POSICIONAMIENTO TERAPÉUTICO DE LOS NUEVOS ANTIFÚNGICOS

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Búsqueda de la Evidencia

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Espectro de actividad antifúngica

Ensayos clínicos en las distintas situaciones

Perfil de seguridad

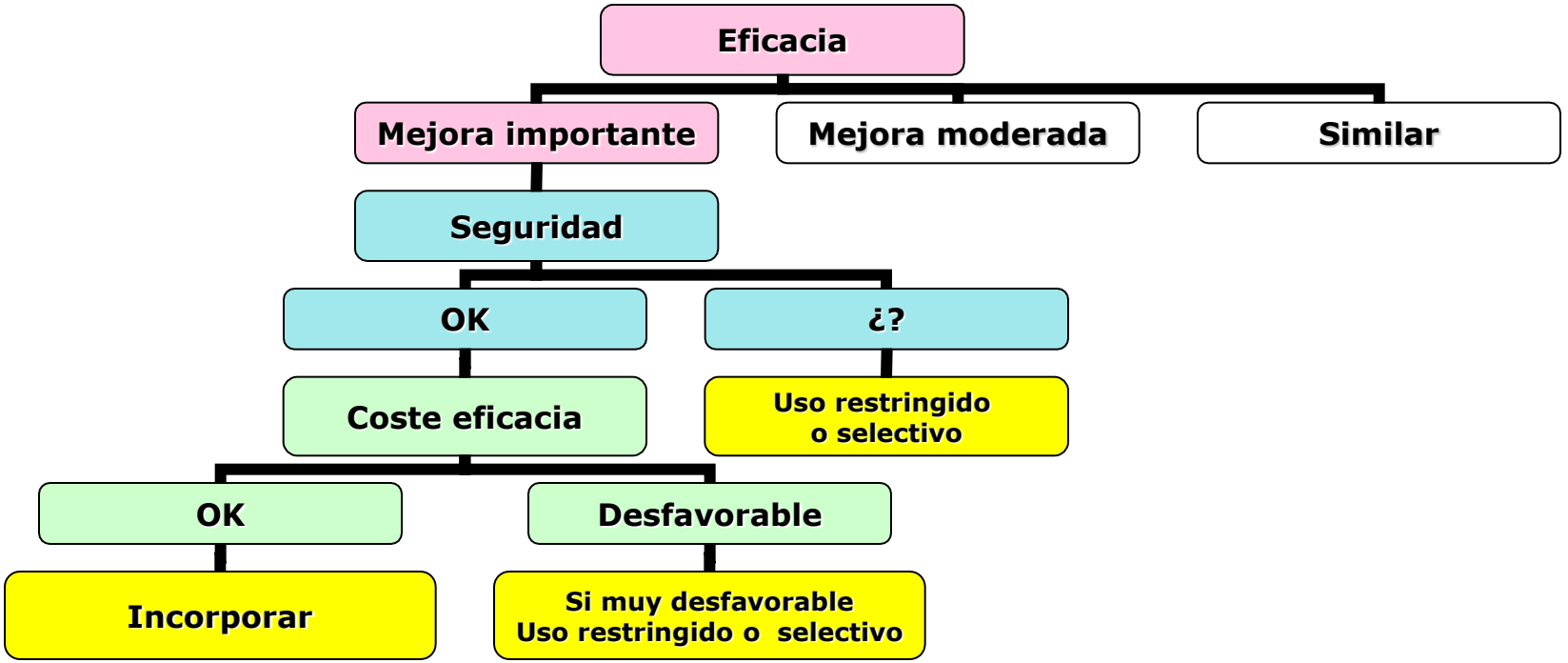
Análisis farmacoeconómico

Guías de Práctica Clínica

Posicionamiento terapéutico

Jerarquización de los criterios primarios y secundarios

Mejora importante de la eficacia

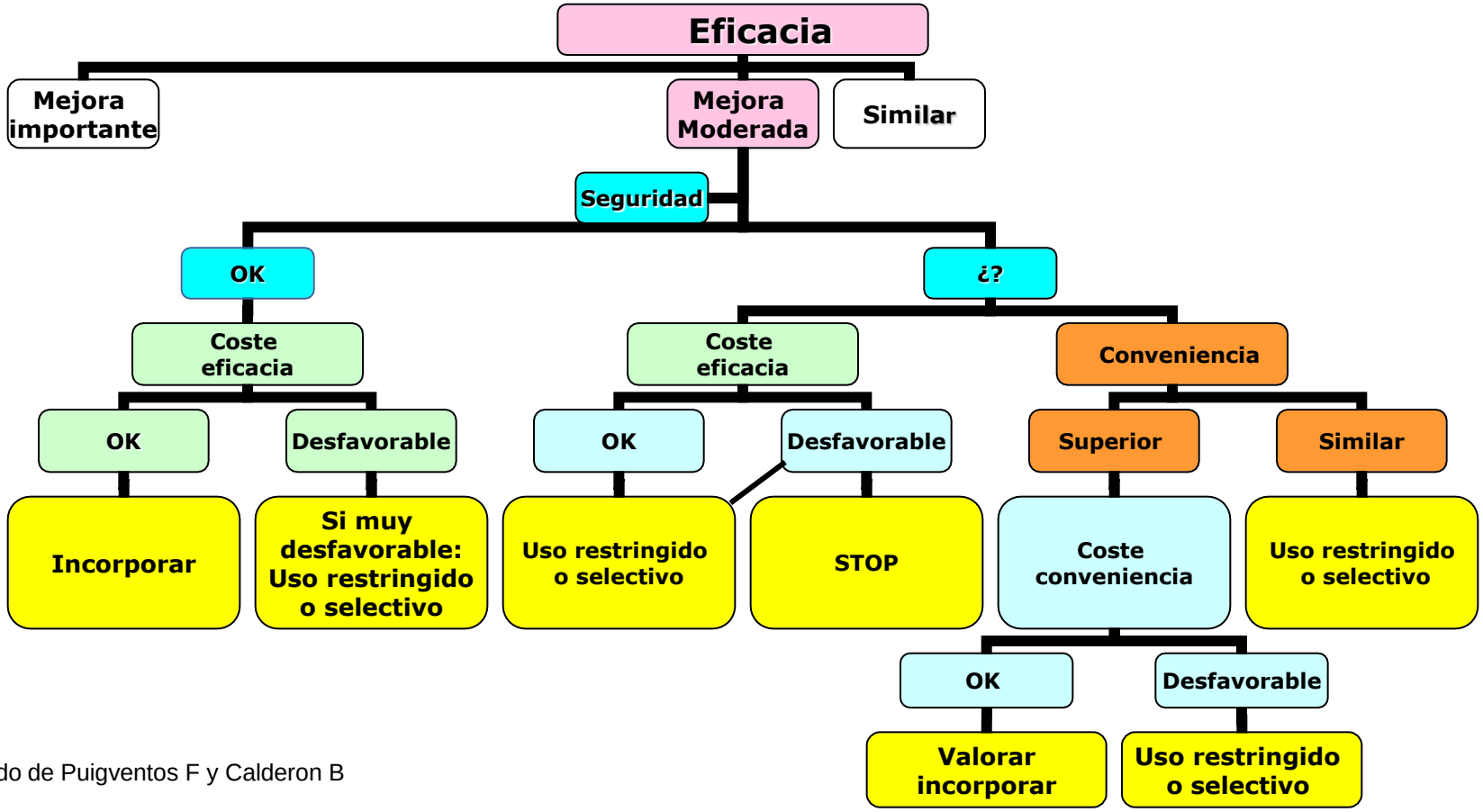


* Tomado de Puigventos F y Calderon B

Posicionamiento terapéutico

Jerarquización de los criterios primarios y secundarios

Mejora moderada de la eficacia

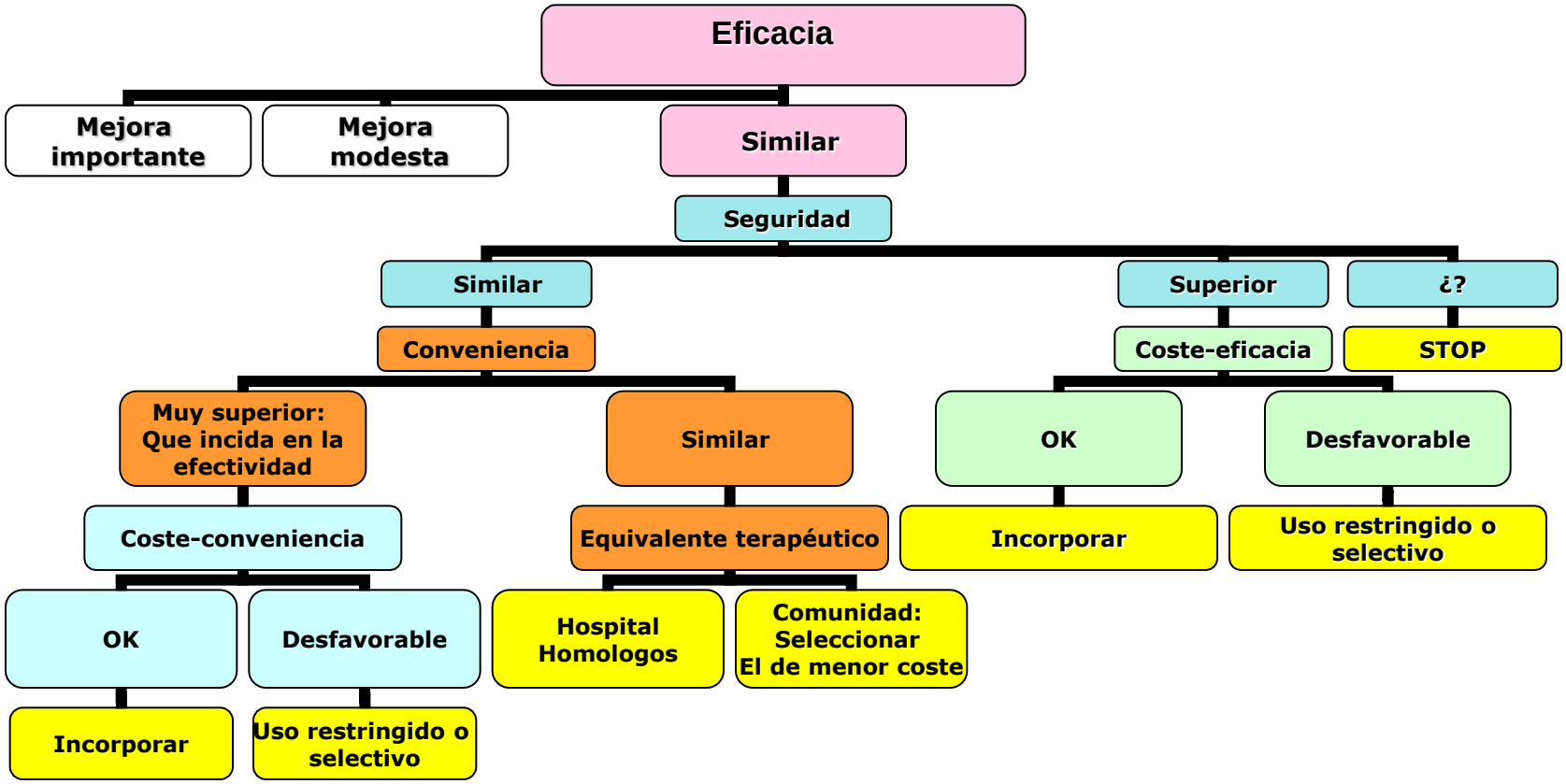


* Tomado de Puigventos F y Calderon B

Posicionamiento terapéutico

Jerarquización de los criterios primarios y secundarios

Eficacia similar



* Tomado de Puigventos F y Calderon B

Agent	Class	Spectrum and clinical indications	Mechanism of action	Advantages	Limitations
AmBd	Polyene	*Candida*, *Aspergillus*, Zygomycetes, and other opportunistic mycoses	Destabilizes the fungal cell membrane. Binds to the sterol ergosterol incorporated in the fungal cell membrane, which creates pores in the membrane and leads to depolarization of the membrane with subsequent cell leakage. In mammalian cells, polyenes bind cholesterol	Broad spectrum of activity, few resistant fungi	Dose-limiting renal and infusion-related toxicity; poor efficacy in immunosuppressed hosts
Lipid formulations of AmB (AmB-L, ABLC, AmB-CD)		Broad spectrum of activity, similar to parent compound		Less toxicity than AmB	Renal, infusion related and other acute toxicities (with AmB-CD having the greatest toxicity, and AmB-L having the lowest); few primary treatment studies; expensive
Voriconazole	Extended spectrum azole	*Aspergillus* and other moulds; *Candida*, especially non-*albicans* and other yeasts	Interfere with sterol synthesis via inhibition of CYP-dependent C-14-α demethylase, a fungal CYP enzyme important in converting lanosterol to ergosterol	Survival advantage vs AmB for IA (recommended primary therapy for most patients); intravenous and oral delivery Possible benefit (both) in combination therapy for aspergillosis and other moulds infections	Extensive drug interactions; visual, liver, skin toxicities; azole cross-resistance in yeasts. Possible need to monitor plasmatic levels for efficacy
Posaconazole		Zygomycetes and other emerging FIs; salvage therapy and prophylaxis in patients with leukaemia or HSCT, not in SOT patients		Activity against Zygomycetes; well tolerated in trials	Oral suspension only; azole cross-resistance
Caspofungin, micafungin, anidulafungin	Echinocandin	*Candida* spp (candidemia, invasive candidiasis), salvage therapy for *Aspergillus*	Inhibition of β-(1,3) glucan synthesis via inhibition of β-(1,3) glucan synthase. Fungal	Well tolerated; anidulafungin more effective vs fluconazole in one study of candidemia; micafungin equal effective vs AmB in one study of candidemia but less toxicity;	Mould activity targeted to *Aspergillus*; potential cyclosporine interaction for caspofungin; expensive. Non activity on the genera *Cryptococcus*

Tabla 1. Espectro del voriconazol, posaconazol

Género o especie fúngica	Actividad
Hongos levaduriformes	
Candida albicans fluconazol-S	+++
Candida albicans fluconazol-R	++
Candida glabrata fluconazol-S	+++
Candida glabrata fluconazol-R	++
Candida krusei	++
Candida lusitaniae anfotericina-S	+++
Candida lusitaniae anfotericina-R	+++
Otras especies de *Candida*	+++
Cryptococcus neoformans	+++
Hongos filamentosos	
Aspergillus[a]	+++
Fusarium[b]	+ / ++
Scedosporium apiospermum[b]	++
Scedosporium prolificans[b]	0 / +
Zigomicetos (*Mucor*, *Absidia*, *Rhizopus*)[a]	0
Hongos dimórficos	
Histoplasma capsulatum	+++
Blastomyces dermatitidis	++
Coccidioides immitis	+++
Penicillium marneffei	+++
Sporothrix schenckii	++

[a]Posaconozol, más activo que el voriconazol
[b]Voriconazol, más activo que el posaconazol

Sensibilidad comparada de hongos filamentosos responsables de infecciones invasoras en pacientes inmunodeprimidos[a].

Especie	Media geomética (μg/ml)		
	Anfotericina	Voriconazol	Posaconazol
Aspergillus fumigatus	1,10	0,42	0,07
Aspergillus flavus	1,26	0,34	0,06
Aspergillus niger	0,70	0,35	0,09
Scedosporium prolificans	–	3,29	>8
Scedosporium apiospermum	–	0,17	0,79
Especies de Fusarium	20,1	8,9	32
Zigomicetos	57,8	41,1	32

Triazoles (in candidiasis)

Fluconazole, itraconazole, voriconazole, and posaconazole demonstrate similar activity against most *Candida* species [25, 26]. Each of the azoles has less activity against *C. glabrata* and *C. krusei*. All of the azole antifungals inhibit cytochrome P450

Fluconazole is readily absorbed, with oral bioavailability resulting in concentrations equal to ~90% of those achieved by intravenous administration. Absorption is not affected by food consumption, gastric pH, or disease state.

	Coste/día (€)	
	oral	I.V.
Fluconazol	2	3
Itraconazol	10	75
Voriconazol	65	340
Posaconazol	120	

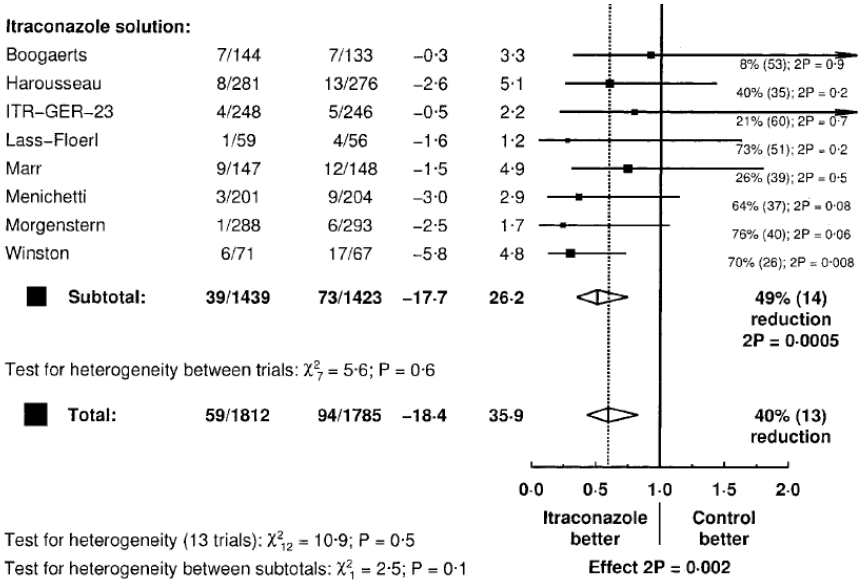
anti-Aspergillus TRIAZOLES (Itraconazol, Voriconazol y Posaconazol)

Fluconazole, which also is an antifungal triazole, is not active against invasive aspergillosis. Voriconazole is FDA approved for the primary treatment of invasive aspergillosis. Itraconazole is licensed for treatment of invasive aspergillosis in patients who are refractory to or intolerant of standard antifungal therapy. Posaconazole is FDA approved for prevention of invasive aspergillosis in neutropenic patients receiving remission induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome and for HSCT recipients with GVHD.

anti-*Aspergillus* triazoles are active in vitro and in vivo against all common species of *Aspergillus*. Although some isolates of *A. fumigatus* have been found to be resistant to itraconazole,

Itraconazole Prevents Invasive Fungal Infections in Neutropenic Patients Treated for Hematologic Malignancies: Evidence From a Meta-Analysis of 3,597 Patients

Conclusion: **Antifungal prophylaxis with itraconazole effectively prevents proven invasive fungal infections and—shown for the first time for antifungal prophylaxis—reduces mortality from these infections and the rate of invasive *Aspergillus* infections in neutropenic patients with hematologic malignancies. Adequate doses of the oral cyclodextrine solution (at least 400 mg/d) or IV formulations (200 mg/d) of itraconazole are necessary for these effects.**



Incidence of proven invasive fungal infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction;

Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients

Patients: 140 patients undergoing allogeneic hematopoietic stem-cell transplantation.

Intervention: Itraconazole (200 mg intravenously every 12 hours for 2 days followed by 200 mg intravenously every 24 hours or a 200-mg oral solution every 12 hours) or fluconazole (400 mg intravenously or orally every 24 hours) from day 1 until day 100 after transplantation.

Table 2. Incidence of Proven Fungal Infections within 180 Days after Transplantation

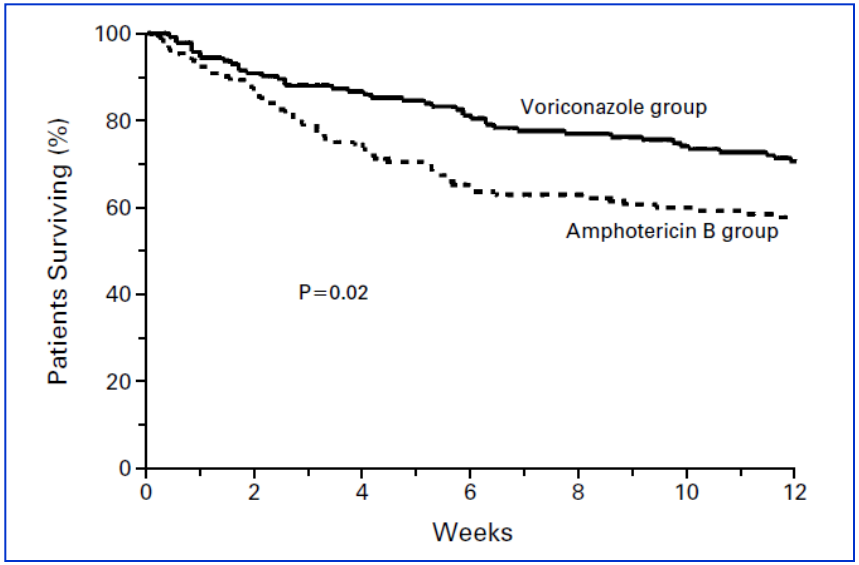
Variable	Itraconazole Group (n = 71)	Fluconazole Group (n = 67)
	n (%)	
Patients with proven fungal infection	9 (13)	19 (28)*
Invasive infection of blood, lungs, brain, liver, or multiple organs	6 (9)	17 (25)†
Superficial infection of oral cavity, skin, or gastrointestinal tract	3 (4)	2 (3)

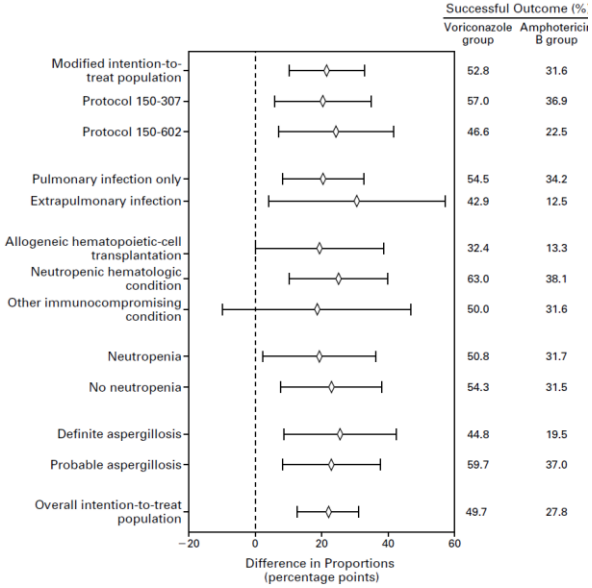
Survival

Thirty-two patients given itraconazole (45%) and 28 patients given fluconazole (42%) died within 180 days af-

The New England Journal of Medicine

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS





Conclusions In patients with invasive aspergillosis, initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B. (N Engl J Med 2002;347:

Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

CID 2007:44 (1 January) • Walsh et al.

An open-label study in patients with invasive aspergillosis and other mycoses who were refractory to or intolerant of conventional antifungal therapy. Data from external control cases were collected **retrospectively**.

Table 3. Responses at end of therapy: overall response, site of infection, and reason for enrollment.

Variable	Posaconazole group (n = 107)	Control group (n = 86)
Overall response		
Complete and partial	45 (42)	22 (26)
Complete	7 (7)	8 (9)
Partial	38 (36)	14 (16)
Stable	10 (9)	7 (8)
Failure	39 (36)	52 (60)
Unable to be determined	13 (12)	5 (6)

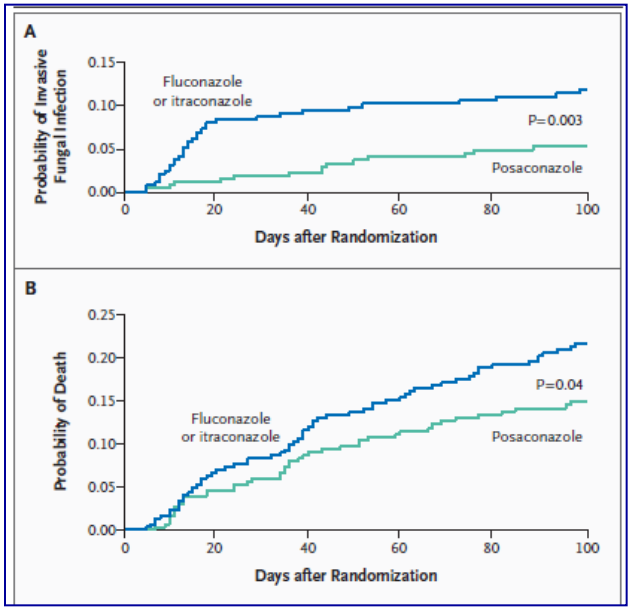
Group, antifungal agent	Posaconazole group		Control group	
	No. of subjects	Duration of therapy, median days	No. of subjects	Duration of therapy, median days
Patients with refractory infection (with or without drug intolerance)	94	…	68	…
Any antifungal agent[a,b]	92	23[c]	68	16[c]
Amphotericin B[d]	33	12	31	10
Lipid formulation of amphotericin B[d]	71	16	41	12
Itraconazole	48	17	31	14
Voriconazole	5	30	NA	NA
Echinocandins	5[e]	74	NA	NA

- The study predates extensive use of **echinocandins** and **voriconazole**
- The data for the posaconazole recipients on protocol were collected **prospectively**, whereas the data for the control patients were collected **retrospectively**
- Case patients and control subjects seem to be fundamentally **different** (subjects who were not treated with posaconazole came from institutions that did not offer posaconazole or were not considered to be appropriate recipients of this medication

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

N Engl J Med 2007;356:348-59.

Patients with neutropenia resulting from chemotherapy for **AML** or **MDS** received prophylaxis with each cycle of chemotherapy until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first.
A total of **304** patients were randomly assigned to receive **posaconazole**, and 298 patients were randomly assigned to receive **fluconazole (240)** or **itraconazole (58**).
On the basis of local practices, investigators selected either fluconazole or itraconazole (¿?).



The incidence of aspergillosis among patients who had received **itraconazole** prophylaxis was **unexpectedly high** and was similar to that in the fluconazole group.

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Post hoc analysis of posaconazole versus itraconazole only

The same *post hoc* analysis limited to centers where itraconazole was the comparator did not show a difference between the study groups: incidence of proven and probable invasive fungal infections during the treatment period was 3 (5 percent) of 65 posaconazole patients and 6 (10 percent) of 58 itraconazole patients (95 percent confidence interval, -0.2 percent to 0.04 percent, P = 0.22). At 100 days, 6 (9 percent) of 65 posaconazole patients and 7 (12 percent) of 58 itraconazole patients had a proven or probable fungal infection (95 percent confidence interval, -0.1 percent to 0.1 percent, P = 0.61).

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

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

Randomized, double-blind trial, in 600 patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy.
The primary end point was the **incidence of proven or probable invasive fungal infections** from randomization to day 112 of the fixed treatment period.

Posaconazole was considered to be **noninferior** to fluconazole, if the upper limit of the 95% CI for the adjusted odds ratio did not exceed a maximum value corresponding to a relative difference of **15 %**

Pathogen or Pathogen Group	Posaconazole Group (N=301)	Fluconazole Group (N=299)	Odds Ratio (95% CI)	P Value
	no. (%)			
Fixed treatment period				
All proven and probable invasive fungal infections*	16 (5.3)	27 (9.0)	0.56 (0.30–1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13–0.75)	0.006

CONCLUSIONS

Posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with GVHD. It was superior in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections. (ClinicalTrials.gov number,

Echinocandins: Caspofungin, Micafungin, and Anidulafungin

Caspofungin, anidulafungin, and micafungin are available only as parenteral preparations [42–44]. The MICs of the echinocandins are low for a broad spectrum of *Candida* species, including *C. glabrata* and *C. krusei*. *C. parapsilosis* demonstrates less in vitro susceptibility to the echinocandins than do most other *Candida* species, which raises the concern that *C. parapsilosis* may be less responsive to the echinocandins. However, in several clinical trials, this has not been demonstrated [45,

Echinocandins may be useful in patients with probable or proven **invasive aspergillosis** that is **refractory** to or intolerant of other therapies

All echinocandins are generally well tolerated, and the most frequently reported adverse effects include **increased liver aminotransferase** enzyme levels, gastrointestinal upset, and headaches.
Echinocandins appear to have no significant potential for drug interactions mediated by the CYP450 enzyme system. However, **cyclosporine** increases the area under the curve of **caspofungin** by 35%

Caspofungin Spectrum of Activity

- In vitro activity against *Aspergillus* and *Candida* spp.
- In vitro, no cross-resistance to *Candida* spp. with intrinsic or acquired resistance to fluconazole, amphotericin B or flucytosine
- No activity against *Cryptococcus neoformans*
- Activity against other fungi less well defined

COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

N Engl J Med 2002;347:2020-9

Patients with clinical evidence of infection and a **positive culture for candida** spp were stratified according to the severity of disease (APACHE II score), and the presence or absence of neutropenia and randomly assigned to caspofungin or amphotericin B.

Efficacy was measured in terms of the **overall response** at the end of I.V. therapy. The **noninferiority** of caspofungin would be demonstrated if the two-sided 95 % confidence interval for the difference in efficacy was not lower than **-20.0 %**

Time Point	Modified Intention-to-Treat Analysis		Patients Who Met Criteria for Evaluation	
	Caspofungin (N=109)	Amphotericin B (N=115)	Caspofungin (N=88)	Amphotericin B (N=97)
	no. with a favorable response/total no. (%)			
End of intravenous therapy	80/109 (73.4)	71/115 (61.7)	71/88 (80.7)	63/97 (64.9)*

Difference: - 12.7 % (95 % confidence interval, -0.7 to 26.0; P=0.09)

The mortality rate among all patients was similar in the two treatment groups

Conclusions Caspofungin is at least as effective as amphotericin B for the treatment of invasive candidiasis and, more specifically, candidemia. (N Engl J Med

Efficacy and Safety of Caspofungin for Treatment of Invasive Aspergillosis in Patients Refractory to or Intolerant of Conventional Antifungal Therapy

Methods. We investigated the efficacy and safety of caspofungin in the treatment of IA. Ninety patients with IA who were refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B, or triazoles were enrolled to receive caspofungin.

A favorable response to caspofungin therapy was observed in 37 (45%) of 83 patients, including 32 (50%) of 64 with pulmonary aspergillosis and 3 (23%) of 13 with disseminated aspergillosis. Two patients discontinued caspofungin therapy because of drug-related adverse events. Drug-related nephrotoxicity and hepatotoxicity occurred infrequently.

Conclusion. Caspofungin demonstrated usefulness in the salvage treatment of IA.

Table 3. Distribution of patients with invasive aspergillosis, by type and duration of previous antifungal therapy.

Previous antifungal therapy	No. (%) of patients, by response to therapy	
	Refractory[a] (n = 71)	Intolerant (n = 12)
Type		
Amphotericin B deoxycholate	14 (19.7)	6 (50.0)
Lipid formulation of amphotericin B (any preparation)	20 (28.2)	3 (25.0)
Itraconazole	14 (19.7)	1 (8.3)
Voriconazole	1 (1.4)	0
>1 Antifungal drug	22 (31.0)	2 (16.7)
Duration, days		
≤14	24 (33.8)	10 (83.3)
15–21	12 (16.9)	0
22–28	3 (4.2)	0
>28	32 (45.1)	2 (16.7)

Open-Label, Randomized Comparison of Itraconazole versus Caspofungin for Prophylaxis in Patients with Hematologic Malignancies

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2006, p. 143–147

Open-label, randomized study, to compare caspofungin with Ii.V. itraconazole for antifungal prophylaxis in patients undergoing induction chemotherapy for AML or MDS

Patient criterion	No. of patients (%) in treatment group:		*P* value
	Itraconazole	Caspofungin	
Total randomized	92	108	
Did not receive study drug	2	1	
Total evaluated (intent-to-treat group)[a]	90	107	
Excluded from efficacy analysis			
Received concomitant fluconazole[b]	2	0	
Received less than 3 days of prophylaxis[c]	2	1	
Evaluated for efficacy	86	106	
Completed prophylaxis with no evidence of documented fungal infection	44 (51)	55 (52)	0.92
Developed documented invasive fungal infection	5 (6)	7 (6)	0.83
Developed persistent fever or pulmonary infiltrates of unknown etiology	29 (34)	40 (37)	0.56
Withdrew because of side effects	8 (9)	4 (5)	0.12

In conclusion, intravenous itraconazole and caspofungin provided **similar** protection against invasive fungal infection during induction chemotherapy, and both drugs were well tolerated

Anidulafungin versus Fluconazole for Invasive Candidiasis

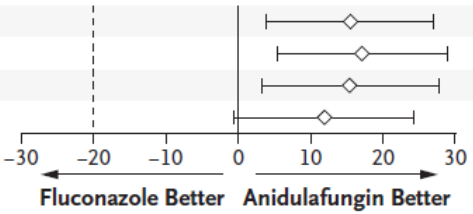
N Engl J Med 2007;356:2472-82.

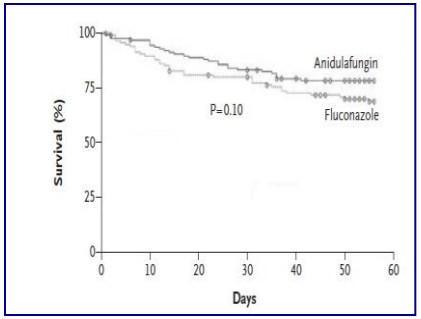
Adults with invasive candidiasis were randomly assigned to receive either I.V. **anidulafungin** or I.V. **fluconazole**. All patients could receive oral fluconazole after **10 days** of I.V. therapy. Primary efficacy endpoint: **global response (clinical and microbiologic) at the end of I.V. therapy**

Noninferiority stated if the lower limit of the two-sided 95% C.I. was **> –20 %.**

El tratamiento IV tuvo una duración superior en el gupo de Anidulafungina (14 vs 11 d). Este hecho pudo favorecer al grupo que recibió un tto I.V. más prolongado.

End Point	Global Success		Absolute Percent Difference between Treatments (95% CI)
	Fluconazole Group (N=118)	Anidulafungin Group (N=127)	
	no. (%)		
End of intravenous therapy	71 (60.2)	96 (75.6)	15.4 (3.9 to 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 to 29.0)
2-Week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 to 27.7)
6-Week follow-up	52 (44.1)	71 (55.9)	11.8 (–0.6 to 24.3)





CONCLUSIONS

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

Anidulafungin Versus Fluconazole for the Prevention of Fungal Infections in Liver Transplant Recipients

This study is not yet open for participant recruitment.
Study NCT00841971 University of Pittsburgh
First Received: February 11, 2009 Last Updated: January 12, 2010

Anidulafungin Prophylaxis in Patients With Hematologic Malignancies (ECALTA)

This study is currently recruiting participants.
Elisabethinen Hospital, July 2009

Anidulafungin Plus Voriconazole Versus Voriconazole For The Treatment Of Invasive Aspergillosis

This study is currently recruiting participants.
Study NCT00531479. Pfizer. Last Updated: Jan 2010

Anidulafungin in Combination with Amphotericin B against *Aspergillus fumigatus*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2009, p. 4035–4039

Indifference was the only type of interaction observed in vitro. Anidulafungin at 1 and 5 mg/kg of body weight/day, amphotericin B at 1 mg/kg/day, and combination therapy prolonged the survival of mice with invasive aspergillosis.
Overall, **the combination was not superior to the most active single drug**

Micafungin versus Caspofungin for Treatment of Candidemia and Other Forms of Invasive Candidiasis

Clinical Infectious Diseases 2007; 45:883–93

Randomized, double-blind trial comparing **micafungin** (**100** and **150** mg daily) with **caspofungin** (70 mg followed by 50 mg daily).
Primary end point: **treatment success** (clinical & mycological) at the end of I.V. therapy.

Variable	Micafungin arms: 100 mg arm (*n* = 191)	Micafungin arms: 150 mg arm (*n* = 199)	Caspofungin arm (*n* = 188)
Duration of therapy, median days (range)[a]	14 (1.0–61.0)	14 (1.0–56.0)	14 (1.0–43.0)
Treatment success[b]			
Investigators	146 (76.4)	142 (71.4)	136 (72.3)
Data review panel	139 (72.8)	139 (69.8)	133 (70.7)
Clinical success			
Overall	167 (87.4)	174 (87.4)	164 (87.2)
Candidemic[c]			
Complete response	128/163 (78.5)	136/168 (81.0)	123/161(76.4)
Partial response	15/163 (9.2)	12/168 (7.1)	21/161 (13.0)
Noncandidemic			
Complete response	14/28 (50.0)	17/30 (56.7)	15/26 (57.7)
Partial response	10/28 (35.7)	9/30 (30.0)	5/26 (19.2)
Mycological success	169 (88.5)	166 (83.4)	158 (84.0)

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.

Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial

Lancet 2007; 369: 1519–27

Double-blind, randomised, non-inferiority study to compare micafungin (100 mg/day) with liposomal amphotericin B (3 mg/kg per day).
Primary endpoint: treatment success (clinical and mycological) at the end of treatment

	Micafungin		Liposomal amphotericin B		Difference in proportions (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	202	181 (89·6%)	190	170 (89·5%)	0·1% (–5·9 to 6·2)
Complete response*		159 (78·7%)		148 (77·9%)	
Partial response*		22 (10·9%)		22 (11·6%)	
Neutropenic status					0·7% (–5·3 to 6·7)†
<500 cells per µL at baseline	24	18 (75·0%)	15	12 (80·0%)	
≥500 cells per µL at baseline	178	163 (91·6%)	175	158 (90·3%)	
<500 cells per µL at end of therapy (persistent neutropenia)	10	5 (50·0%)	7	5 (71·4%)	

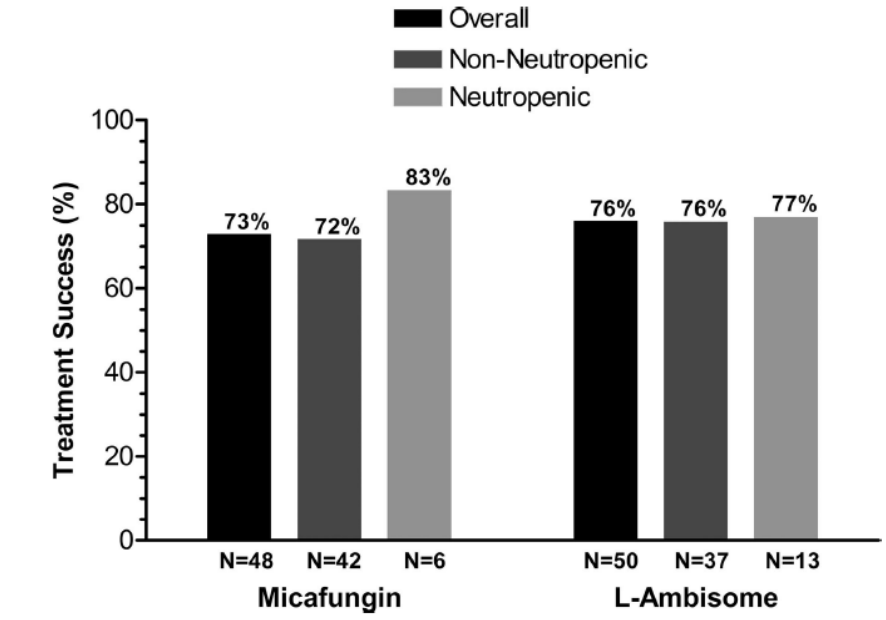
Interpretation Micafungin was as effective as—and caused fewer adverse events than—liposomal amphotericin B as first-line treatment of candidaemia and invasive candidosis.

Micafungin Versus Liposomal Amphotericin B for Pediatric Patients With Invasive Candidiasis

Substudy of a Randomized Double-Blind Trial

(*Pediatr Infect Dis J* 2008;27: 820–826)

Statistical analyses were descriptive, as the sample size meant that the study was not powered for hypothesis testing.



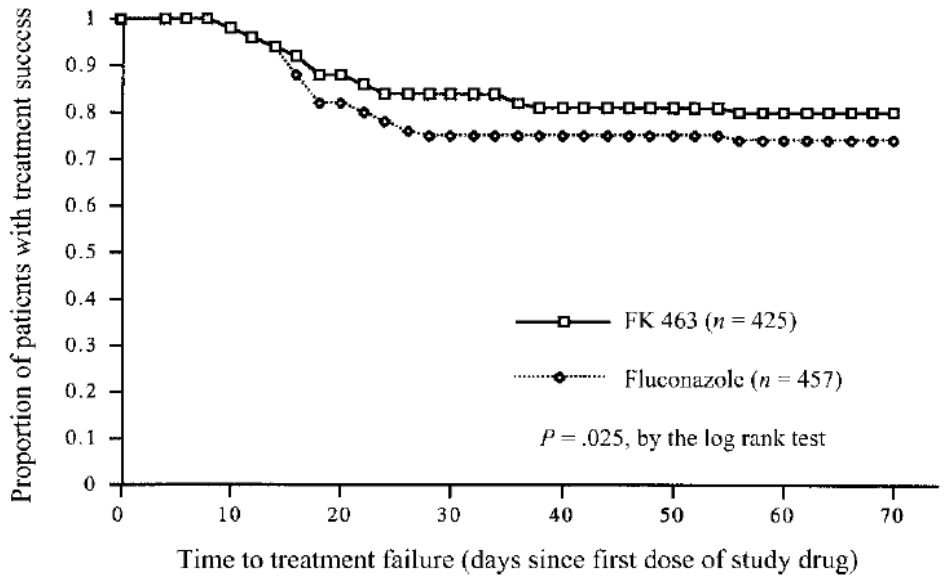
Conclusions: Micafungin seems to be **similarly effective** and **as safe** as liposomal amphotericin B for the treatment of invasive candidiasis in pediatric patients.

Micafungin versus Fluconazole for Prophylaxis against Invasive Fungal Infections during Neutropenia in Patients Undergoing Hematopoietic Stem Cell Transplantation

Clinical Infectious Diseases 2004; 39:1407–16

Randomized, double-blind trial of 882 adult and pediatric patients. Success was defined as the absence of suspected, proven, or probable IFI through the end of therapy and as the absence of proven or probable IFI through the end of 4-week after treatment.

Micafungin was not statistically inferior to fluconazole if the 95% lower confidence bound on the difference in success rates was **>10%**



Overall treatment success rate was 80.0% vs. 73.5%; absolute difference: +6.5%; 95% CI, 0.9%–12%; *P*= 0.03)

MICAFUNGINA (SEGURIDAD)

Risks

Micafungin induced irreversible FAH and liver tumours in rat after treatment for 3 month and longer. The mechanism for FAH and tumour development has not been elucidated. Based on the NOAEL for FAH development a threshold for tumour development is at 10 mg/kg/day, which is in the therapeutic range.

The relevance of this finding for the therapeutic use in patients can not be excluded.
Liver function should be carefully monitored during micafungin treatment.
To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended.
At this threshold for tumour development, the AUC in female rats is in the range of human AUCs at therapeutic doses, i.e. there aren't any safety margins at least for the high therapeutic doses (safety factor for adult patients at the 150 mg/day dose: 1.2).
Especially in paediatric patients the safety margin at a dose of 4 mg/kg is < 1 (0.7)

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Candidemia			
Nonneutropenic adults	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin[a] (A-I). For species-specific recommendations, see text.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)	Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in
Neutropenic patients	An echinocandin[a] or LFAmB 3–5 mg/kg daily (A-II). For species-specific recommendations, see text.	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid (B-III)	An echinocandin or LFAmB is preferred for most patients. Fluconazole is recommended for patients without recent azole exposure and who are not critically ill.

Table 3. General patterns of susceptibility of *Candida* species.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

NOTE. I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Suspected candidiasis treated with empiric antifungal therapy			
Nonneutropenic patients	Treat as above for candidemia. An echinocandin or fluconazole is preferred (B-III).	LFAmB 3–5 mg/kg daily or AmB-d 0.5–1 mg/kg daily (B-III)	For patients with moderately severe to severe illness and/or recent azole exposure, an echinocandin is preferred. The selection of appropri-
Neutropenic patients	LFAmB 3–5 mg/kg daily, caspofungin 70-mg loading dose, then 50 mg daily (A-I), or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or itraconazole 200 mg (3 mg/kg) bid (B-I)	In most neutropenic patients, it is appropriate to initiate empiric antifungal therapy after 4 days of persistent fever despite antibiotics.

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
PROPHYLAXIS IN HIGH RISK PATIENTS			
Solid Organ Transp.	**Fluconazole**	**LAmB 1-2 mg/Kg**	**7-14 days**
ICU patients (if high incidence)	**Fluconazole**		
Chemother. Ind. Neutropenia	**Fluconazole**	**Caspofungin, Posaconazole or Itraconazole**	**Start with QT during neutrop.**
SCT with Neutropenia	**Fluconazole or Posaconazole**	**Micafungin**	**during neutrop.**

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not esta-	Primary combination therapy is not routinely recommended based on lack of clinical data; ad-
Empirical and preemptive antifungal therapy	For empirical antifungal therapy, L-AMB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), itraconazole (200 mg every day IV or 200 mg BID), voriconazole (6 mg/kg IV every 12h for 1 day, followed by 3 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	…	Preemptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result)
Prophylaxis against invasive aspergillosis	Posaconazole (200 mg every 8h)	Itraconazole (200 mg every 12 h IV for 2 days, then 200 mg every 24 h IV) or itraconazole (200 mg PO every 12 h); micafungin (50 mg/day)	Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML and MDS)

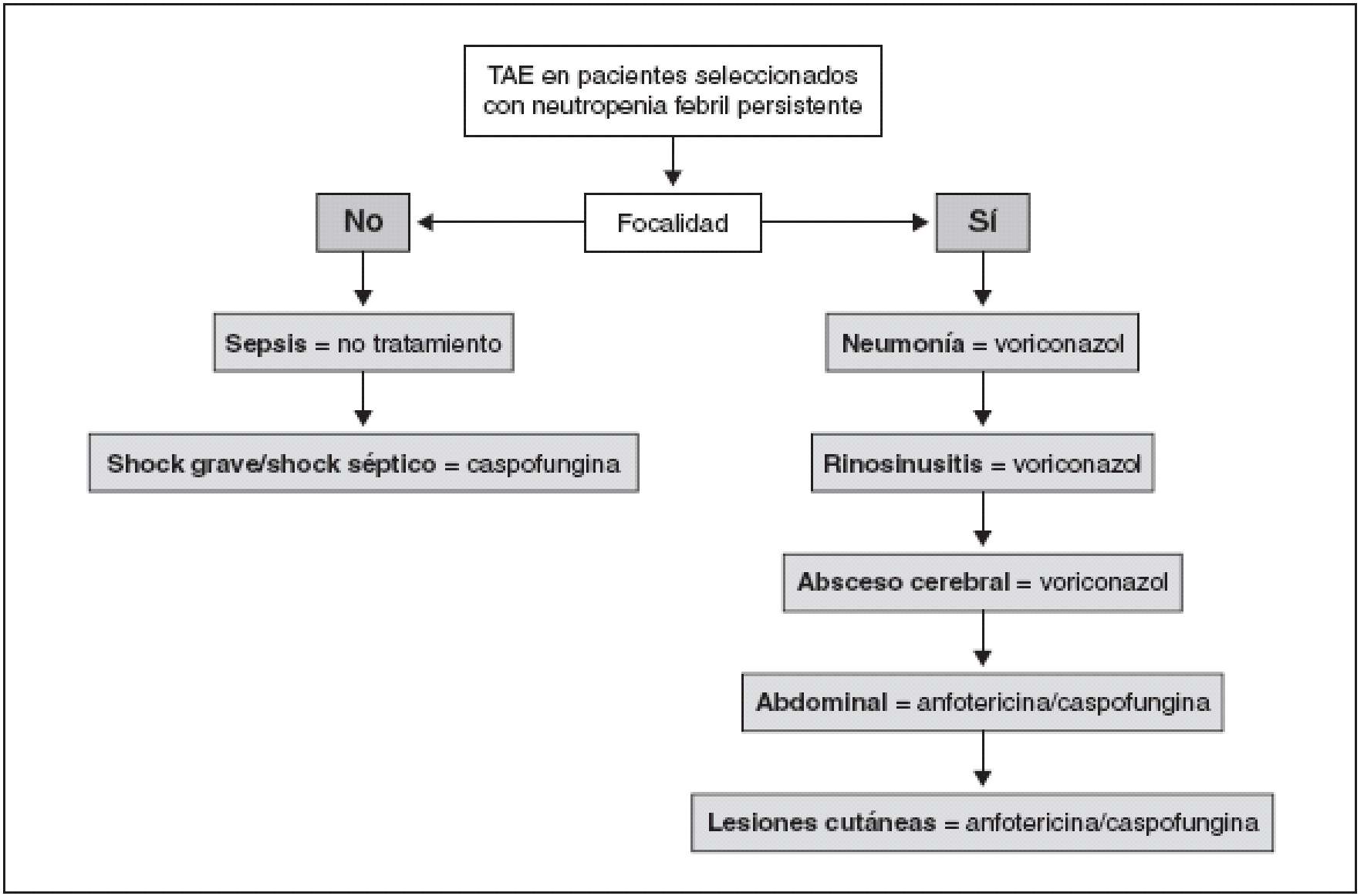
Tratamiento antifúngico empírico en pacientes seleccionados con fiebre persistente y neutropenia

José Miguel Cisneros[a], Ildefonso Espigado[b], Antonio Rivero[c], Fernando Lozano de León[d], Jorge Parra[e], Antonio Ramón Collado[f], José Manuel Lomas[g], Jerónimo Pachón[a] y Sociedad Andaluza de Enfermedades Infecciosas

La Sociedad Americana de Enfermedades Infecciosas recomienda iniciar el TAE en los pacientes con fiebre después de 5-7 días de tratamiento antibacteriano y en los que la resolución de la neutropenia no es inminente. Sin embargo, el TAE no ha demostrado mayor eficacia que el placebo, no obtiene mejores resultados que el tratamiento antifúngico dirigido, su efectividad es mínima, no es inocuo y, con la mayoría de los antifúngicos, es muy poco eficiente. Por todas estas razones consideramos que la citada recomendación del TAE no está justificada. En su lugar proponemos la realización del TAE en pacientes

TABLA 4. Tratamiento antifúngico empírico en pacientes seleccionados según el síndrome clínico

Síndrome clínico	Etiología más probable	Prueba diagnóstica	Tratamiento de elección	Alternativo
Fiebre sin focalidad				
Sepsis	No fúngica	Galactomanano	No	No
Sepsis grave/shock séptico	*Candida*	Hemocultivos	Caspofungina	Anfotericina*
Fiebre con focalidad				
Neumonía	*Aspergillus*	BAL	Voriconazol	Caspofungina
Sinusitis	*Aspergillus*	Rinoscopia	Voriconazol	Caspofungina Anfotericina*,**
Absceso cerebral	*Aspergillus*	Biopsia cerebral	Voriconazol	Caspofungina
Abdominal	*Candida*	Ecografía	Anfotericina* Caspofungina	Fluconazol
Lesiones cutáneas	*Candida*	Biopsia cutánea	Anfotericina* Caspofungina	Fluconazol


TAE en pacientes seleccionados con neutropenia febril persistente
Focalidad
No
Sí
Sepsis = no tratamiento
Shock grave/shock séptico = caspofungina
Neumonía = voriconazol
Rinosinusitis = voriconazol
Absceso cerebral = voriconazol
Abdominal = anfotericina/caspofungina
Lesiones cutáneas = anfotericina/caspofungina

Evaluación del TAE en pacientes seleccionados

Se reevaluará a las 48-72 h a la luz de los resultados de las pruebas diagnósticas y de la evolución del paciente. Si se ha establecido el diagnóstico de IFI, se deberá indicar el tratamiento antifúngico recomendado para la IFI. Si se ha establecido otro diagnóstico (p. ej., bacteriemia por *P. aeruginosa*) que justifica la clínica, indicar el tratamiento específico y suspender el TAE. Si continúa sin diagnóstico etiológico y el paciente continúa estable o con mejoría, se deberá mantener el TAE considerando su simplificación a fluconazol, itraconazol o voriconazol oral en función de la profilaxis previa y de los resultados del galactomanano, y realizar una nueva evaluación del paciente en 48-72 h. Por

Tratamiento de las infecciones fúngicas invasoras

Jerónimo Pachón, José Miguel Cisneros, Antonio Ramón Collado-Romacho, José Manuel Lomas-Cabezas, Fernando Lozano de León-Naranjo, Jorge Parra-Ruiz y Antonio Rivero-Román por la Sociedad Andaluza de Enfermedades Infecciosas (SAEI)

TABLA 2. **Resumen de las indicaciones del tratamiento en la candidiasis invasora**

Situación	Tratamiento de elección	Tratamiento alternativo
Candidemia		
Estable sin neutropenia ni azoles	Fluconazol [AI]	ABD, caspofungina o voriconazol [AI]
Estable con neutropenia o azoles	ABD o caspofungina [AI]	Fluconazol, ABL
Sepsis grave/shock séptico	Caspofungina o ABD [AIII]	ABL
Candidiasis diseminada crónica	Fluconazol [BIII] ABD	Caspofungina Voriconazol ABL
Candidiasis urinaria	Fluconazol [BII] ABD [BII]	
Peritonitis	Fluconazol [BIII] ABD	ABL Caspofungina
Neumonía	Igual que la candidemia	

Aspergilosis Invasora:

-Voriconazol

- Caspofungina en caso de refractariedad o intolerancia a Voriconazol

Tratamiento de las infecciones causadas por otros hongos filamentosos

Mucormicosis	Anfotericina B lipídica
Scedosporium	Voriconazol
Fusarium	Voriconazol
Zigomycetos (Mucor)	Posaconazol

Costes asociados al tratamiento antifúngico

	Coste/día (€)	
	oral	I.V.
Fluconazol	2	3
Itraconazol	10	75
Voriconazol	65	340
Posaconazol	120	
Anfotericina B Compl Lipídico		≈400
Anfotericina B Liposomal		≈500
Equinocandinas		450

Comisión de Infecciones y Antibioterapia **Comisión de Farmacia y Terapéutica**

Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

SOLICITUD DE ANTIFÚNGICOS DE USO RESTRINGIDO

(POR FAVOR, pegar etiqueta del paciente o rellenar todos los datos) **Nombre del paciente**_____ **Servicio** _____ **Cama** _____ **Nº Hº** _____	**Facultativo:** **Fecha y firma:**

VORICONAZOL

- ❑ **Aspergilosis invasora** definida o probable en adultos y en niños de 2 o más años de edad.
- ❑ Tratamiento oral de la **candidiasis esofágica** por refractaria / resistente al tratamiento con fluconazol e itraconazol.
- ❑ Tratamiento de infecciones fúngicas por ***Scedosporium y Fusarium spp***.

Pauta de administración: 6 mg/Kg IV c/12 h el 1er día y 4 mgKg/IV c/12 h durante al menos 7 días.
Pasar a vía oral 200 mg c/12 h lo antes posible.

CASPOFUNGINA/ANIDULAFUNGINA (Equivalentes terapéuticos)

Tratamiento de la **candidiasis invasiva** en pacientes adultos **no neutropénicos** con contraindicación, intolerancia o falta de respuesta a **Fluconazol**

CASPOFUNGINA

- ❑ Tratamiento de la **candidiasis invasiva** en pacientes adultos con ***neutropenia***.
  Tratamiento empírico de pacientes ***oncohematológicos, con neutropenia febril*** persistente post-quimioterapia, sin respuesta al tratamiento antimicrobiano, **en pacientes con contraindicación, intolerancia o falta de respuesta a Fluconazol**

- ❑ Tratamiento de la **aspergilosis invasiva** definida o probable si existe:
  - Fracaso al tratamiento con Voriconazol en pacientes adultos
  - Intolerancia a Voriconazol o insuficiencia renal moderada-grave (Cr> 2 mg/dL) en el curso del tratamiento con Voriconazol intravenoso, e imposibilidad de pasar a la vía oral de Voriconazol.

Pauta de administración: Dosis de carga inicial: 70 mg IV el 1º dia, seguido de 50 mg IV/día

ANIDULAFUNGINA

- ❑ Tratamiento de la **candidiasis invasiva** en pacientes adultos ***no neutropénicos*** *con sospecha de* ***resistencia a fluconazol*** en las siguientes circunstancias:
  - *Tratamiento simultáneo con Ciclosporina, Tacrólimus o Rifampicina*
  - *Insuficiencia Hepática*

Pauta de administración: 200 mg IV el 1º dia, seguido de 100 mg IV/día

ANFOTERICINA B (PRESENTACIONES LIPÍDICAS)

- ❑ Tratamiento de aquellas micosis invasoras que presenten contraindicación, intolerancia o falta de respuesta al uso de Caspofungina, Anidulafungina y Voriconazol.
- ❖ *Se utilizará como primera opción Anfotericina B complejo lipídico y si el paciente presenta nefrotoxicidad, disfunción de órganos o falta de repuesta a esta última, pasar a Anfotericina B liposómica*

Especificar causa:

POSACONAZOL

- ❑ Profilaxis de IFI en pacientes de alto riesgo que han recibido un **alo-TPH no emparentado** (inmunosupresión intensa)
- ❑ Infección por Zigomycetos, Fusarium o Scedosporium

MICAFUNGINA

- ❑ Candidemia y candidiasis invasiva en **neonatos**, en caso de contraindicación, intolerancia o falta de respuesta a Anfotericina B liposomal

VORICONAZOL

• **Aspergilosis invasora** definida o probable en adultos y en niños de 2 o más años de edad.

• Tratamiento oral de la **candidiasis esofágica** refractaria / resistente al tratamiento con fluconazol e itraconazol.

• Tratamiento de infecciones fúngicas por ***Scedosporium y Fusarium spp***.

Pauta de administración: 6 mg/Kg IV c/12 h el 1er día y 4 mgKg/IV c/12 h durante al menos 7 días.
Pasar a vía oral 200 mg c/12 h lo antes posible

CASPOFUNGINA/ANIDULAFUNGINA (Equivalentes terapéuticos)

• Tratamiento de la **candidiasis invasiva** en pacientes adultos **no neutropénicos** con contraindicación, intolerancia o falta de respuesta a **Fluconazol**

CASPOFUNGINA

• Tratamiento de la **candidiasis invasiva** en pacientes adultos con ***neutropenia*.**

• Tratamiento empírico de pacientes ***oncohematológicos, con neutropenia febril*** persistente post-quimioterapia, sin respuesta al tratamiento antimicrobiano, **en pacientes con contraindicación, intolerancia o falta de respuesta a Fluconazol**

• Tratamiento de la **aspergilosis invasiva** definida o probable si existe:

- Fracaso al tratamiento con **Voriconazol** en pacientes adultos
- Intolerancia a Voriconazol o insuficiencia renal moderada-grave (Cr> 2 mg/dL) en el curso del tratamiento con Voriconazol intravenoso, e imposibilidad de pasar a Voriconazol por vía oral.

ANIDULAFUNGINA

• Tratamiento de la **candidiasis invasiva** en pacientes adultos ***no neutropénicos*** *con sospecha de* ***resistencia a fluconazol*** en las siguientes circunstancias:

- *Tratamiento simultáneo con Ciclosporina o Rifampicina*
- *Insuficiencia Hepática*

MICAFUNGINA

• Candidemia y candidiasis invasiva en **neonatos**, en caso de contraindicación, intolerancia o falta de respuesta a Anfotericina B liposomal

ANFOTERICINA B (PRESENTACIONES LIPÍDICAS)

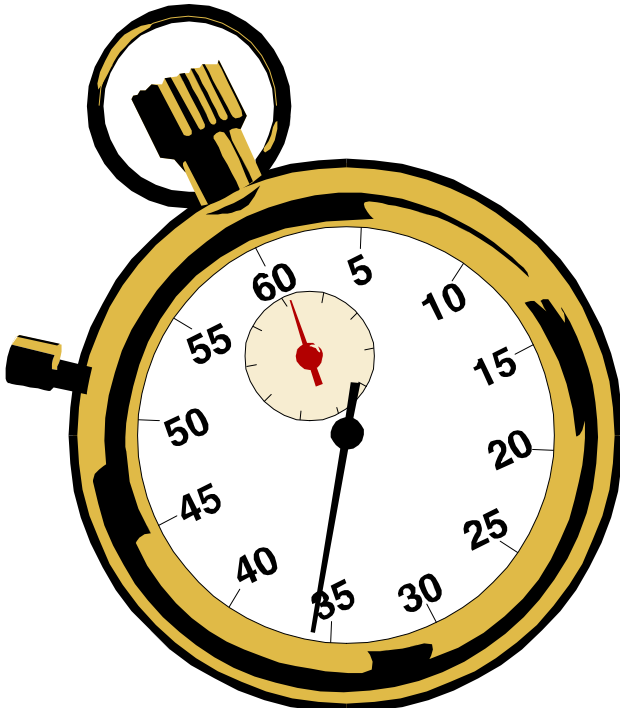
• Tratamiento de aquellas IFI que presenten contraindicación, intolerancia o falta de respuesta al uso de Equinocandinas y Voriconazol.

*Se utilizará como primera opción **Anfotericina B complejo lipídico** y si el paciente presenta nefrotoxicidad, disfunción de órganos o falta de repuesta a esta última, **Anfotericina B liposómica***

POSACONAZOL

• Profilaxis de IFI en pacientes de alto riesgo que han recibido un **alo-TPH no emparentado** (inmunosupresión intensa)

• Infección por Zigomycetos (Mucor)



Gracias!