Profilaxis antifúngica en pacientes onco-hematológicos: evidencias y recomendaciones

R. de la Cámara
Hospital de la Princesa

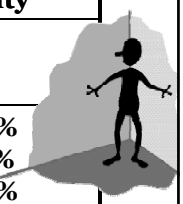
Simposio
Profilaxis de las Infecciones Fúngicas Invasivas en el paciente Onco-hematológico

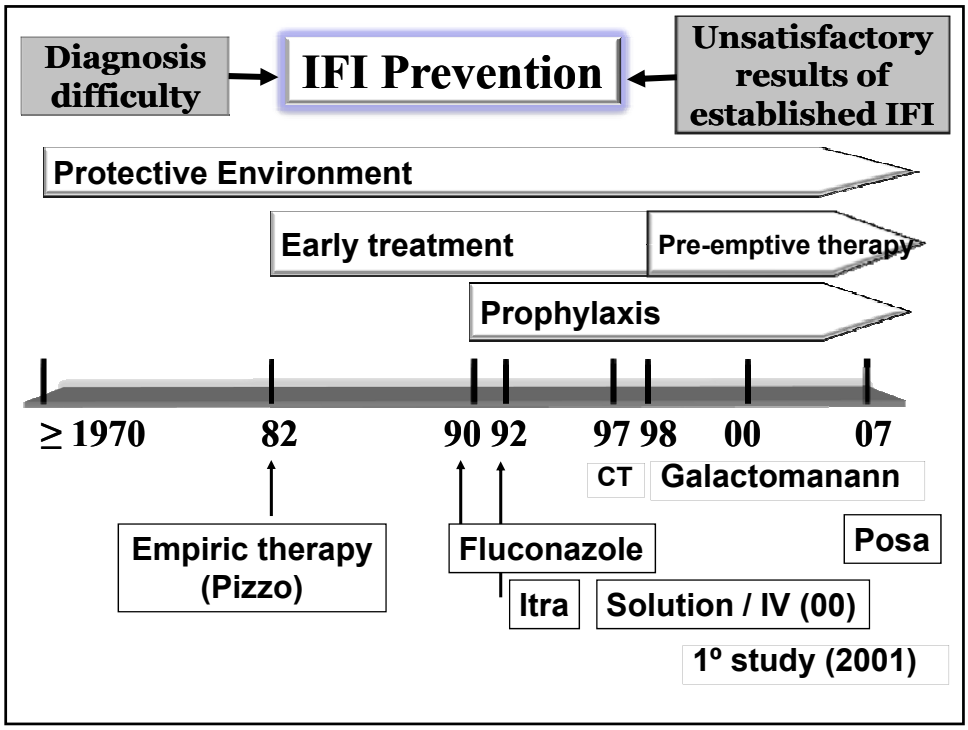
ARAGOZA SEFH

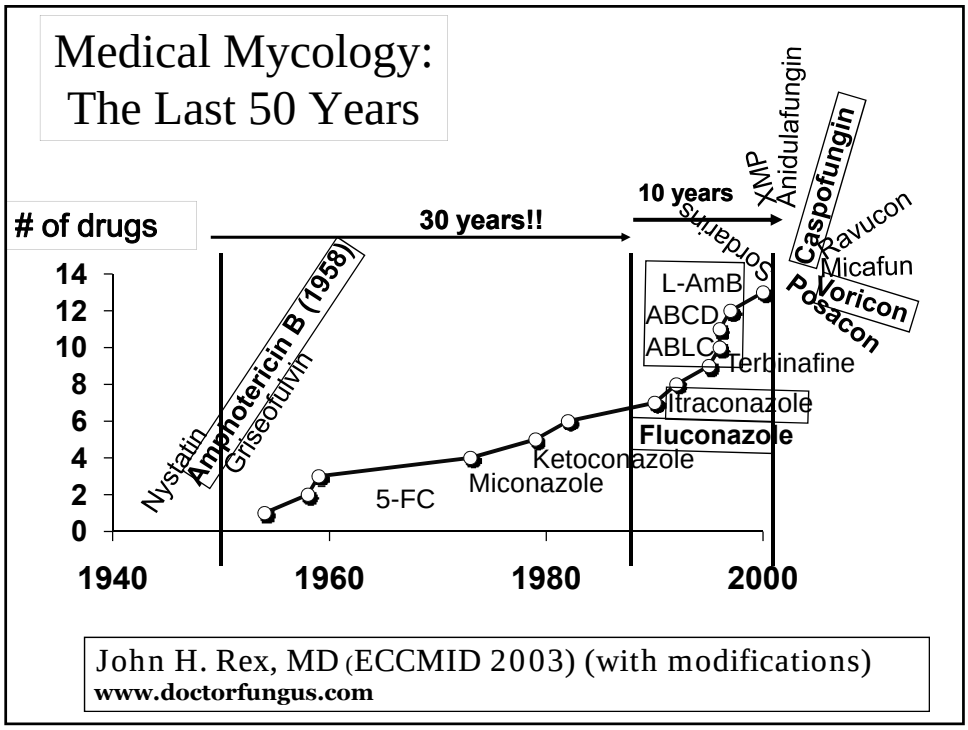
Zaragoza, 24 Septiembre 2009

Treatment of established IFI: clearly unsatisfactory

Moulds	Mortality
Aspergillosis Global CNS / SCT / Disseminated	50% 88%
Fusariosis Global Persistant neutropenia SCT	50-80% ≈ 100% 80-90%
Zygomycosis Global / SCT	40% / 80%
***Scedosporium* spp**	≈ 100%
Yeasts	
Candidiasis Global SCT candidemia Tisular invasion	30-40% 20-40% 90%
***Trichosporon* spp**	65%




Diagnosis difficulty
IFI Prevention
Unsatisfactory results of established IFI
Protective Environment
Early treatment
Pre-emptive therapy
Prophylaxis
≥ 1970
82
90 92
97 98
00
07
CT
Galactomanann
Empiric therapy (Pizzo)
Fluconazole
Posa
Itra
Solution / IV (00)
1º study (2001)


Medical Mycology:
The Last 50 Years
# of drugs
30 years!!
10 years
XMP
Anidulafungin
Caspofungin
Ravucon
Micafun
Voricon
Posacon
Sordarins
L-AmB
ABCD
ABLC
Terbinafine
Itraconazole
Fluconazole
Ketoconazole
Miconazole
5-FC
Nystatin
Amphotericin B (1958)
Griseofulvin
14
12
10
8
6
4
2
0
1940
1960
1980
2000
John H. Rex, MD (ECCMID 2003) (with modifications)
www.doctorfungus.com

Antifungals

Before 2000 ‹ **After**

- **Amphotericin B**
  (discover in1953) 1957
  - ABLC 1995
  - LAmb 1997
- **First systemic azole**
  Miconazol (D 1969) 1978
- **First triazole: Fluconazole**
  (discover in 1982) 1990
- **Fiirst anti-*Aspergillus* triazole Itraconazole**
  - Capsules 1992

- **Itraconazole**
  - –Oral solution USA 1997 E 2001
  - –Iv USA 2000 E 2004
- **1º Candin: Caspofungin** 2001
- **Voriconazole (1º triazole 2ª generation)** 2002
- **Posaconazole** 2007
- **Micafungin, Anidalofungin** 2008

– **Under study:** aminocandin isavuconazole, ravuconazole, albaconazole

Profilaxis antifúngica

Principios	• **Pros /contras** • **Definiciones**
¿A quién?	• **Grupos de riesgo**
¿Con qué?	• **Experiencia clínica:** • **64 ensayos randomizados** • **9 metaanálisis**
Recomendaciones	• **IDSA** (Infectious Diseases Society of America) • **NCCN** (National Comprenhensive Cancer Network) • **ECIL** (European Conference on Infection in Leukemia)

Profilaxis antifúngica

Principios

- **Pros /contras**
- **Definiciones**

Bien definidas

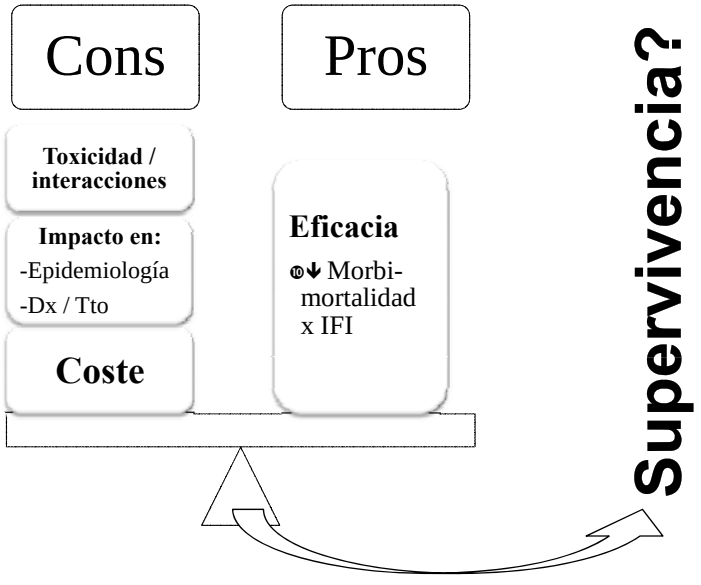
Infección Fúngica Invasiva (IFI): criterios de consenso

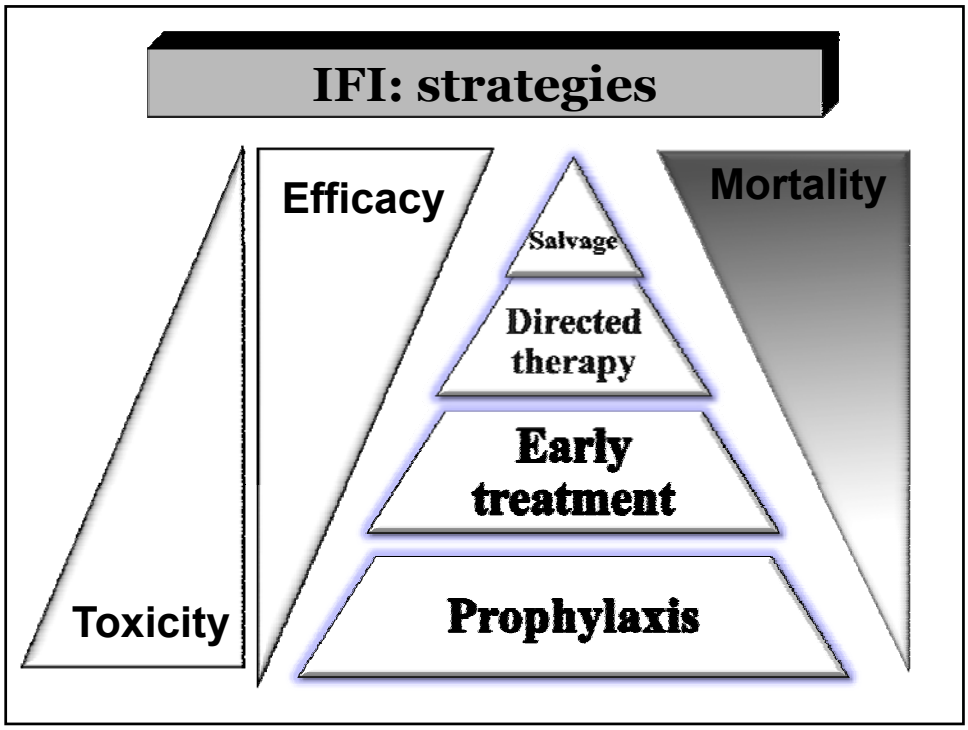
- **Primeras:** Ascioglu (CID 2002)
- **Actuales:** De Pauw (CID 2008)

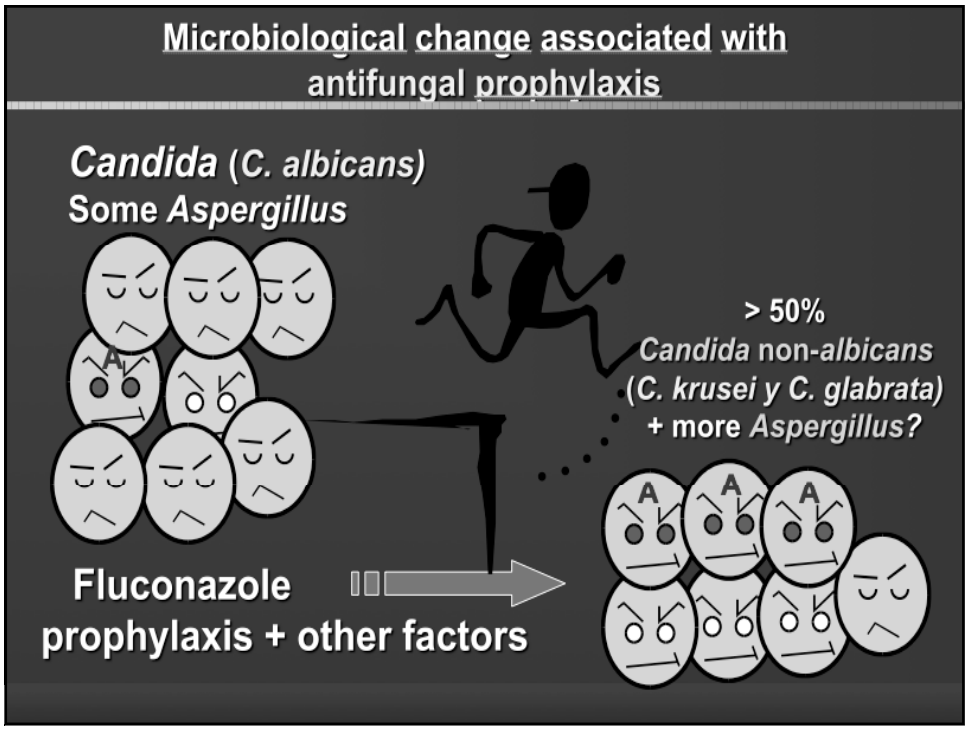
Profilaxis

- **Primaria:** numerosos estudios randomizados
- **Secundaria:** ningún estudio randomizado

Profilaxis antifúngica




IFI: strategies
Efficacy
Mortality
Toxicity
Salvage
Directed therapy
Early treatment
Prophylaxis


Microbiological change associated with antifungal prophylaxis
Candida (C. albicans)
Some Aspergillus
> 50%
Candida non-albicans
(C. krusei y C. glabrata)
+ more Aspergillus?
Fluconazole
prophylaxis + other factors

IFI: evolución

1990's •*Candida* el patógeno más importante

- •Fluconazol: el "gold standard" para profilaxis
- •Opciones: Fluconazol: sí / no
  Itraconazol: puede / no

2000's Situación más complicada

- • Patógenos principales: Filamentosos, *Aspergillus*++
- •Profilaxis: cambio de fluconazol ➔anti-filamenosos
- •Opciones: Fluco, Posa, Itra, Vori
  Micafungina
  Anfotericina lipídica (iv, inhalada)

Who should receive prophylaxis?

Only Patients at high risk of Invasive Fungal Infection

But,… What is high-risk?

- Several well-known **risk factors**
- **In spite of many studies, thousands of patients included**
  - **still no consensus!**

Evidence-based review of antifungal prophylaxis in neutropenic patients with haematological malignancies

Axel Glasmacher[1]* and Archibald Grant Prentice[2]

Background: There is still no consensus on the efficacy of antifungal prophylaxis in neutropenic patients after more than 50 clinical trials.

Journal of Antimicrobial Chemotherapy (2005) **56**, *Suppl. S1*, i23–i32

Who should receive prophylaxis?

Swindon, England

Evidence-based review of antifungal prophylaxis in neutropenic patients with haematological malignancies

Axel Glasmacher[1]* and Archibald Grant Prentice[2]

***Background*: There is still no consensus on the efficacy of antifungal prophylaxis in neutropenic patients after more than 50 clinical trials.**

Journal of Antimicrobial Chemotherapy (2005) **56**, *Suppl. S1*, i23–i32

Profilaxis Antifúngica: fármacos

Aprobados

Azoles
- **Fluconazol** (oral / iv)
- **Itraconazol** (solución)
- **Posaconazol**
  - LAM / MDS
  - TPH + EICH

Equinocandinas
- **Micafungina** (*Candida*)
  - TPH alogénico
  - Neutropenia de >10 días

No aprobados, pero estudiados

Azoles
- **Voriconazol**
  - 2 ensayos en TPH
  - día 0-100 (no publicados)

Anfotericina
- **Deoxicolato**
- **liposomal**

Candinas
- **Caspofungina**

Profilaxis para *Candida*: situación óptima

- **Generalmente sensible a muchos antifúngicos**
- **Periodo de riesgo "corto" (semanas)**
  - **Patógeno de la fase de neutropenia**
- **Antifúngico estándar: fl**

Bueno
Bien tolerado
Barato

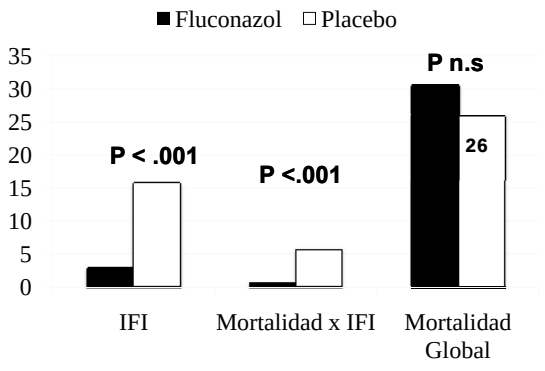
IDEAL

- **Administración cómoda**
- **Buena absorción oral**
- **Bien tolerado**
- **Escasas interacciones**
- **Bar**

"Lo que todo antifúngico desearía ser"

Profilaxis para *Candida* en TPH: funciona

Receptores de TPH		Incidencia IFI (%)		
Estudio	nº	Fluconazol	Placebo	P
Goodman (NEJM 1992)	356	**2.8**	**15.8**	<0.001
Slavin (JID 1995)	300	**7**	**18**	0.004



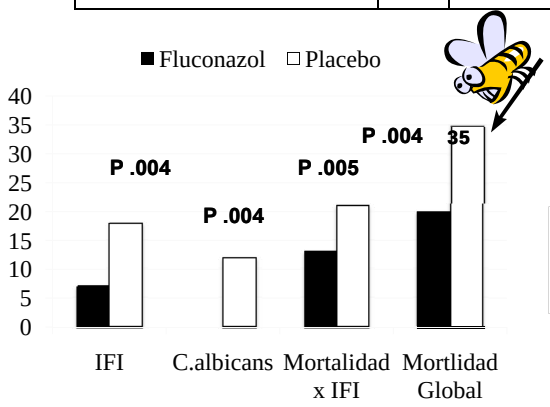
- **TPH**
  - **50 % alogénicos**
  - **50 % autólogos**
- **Fluco vs Placebo→ >10^3 PMN**
- **Supervivencia: hasta +90**

- **Fluconazol**
  - **Reduce IFI x *Candida***
  - **Mortalidad x IFI**

***Goodman. NEJM* 1992;326:845**

Profilaxis para *Candida* en TPH: funciona

Receptores de TPH		Incidencia IFI (%)		
Estudio	nº	Fluconazol	Placebo	P
Goodman (NEJM 1992)	356	**2.8**	**15.8**	<0.001
Slavin (JID 1995)	300	**7**	**18**	0.004



- **TPH**
  - **88 % alogénicos**
  - **12 % autólogos**
- **Fluco vs Placebo → day 75**
- **Supervivencia: hasta +110**

- **Fluconazol**
  - **Reduce IFI x *Candida***
  - **Aumenta supervivencia**

***Slavin MA. JID* 1995;171:1545**

Profilaxis para *Aspergillus* ¿funciona?

Situación claramente más difícil que la *Candida*

- **Hongo menos sensible a antifúngicos**
- **Periodo de riesgo "largo" en TPH (meses)**

- **Evidencias**
  - **Disminución incidencia en ensayo randomizado:**
    - **Frente a otro antifúngico: sólo Posaconazol**
    - **Frente a placebo: anfotericina liposomal inhalada**
  - **Disminución de incidencia en metaanálisis: itraconazol**
  - **Tendencias**
    - **Voriconazol** (vs fluconazol): 2.3% vs 5.4% **P 0.05 (ASH 2007)**
    - **Micafungina**(vs fluconazol): 0.2% vs 1.5% **P 0.07 (CID 2004)**

Itraconazol profiláctico: metaanálisis

- **Estudios randomizados vs placebo, polieno o fluconazol**
- **En pacientes oncohematológicos, neutropénicos**
  - **Estudios 13, Pacientes 3597**

- **La solución, pero no las cápsulas, a dosis adecuadas**
  - **↓ IFI , ↓ aspergilosis y mortalidad x IFI**

- **Efecto dosis-respuesta**
- **Solución oral: 200mg /12h (= 2.5 mg/kg/12h)**
- **IV: 200mg /día**
  - **más dosis: más tóxico y no mas eficaz**
  - **menos: No eficaz**

***Glasmacher. JCO* 2003;21:4615**

*Antifungal prophylaxis with **Posaconazol** in **Neutropenic patients***

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

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

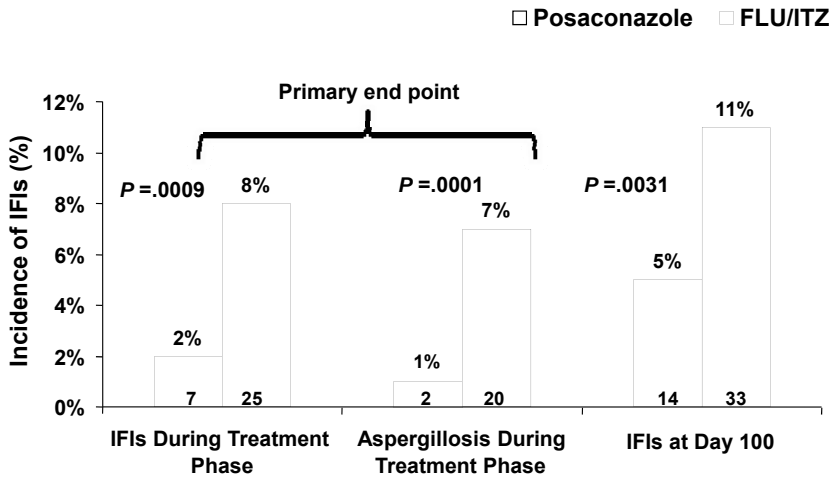
Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

Posaconazole (304)
3x 200 mg

VS

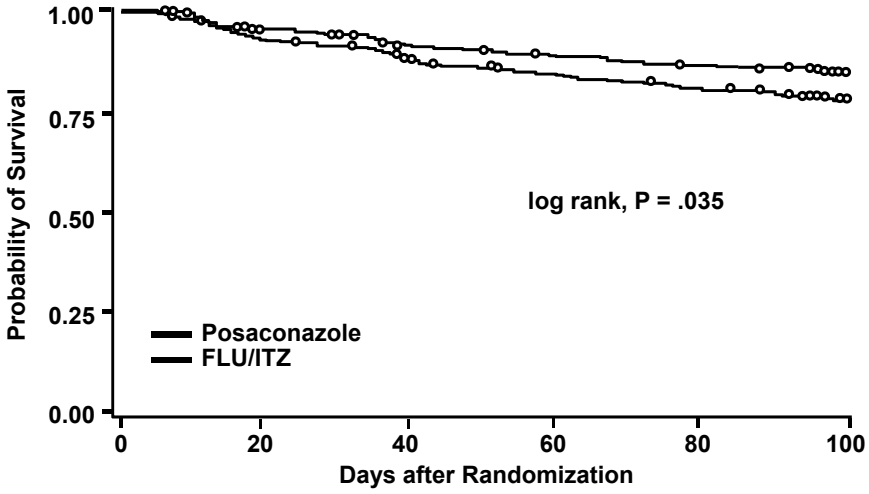
(298) Fluconazole
1x 400 mg
Or
Itraconazole (solution)
2x 200 mg

Proven or Probable IFIs During Treatment and 100 Days Postrandomization



Cornely O. 2008 (with modifications)

Overall Mortality – Time to Death



Cornely O. 2008 (with modifications)

Censoring time is last contact or day 100.

Conclusions

In AML/MDS patients undergoing induction chemotherapy

- Posaconazole prophylaxis compared to FLU/ITZ resulted in significant benefits:
  - overall survival
  - IFI-related survival

- Posaconazole was superior to FLU/ITZ in preventing Overall proven/probable IFIs and Aspergillosis
- Safety and tolerability profiles were comparable

Cornely O. 2008 (with modifications)

*Antifungal prophylaxis with **Posaconazol** in a Risk-targeting strategy*

The NEW ENGLAND JOURNAL of MEDICINE

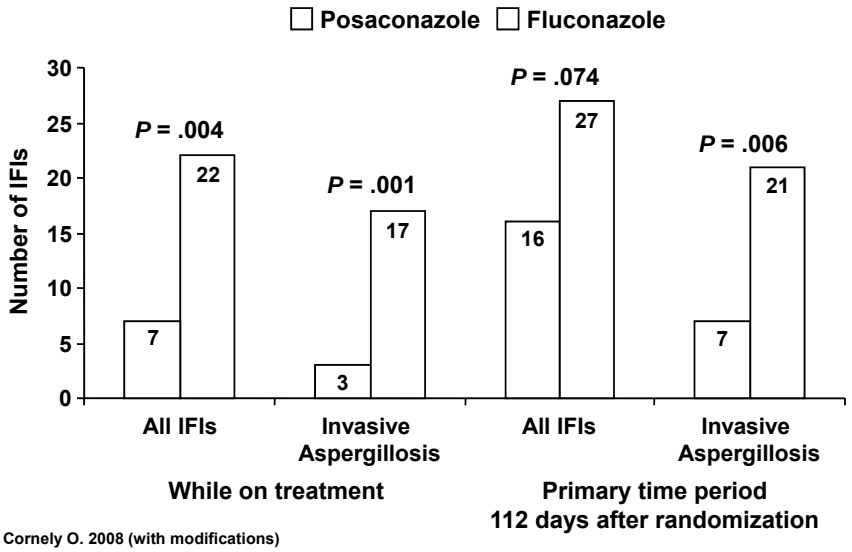
ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

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

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

- **Double-blind**
- **600 patients: 301 Posaconazole vs 299 Fluconazole**

Incidence of Proven/Probable IFIs



Cornely O. 2008 (with modifications)

Posaconazole or fluconazole in allogeneic HSCT recipients with graft-versus-host disease

Summary

Posaconazole compared with fluconazole

1. Prevents better invasive aspergillosis
2. Is as effective in preventing other IFIs
3. Reduces IFI-related mortality
4. Tolerability is good, similar to fluconazole

Risk-targeting prophylactic strategies work

Ullman A. NEJM 2007; 356 (4): 335-347

Prophylaxis Guidelines

IDSA (Infectious Diseases Society of America)

- **Candidiasis management (CID 2009; 48: 503)**
- **Aspergillosis treatment (CID 2008; 46: 327)**

NCCN 2009 (National Comprehensive Cancer Network)
http://www.nccn.org

CDC, IDSA, ASBMT (**MMWR 2000**; 49 (RR-10): 1-125)

SCT patients. Outdated. **New, co*ming soon!!***

ECIL (European Conference on Infections in Leukemia)
1st 2005 / 2nd 2007 (**Eur J Can suppl 2007; 5:1-59**)

- ***Guidelines: can recommend the use of antifungals not registered*** *for this indication, and vice versa*

Guidelines: Who and what?

- **Agreement on "who":** high-risk patients
- **No agreement on specific drug** recommendations

- **IDSA**: -**Allogeneic SCT with GVHD at high-risk for InvA**
  -**AML or MDS at high risk for InvA**
- **NCCN**: -**Patients at high / intermediate risk IFI**
  Not for all patients; Not for low risk patients
- **ECIL**: **Patients with an expected IFI incidence ≥ 10%**
  Acute leukemias, high-risk MDS, SCT (Allo > Auto)

InvA: invasive aspergillosis

Rating system for Recommendations

- **ECIL**
  - **A, B, C, D, E / I, II, III** ("Traditional" system)
- **IDSA 2008/2009** **(IDSA & USPHS)**
  - **A, B, C / I, II, III**
- **NCCN system**
  - **1, 2A, 2B, 3**

Rating system: Traditional IDSA/USPHS

Strength of recommendations

A	B	C	D	E
Strong evidence for efficacy	Moderate evidence for efficacy	Insufficient evidence	Moderate evidence against	Strong evidence against
Strongly recommended	Generally recommended	Optional	Generally Not recommended	Never recommended

Quality of evidence supporting recommendation

I	II	III
Randomized study	Well-designed trial without randomization	Expert opinions, descriptive studies

Dr. E.Carreras (modified)

MMWR 2000; 49 (RR-10): 1-125

Rating system: IDSA 2008 / 2009

Strength of recommendations

A	B	C	D	E
Good evidence	Moderate evidence	Poor evidence	Moderate evidence against	Strong evidence against
To support a recommendation FOR or AGAINST USE			Generally Not recommended	Never recommended

Quality of evidence supporting recommendation

I	II	III
Randomized study	Well-designed trial without randomization	Expert opinions, descriptive studies

Dr. E.Carreras (modified)

Summary Guidelines for AML /MDS

	Antifungal	ECIL	NCCN 09	IDSA 08	IDSA 09
Agreement	Posaconazole	A I	1	A I	A I
	Itraconazole (solution/IV)	B I	No rated	B I	A I
	Itraconazole (capsules)	E I	NC	Ineffective	NC
	Amphotericin	C I	2 B	Efficacy not demostrated	NC
Disagreement	Voriconazole	NC	2 B	ND	NC
	Fluconazole	C I	2 A (A.L.L.) 1 (ATPH +mucositis)		AI
	Micafungin	Insuficient data	1 (ATPH + mucositis)	Limited utility	Caspo BII

- **IDSA 08**: focused on *Aspergillus*
- **IDSA 09:** focused on candidiasis

ECIL: acute leukemia (all)

ND: No data
NC: No commented
ATHP: Autologous-SCT

Summary Guidelines for Allogeneic SCT

	Antifungal	ECIL	NCCN 09	IDSA 08	IDSA 09
Agreement	Posaconazole (GVHD)	A I	1	A I	
	Fluconazole	A I	1		AI
	Itraconazole (solution/ IV)	B I	2B	B I	NC
	Itraconazole (capsules)	E I	NC	Ineffective	
	Amphotericin	C I	2 B	Efficacy not demostrated	NC
Disagreement	Posaconazole (neutropenia)	NC	2 B	NC	AI
	Voriconazole	NC	2 B	ND	NC
	Micafungin	C I	1	Limited utility	AI

- **IDSA 08**: focused on *Aspergillus*
- **IDSA 09:** focused on candidiasis

ND: No data
NC: No commented

¿Son necesarias las guías?

- **Difícil estar al día, gran cantidad de información**
  - **Profilaxis IFI (I/08):** 64 estudios randomizados
    9 metaanálisis

¿Son necesarias las guías?

Ingente Información → Revisión Literatura

Información confusa / ausente → Opinión de Experto

- **Falta de estudios para determinados aspectos**
- **Resultados/acciones discrepantes**
- **Antifúngicos con usos distintos de ficha técnica**
  - ✓ **Sin indicación,** **pero Sí** se recomienda su uso
  - ✓ **Con indicación,** **pero No** se recomienda

Fluconazol profiláctico en TPH

TPHS		Incidencia IFI (%)		
Randomizado	nº	Fluco	Placebo	P
Goodman (NEJM 92)	356	2.8	15.8	<0.001
Slavin (JID 1995)	300	7	18	0.004

Sí profilaxis

NO profilaxis

685 Alo-TPH	Candidiasis
Jantunen (2004) No fluconazol	1.3%
Goodman & Slavin Fluconazol profiláctico	2.1%

¿Son necesarias las guías?

SI

Ingente Información → Revisión Literatura

Información confusa / ausente → Opinión de Experto

Práctica clínica compleja / conflictos → Respaldo "legal"

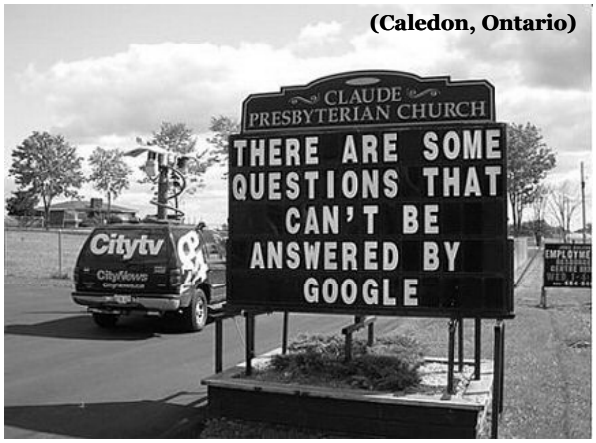
Guías

Síntesis / discusión → Recomendaciones / gradación

Guías en la Práctica: ¿cómo aplicarlas?

1. •*NO EXIGIRLAS para lo que no están pensadas*
2.
3.
4.

(Caledon, Ontario)



Guías en la Práctica: ¿cómo aplicarlas?

1. •***NO EXIGIRLAS para lo que no están pensadas***

2. •***Las guías No suplen al médico, le ayudan***
   (El código de circulación No suple al buen conductor)

3. • **Las guías Requieren Adaptación a nuestro medio**
   - **Epidemiología local**
   - **Logística (TAC, AGA)**
   - **Economía**

4. •***Las guías son recomendaciones, No leyes***
   - **No pueden preveer todas las situaciones. Se pueden "saltar"**

Profilaxis antifúngica: evidencias

Numerosos ensayos, pero persiste la controversia

- **Fluconazol en TPH alogénico ¿Es el mejor agente actualmente?**
  - **Para *Candida*:** sí
  - **Pero *Candida* no es el problema ahora!**
- **Agentes con actividad frente hongos filamentosos**
  - **Posaconazol:** la mejor evidencia
- **Grupos de pacientes por estudiar**
  - **LAL**

Is Fluconazole now the ideal agent for prophylaxis when *moulds*, particularly *Aspergillus*, are the main pathogens?

Antifungal Prophylaxis in Cancer Patients After Chemotherapy or Hematopoietic Stem-Cell Transplantation: Systematic Review and Meta-Analysis

J Clin Oncol 25:5471-5489. © 2007

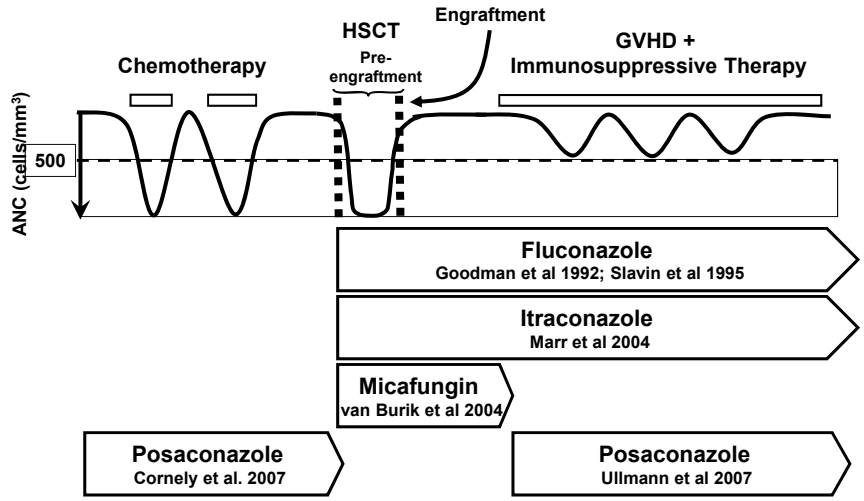
Eyal Robenshtok, Anat Gafter-Gvili, Elad Goldberg, Miriam Weinberger, Moshe Yeshurun, Leonard Leibovici, and Mical Paul

Randomized studies: 64 (12,986 patients)

- **Prophylactic fluconazole (global):**
  - **Invasive *Candida:*** **decrease** **RR 0.43 (0.28-0.68)**
  - ***Aspergillus:*** **increase, trend** **RR 1.40 (0.85-2.32)**

- **Prophylactic fluconazole vs anti-mould agent**
  - **Any IFI:** **increase** **RR 1.53 (1.23-1.89)**
  - ***Documented Asper.*:** **increase** **RR 2.1 (1.10-4.12)**
  - **IFI related Mortality:** **increase** **RR 1.53 (1.23-1.89)**
  - **Global Mortality:** **increase, trend** **RR 1.14 (0.95-1.37)**

Prophylaxis In Hematopoietic Stem Cell Recipients Overview of Studies



Goodman JL et al. *N Engl J Med*. 1992;326:845-851.
Slavin MA et al. *J Infect Dis*. 1995;171:1545-1552.
van Burik JA et al. *Clin Infect Dis*. 2004;39:1407-1416.
Marr KA et al. *Blood*. 2004;103:1527-1533.

Cornely O. 2008 (with modifications)

Different Risk Groups for IFI

High~15-30 %

Allo-PBSCT
>40 years
Non-CML
Graft failure
Steroids
GVHD
AML
>40 years; HD Ara-C
Performance

Moderate 5-15%

Allo-PBSCT
>40 years
Mismatch
MUD

AML

Low~1-5%

Allo-PBSCT
<40 y; CML-CP
Auto-PBSCT
AML (7+3)

Tahsine Mahfouz & Elias Anaissie. **Curr Opnin Investig Drugs 2003, 4:974**

Aerosolized Liposomal Amphotericin B for the Prevention of Invasive Pulmonary Aspergillosis during Prolonged Neutropenia: A Randomized, Placebo-Controlled Trial

CID 2008:46 (1 May) • 1401

Bart J. Rijnders,[1,4] Jan J. Cornelissen,[2] Lennert Slobbe,[3] Martin J. Becker,[3] Jeanette K. Doorduijn,[2] Wim C. J. Hop,[6] Elisabeth J. Ruijgrok,[7] Bob Löwenberg,[2] Arnold Vulto,[5] Pieternella J. Lugtenburg,[2] and Siem de Marie[4]

EDITORIAL COMMENTARY

Aerosolized Antifungal Prophylaxis: The Winds of Change?

John R. Perfect
Department of Medicine, Duke University Medical Center, Durham, North Carolina

CID 2008:46 (1 May) • 1409

From an efficacy standpoint, this is the most robust clinical study to date to support the value of aerosolized drug prophylaxis to prevent invasive aspergillosis.

it represents an alternate strategy for prophylaxis for these high-risk patients with neutropenia.

Anfo-liposomal inhalada profiláctica: métodos

Estudio randomizado, doble ciego con placebo, en pacientes oncohematológicos con neutropenia > 10 días

- **Inhalación: Amb-L 12.5 mg o placebo x 2 d / sem**
- **Hasta > 300 PMN**

Profilaxis IFI
•Todos recibían Fluconazol

AGA
•Suero: 2 veces/sem
•LBA

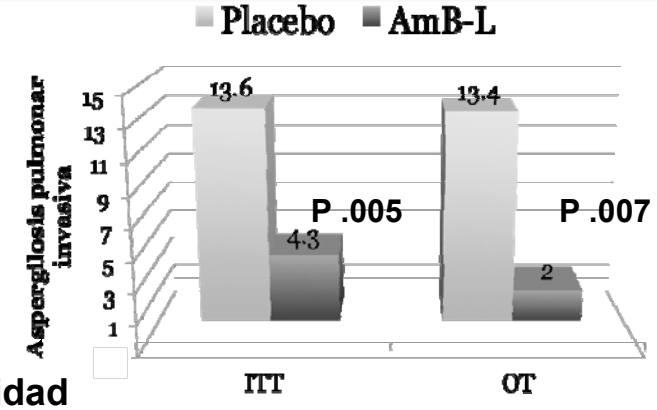
Objetivo primario
•Aspergilosis invasiva pulmonar (probada/probable)

Table 1. Baseline characteristics of the study participants.

271 (407 episodios)

Characteristics	Liposomal amphotericin B (*n* = 139)	Placebo (*n* = 132)	*P*
Age, mean years (range)	49 (18–73)	50 (20–74)	.64
Male sex/female sex	77/62	81/51	.33
HEPA filtration[a]	108	100	.77
Hematologic disease			
AML-MDS	65	67	.54
Other	74	65	
Hematologic treatment			
Chemotherapy	100	85	.19
Autologous HSCT	25	31	.29
Allogeneic HSCT	14	16	.70
Disease status			
Untreated	73	64	.54
Other[b]	66	68	
Treatment followed by allogeneic HSCT[c]	16	14	.85

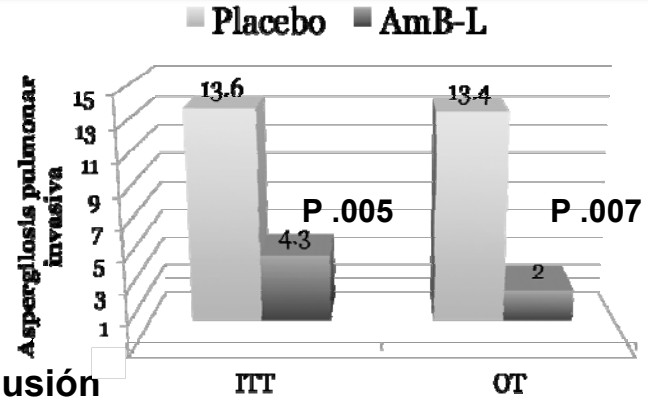
Anfo-liposomal inhalada profiláctica: resultados



Seguridad
•**AmB-L bien tolerada:** más tos vs placebo (16 vs 1 caso) P .002
•**Creatinina:** no variación respecto la basal

ITT: intention to treat OT: On-treatment

Anfo-liposomal inhalada profiláctica: resultados



Conclusión

- **La anfotericina liposomal inhalada previene la aspergilosis pulmonar invasiva** en pacientes neutropénicos de alto riesgo

International Consensus definitions of IFI
(de Pauw, B. CID 2008; 46: 1813)

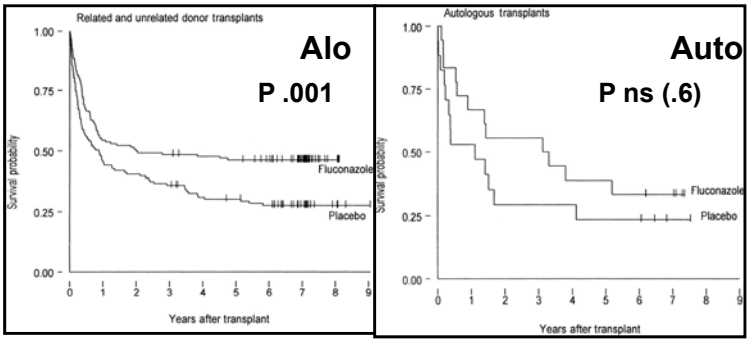
<u>3 categories</u> based on the level of Certainty
- Proven - Probable - Possible

Probable and possible IFD are based on 3 elements:
- host factors
- clinical manifestations
- mycological evidence
} **changed from previous 2002**

Proven IFI	**Fungemias**
	Deep tissue infections
	Cryptococcosis
	Endemic fungal infections

Profilaxis para *Candida* en TPH: funciona

- Resultados a largo plazo (8 años) del estudio de Slavin (1995)
  - El fluconazol aumenta la supervivencia en alo-TPH



- Recomendación CDC/IDSA/ASBMT (2000): Hasta el injerto:
  - En todos los alogénicos (AI). En subgrupos de auto (BIII)
  - Dosis: 400 mg/día (200 mg* =)

**MacMillan. Am J Med* 2002;112:369

Marr KA. Blood 2000;171:1545

Fluconazol profiláctico: estudios del FHCRC (1,2)

- Misma población de pacientes en ambos estudios (300)
- Marr KA et al (2000): seguimiento del primero (Slavin 1995)

¡Pero hay diferencias!

- Cambios en características de los pacientes
  - Cambio de sexo: 1 paciente
  - C ambio tipo habitación (LAF): 8 pacientes
- EICH-aguda y fluconazol
  - Slavin (1995): aumenta incidencia II-IV (P .036)(= Goodman 92)
  - Marr (2000): no diferencia en incidencia
    - EICH-agudo intestinal III-IV: disminuye con el fluconazol (P .02)
- Supervivencia
  - Slavin (1995): no se explican bien la causa del ⇑ supervivencia
  - Marr (2000): atribuida a ⇓ mortalidad x *Candida* (precoz y tardía)

(1)Slavin MA. JID 1995;171:1545 *(2) Marr KA. Blood* 2000;171:1545

Profilaxis con Itraconazol en alo-TPH: funciona (si lo toma)

Receptores de TPH		Incidencia IFI (%)		
Estudio	nº	Itraconazol	Fluco	P
Winston (AIM 2003)	356	**9**	**25**	0.01
Marr (Blood 2004)	300	**13**	**16**	n.s
En Tto		**7**	**15**	0.03

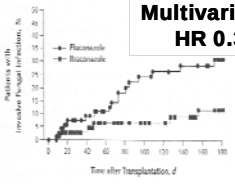
P n.s

P .02

P n.s

- **Itra vs Fluco → +100**

Multivariable HR 0.3



- **Itraconazol**
  - **Reduce IFI x 3**
  - **Más tóxico TGI**

***Winston. An Inter Med* 2003;138:705**

Profilaxis con Itraconazol en alo-TPH: funciona (si lo toma)

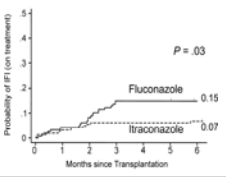
Receptores de TPH		Incidencia IFI (%)		
Estudio	nº	Itraconazol	Fluco	P
Winston (AIM 2003)	356	**9**	**25**	0.01
Marr (Blood 2004)	300	**13**	**16**	n.s
En Tto		**7**	**15**	0.03

P n.s

P .001

P .03

- **Itra vs Fluco → +120-180**



- **Itraconazol Reduce IFI**
  - **Global x 2**
  - **Filamentosos 60%**
- **Más tóxico TGI**

***Marr. Blood* 2004;103:1527**

Itraconazol profiláctico: estudios en alo-TPH (1,2)

- **Importantes diferencias en la posología (entre otras)**

	Winston	Marr
Inicio	+1	Con acondicionamiento
Dosificación	200 mg/12	2.5 mg/kg x 3 d/día
Uso iv	Inicial x 14d Luego libre	Inicial: PO / iv Luego: restringido

- **El inicio del itra: al terminar el acondicionamiento**
- **Posología: oral 200mg /12h (= 2.5 mg/kg/12h) ó 200mg iv/d**

  más dosis ⇒ más tóxico y no mas eficaz
- **Fase inicial iv y su uso libre después: mejora tolerancia y disminuye discontinuaciones (36% ⇒ 8.5%)**

(1) Winston. An Inter Med 2003;138:705 *(2) Marr. Blood* 2004;103:1527

Criterio para empleo de Profilaxis

- **ECIL**: **Pacientes con incidencia IFI ≥ 10%**
  - Leucemias agudas, MDS de alto riesgo, TPH (Alo > Auto)
- **NCCN**: **Pacientes de alto riesgo de infección (ver tabla)**

  Determinados pacientes de riesgo intermedio
- **IDSA**: **TPH alogénico con EICH en alto riesgo de AInV**

  LAM y MDS en alto riesgo de AInV

AInV: Aspergilosis invasora

Guidelines: Therapeutic Drug Monitoring

Antifungal	ECIL**	NCCN	IDSA 08*	IDSA 09
Itraconazole	B III ≥ 0.5 µg/ml thorough	NC	A III In InvA treatment (if oral)	Should be considered
Posaconazole	B III	NC	B III	NC
Voriconazol	NC	NC	B III In InvA treatment (specially oral)	Should be considered

- **IDSA 08**: focused on *Aspergillus*
- **IDSA 09:** focused on candidiasis

ND: No data
NC: No commented

What do we know?
Breakthrough IFI on Posaconazole prophylaxis

- **Two randomized studies*: 605 patients on posaconazole**
- **IFI** (proven / probable): **22 (3.6%)**
  - **-Aspergillosis: 9** (7 diagnosed by GM) **-Candidiasis: 7**
  - -Moulds (not specified): 3 -Others: 3
- **Plasma levels (IFI vs no-IFI):**
  - **Neutropenic Study:** no difference
  - **SCT study:** lower in those who developed IFI (5 cases)
    - C_{av} 611 vs 922 ng/ml (66% less) (Pharmacotherapy 2007)

- **The majority are aspergillosis and candidiasis**
  - Most aspergillosis diagnosed by GM
- **Relation with levels: not clear**

*(Cornely O. NEJM 2007; Ullman A NEJM 2007)

What do we know?
Breakthrough IFI on Itraconazole prophylaxis

Glasmacher A (Mycoses 1999): 20 IFI (among 307 chemos)
- **Yeast 2** (*C.glabrata, B.capitatum)*
- **Moulds 18** (2 *A.fumigatus,* 6 mould in tissue, 10 by image) **No GM**
- **Plasma levels** (20 **IFI vs** 150 **no-IFI): lower in IFI**
  < 500 ng/ ml: 52% vs 0% (P .03)

Krcmery V (JAC 1998): ***5 Candida*, 4 *Trichosporon*, 1 *C.laurenti***

Zygomycosis on itraconazole prophylaxis

Glasmacher A (ICAAC 05): **1 case**/ 1,812 patients. Randomized trials
Kontoyiannis D (CID 2000): **7 cases** (in 10 years)

•The majority seems to be aspergillosis & candidiasis
•Some other yeasts. Few zygomycosis
•Relation with levels: seems clear (< 500 ng/ml)

What do we know?
Breakthrough IFI on Voriconazole prophylaxis

•Allogeneic SCT. Randomized trial (vori vs Fluco) (ASH 07)
•Vori (305): 7 IA, 3 *Candida*, 2 zygomycosis
•Fluco (295): 16 IA, 3 *Candida*, 3 zygomycosis

Trifilio S (BMT 2007): 10 IFI (among 71 allogeneic SCT)
- **Yeast 6** (5 *C.glabrata, 1 C.krusei).* **Moulds 4** (4 zygomycetes).
- **Plasma levels** (6 *Candida*)**: lower in IFI**
  <2000 ng/ml: 6/44 vs 0/27 if > 2000 ng/ml (p .04)

•The majority are candidiasis, aspergillosis and Zygomycosis (?)
•Relation with levels: suggested (< 2000 ng/ml)

What do we know?
Breakthrough IFI on Voriconazole prophylaxis

- **Allogeneic SCT.** Randomized trial (vori vs Fluco) (ASH 07)
  - Vori (305): 7 IA, 3 *Candida*, 2 zygomicosis
  - Fluco (307): 16 IA, 2 *Candida*, 5 zygomicosis

- **Increase in Zygomycosis incidence (x 3) began before voriconazole was avalaible**
  (Kontoyiannis CID 2000)
- **Voriconazole may have amplified a previous tendency**

- **The majority are candidiasis, aspergillosis and Zygomycosis (?)**
- **Relation with levels: suggested (< 2000 ng/ml)**

Summary What do we know?
Breakthrough IFI on broad spectrum prophylaxis

- **The majority are candidiasis and aspergillosis**
  - **Based on randomized studies (Itra, Vori, Posa) (n=2,722)**
- **The majority of prophylaxis failures,** seems related to
  - **host and drug factors**
  - **And not to resistant pathogens**

- **Breakthrough IFI due to resistant pathogens**
  - **Mainly in single case reports**
  - **Maybe related also to local practices /epidemiology**
    (Voriconazole and zygomycosis)

What can we do?

In addition, management of breakthrough invasive aspergillosis in the context of mould-active azole prophylaxis or suppressive therapy is not defined by clinical trial data but would suggest a switch to another drug class (B-III).

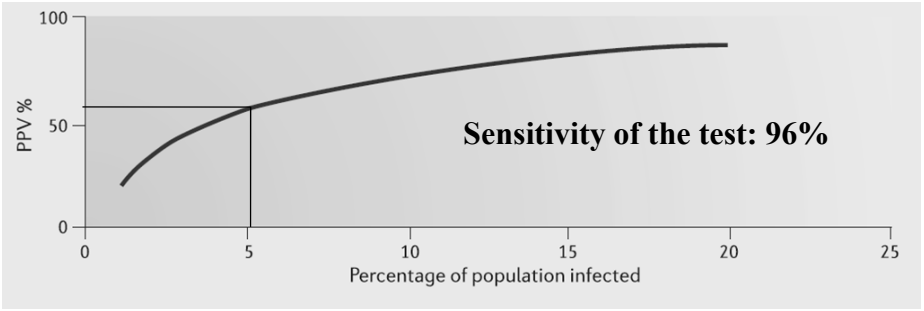
Impacto de la frecuencia de IFI en:
el NNT y en el VPP del galactomanano (AGA)
Sens. *92,6%,* ***Especif.*** *95,4*

Frecuencia basal de IFI	NNT	VPP AGA
15%	8,8	78%
10%	13	69%
8%	16	64%
5%	27	50%
2%	66	29%
0.5%	267	9%

Por tanto, si la incidencia de IFI es baja
No profilaxis
El tratamiento anticipado: No es eficaz

Impact of IFI incidence in the Positive Predictive value (PPV) of a test

The PPV depend on the incidence of the condition



Banoo S. **Nat Rev Micro 2007; 5:S21**

Galactomannan antigenaemia (GM) sensitivity and anti-mould antifungals

42 Invasive aspergillosis vs 269 controls

GM ≥ 0.5	With antifungal*	Without antifungal*	P
Sensitivity	52%	89%	.02
Specificity	91%	92%	n.s
*Antifungal with anti-mould activity			

Anti-Mould antifungal drugs:
- **Lower the GM sensitivity**
- **Do not change the specificity**

Marr KA. CID 2005;40:1762

Liposomal Amphotericin for Aspergillosis

Is it effective?

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group*

Liposomal AmB for Mold Infection • CID 2007:44 (15 May) • 1289

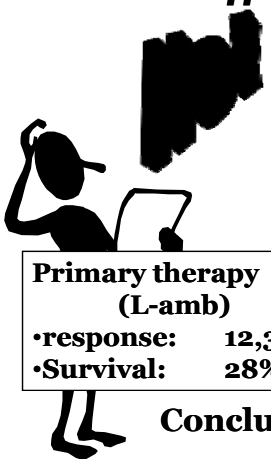
Primary therapy:
- **response: 50%**
- **Survival: 72%**

1st line therapy: 195 patients (AI). Randomized

Conclusions. In highly immunocompromised patients, the effectiveness of 3 mg/kg of liposomal amphotericin B per day as first-line therapy for invasive aspergillosis is demonstrated, with a response rate of 50% and a 12-week survival rate of 72%. The regimen of 10 mg/kg per day demonstrated no additional benefit and higher rates of nephrotoxicity.

Liposomal Amphotericin for Aspergillosis

Is it effective?



Amphotericin B Lipid Complex Versus Liposomal Amphotericin B Monotherapy for Invasive Aspergillosis in Patients With Hematologic Malignancy

Ray Y. Hachem, MD
Maha R. Boktour, MD
Hend A. Hanna, MD, MPH
Rola N. Husni, MD
Harrys A. Torres, MD
Claude Afif, MD
Dimitrios P. Kontoyiannis, MD
Issam I. Raad, MD

Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Cancer March 15, 2008; 112 (6): 12

Primary therapy (L-amb)
- **response: 12,3%**
- **Survival: 28%**

1st line therapy : 158 patients. Retrospective

Conclusions

"… the lípid formulation of AMB as a single agent apperared to be suboptimal."

"This may have been caused in part by the severity of underlying disease in our selected patient population."

International Consensus definitions of IFI
(de Pauw, B. 2008)

•Probable IFI: requires the presence of the 3 elements

Example

Neutropenia
+
Halo sign on CT
+
Galactomanann Pos.

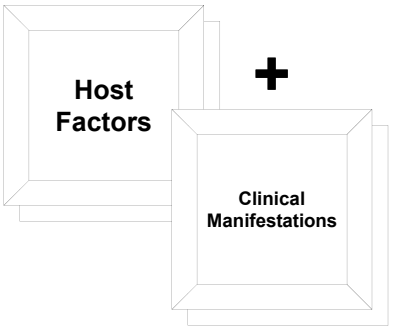
Host Factors + **Clinical Manifestations** + **Microbiology**

↑ Cases?

Serum: One GM test is enough (Previous definitions: 2)

International Consensus definitions of IFI
(de Pauw, B. 2008)

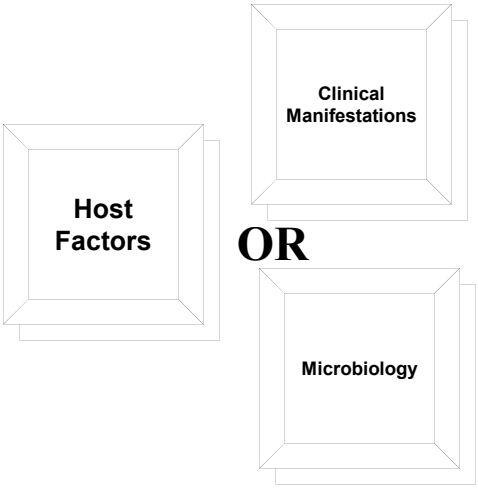
- **Possible IFI:** requires the presence of the following 2



This differs from the previous definitions

Previous Definition (Ascioglu S. 2002)

- **Possible IFI:** requires the presence of 2 of the 3



2008 criteria

Example

Neutropenia

Galactomannan positive

↓ Cases?

NCCN® Practice Guidelines in Oncology – v.1.2008

Prevention and Treatment of Cancer-Related Infections

2 factores determinantes: consenso y nivel de evidencia

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

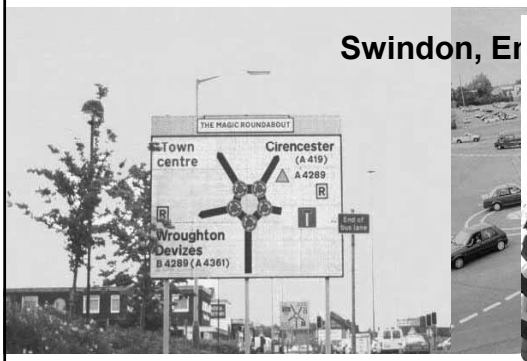
Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

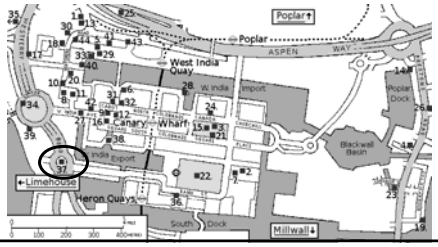
Category 3: There is major NCCN disagreement that the recommendation is appropriate.

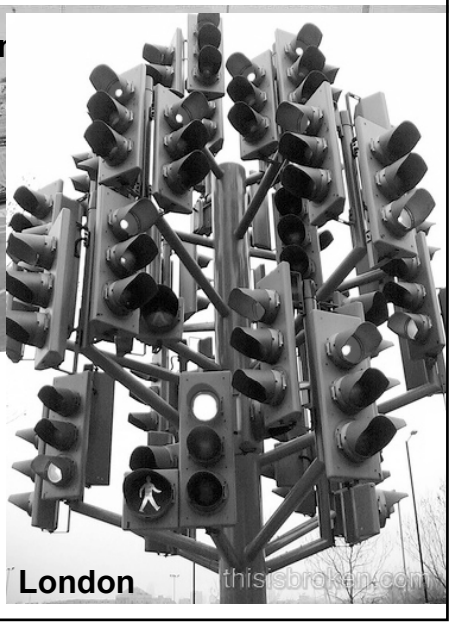
All recommendations are category 2A unless otherwise noted.

Prevention of IFI



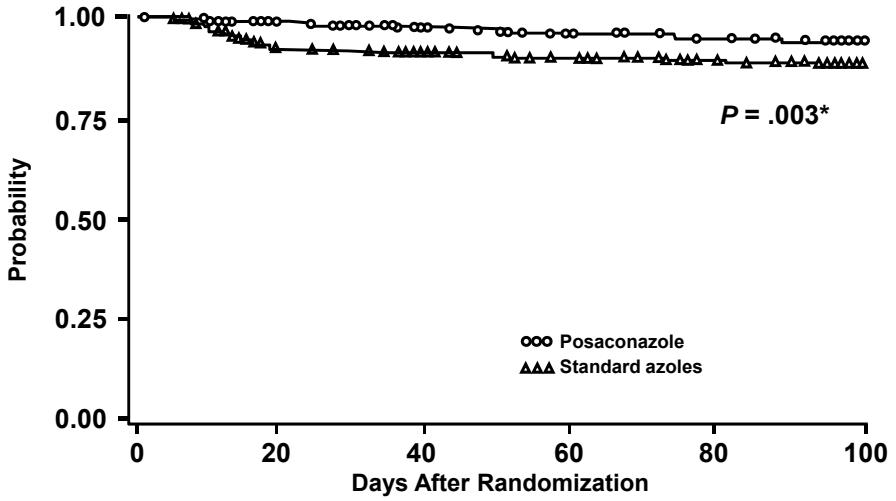
Swindon, En





London

Time to Invasive Fungal Infection



Cornely O. 2008 (with modifications)

Censoring time is last contact or day 100.

Conclusions

- First randomized trial demonstrating efficacy of antifungal prophylaxis in HSCT recipients with severe GVHD
- Posaconazole is effective and safe in the prevention of invasive fungal infections in HSCT recipients during the high-risk period and reduces fungal-related mortality

Cornely O. 2008 (with modifications)

¿Son necesarias las guías?

- *Información práctica/operativa*

- *Respaldo actuaciones*
  - *Fuera de Ficha técnica*
  - *Frente a Farmacia*
  - *Conflictos*
- *Indicación*
  - **General**
  - **Casos particulares**

NCCN National Comprehensive Cancer Network®

(Neutropenic and Non-neutropenic patients)

NCCN Clinical Practice Guidelines in Oncology™

Prevention and Treatment of Cancer-Related Infections

V.2.2009

A not-for-profit alliance of 21 of the world's leading cancer centers

Continue

www.nccn.org

The first European conference on infections in leukaemia (ECIL-1)

EJC SUPPLEMENTS 5 (2007) 43–48

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Primary antifungal prophylaxis in leukaemia patients ☆

Johan A. Maertens[a,*], *Pascale Frère*[b], *Cornelia Lass-Flörl*[c], *Werner Heinz*[d], *Oliver A. Cornely*[e]

1st European Conference Infections in Leukemia **SEPT 2005**

2nd European Conference Infections in Leukemia **SEPT 2007**

Candida Fluconazol