatologia associata

Storia clinica

Papilloma della mucosa vescicale

In passato frequenti episodi di disuria ed ematuria

URINOCOLTURE MULTIPLE:

POSITIVE per "*Candida Glabrata*"

Comorbilità: Diabete mellito di tipo 2, IRC

È stato già sottoposto a trattamento con:

1. **Itraconazolo senza beneficio**
2. **Amfotericina B (lavaggio vescicale)**

Facciamo eseguire alcuni esami di laboratorio

Risultano alterati:

Esame chimico-fisico delle urine:
Piuria, presenza di miceti gemmati.

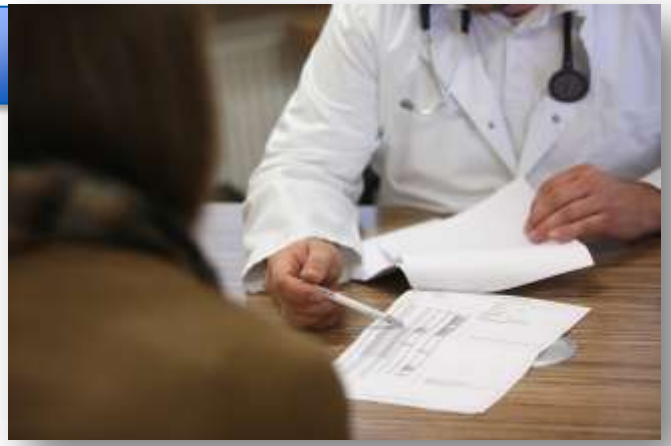
Urinocoltura: POSITIVA per *Candida Glabrata*

Creatininemia: 1.7 mg/dl

Cleareance Creatinina: < 30 mL/min

Il paziente è asintomatico per cui decidiamo di non effettuare alcun tipo di trattamento per la candiduria

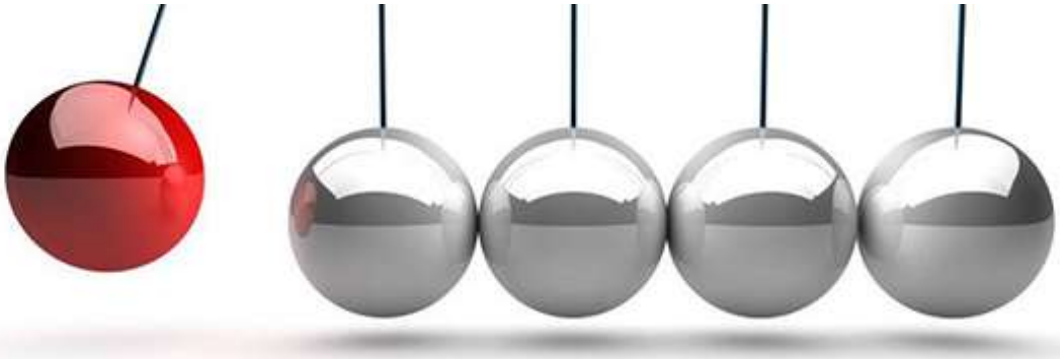
Dopo 2 mesi però…



- **Il paziente torna alla nostra osservazione**
- **Riferisce disuria, ematuria e dolore al fianco da circa 2 settimane**
- **Presenta febbre (TC 38.8° C)**
- **Ha iniziato trattamento con Fluconazolo 200 mg/die per os su consiglio dell'urologo**

Analisi delle urine: piuria, presenza di miceti gemmati. No batteriuria
Emocolture: in corso
ETG Addome: dilatazione bilaterale del tratto urinario superiore

Ed ora cosa fare?



Si decide di ricoverare il paziente ed effettuare trattamento con:

- **CASPOFUNGINA 50 mg/die ev per 10 gg**

↓

Defervescenza rapida
Risoluzione della disuria e del dolore al fianco
Urinocolture: NEGATIVE

- Scegliere di non trattare la candiduria asintomatica nel paziente anziano è sempre la scelta migliore?
- Perché in questo caso sarebbe stato più utile evitare il trattamento con gli azoli?
- La presenza di comorbilità come influisce sulla scelta terapeutica?
- Perché in questo caso la scelta migliore ricade sulla caspofungina, nonostante la sua scarsa concentrazione urinaria?

Conclusioni

There are now enough systemic acting antifungal agents to allow clinicians the luxury of considering the mycological activity, pharmacodynamics, pharmacokinetics, toxicity and drug interaction potential to tailor the antifungal therapy to the patient. However, the antifungal arsenal is still not large enough to relegate agents to the archives. Even though the role of conventional AmB in the treatment of systemic mycoses has dwindled since the lipid AmB formulations improved the safety of this agent, there are still situations that it may be useful.

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Gli antimicotici nella politerapia dell'anziano fragile

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