Nuevos (y no tan nuevos) Antifúngicos en Pediatría

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8º Congreso Argentino de Infectologia Pediatrica
2017

Repertorio

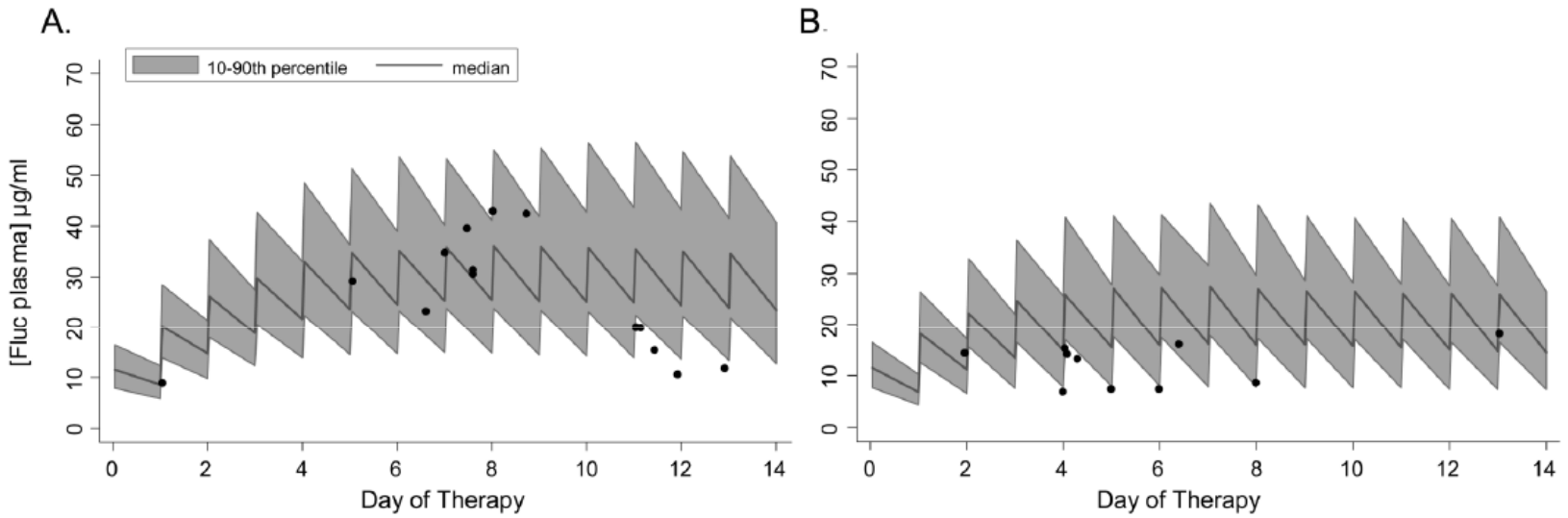
- Amphotericin B deoxycolate
  - Amphoterrible
- Fluconazole
  - Donde todo empezó
  - Itraconazole
- Lipid formulations Amphotericin B
  - ABCD
  - ABLC
  - L-AmB
- Echinocandinas
  - Caspofungin
  - Micafungin
  - Anidulafungin
- Triazoles (Segunda generación)
  - Voriconazole
  - Posaconazole
  - Isavuconazole

Dosis de Fluconazole para Prvencion y Tratamiento de Candidiasis Invasiva en Infantes jovenes

- Estudio farmacokinetico usando modelaje Monte-Carlo basados en un modelo derivado de un estudio previo con 357 muestras de 55 neonatos (23 – 40 semanas de edad, para pronosticar exposicion a fluconazole (mediana, 10^{th} – 90^{th} percentile rango the variabilidad) usando dosis de 3, 6, y 12 mg/kg/dia
- Objectivos de exposicion terapeutica:
  - Tratamiento: AUC_{24} minima de 400 mg*h/L en no menos de 90% de sujetos y un AUC mediana de 600 – 800 mh*h/L para asegurar un indice PK/PD de AUC/MIC $\geq$ 50 for MIC $\leq$ 8 mcg/ml
  - Profilaxis: AUC24 de 100 mg*h/L (equivalente a adultos recibiendo 100 mg/dia). La AUC pronosticada en estado estable se uso para comparar con adultos recibiendo una dosis equivalente

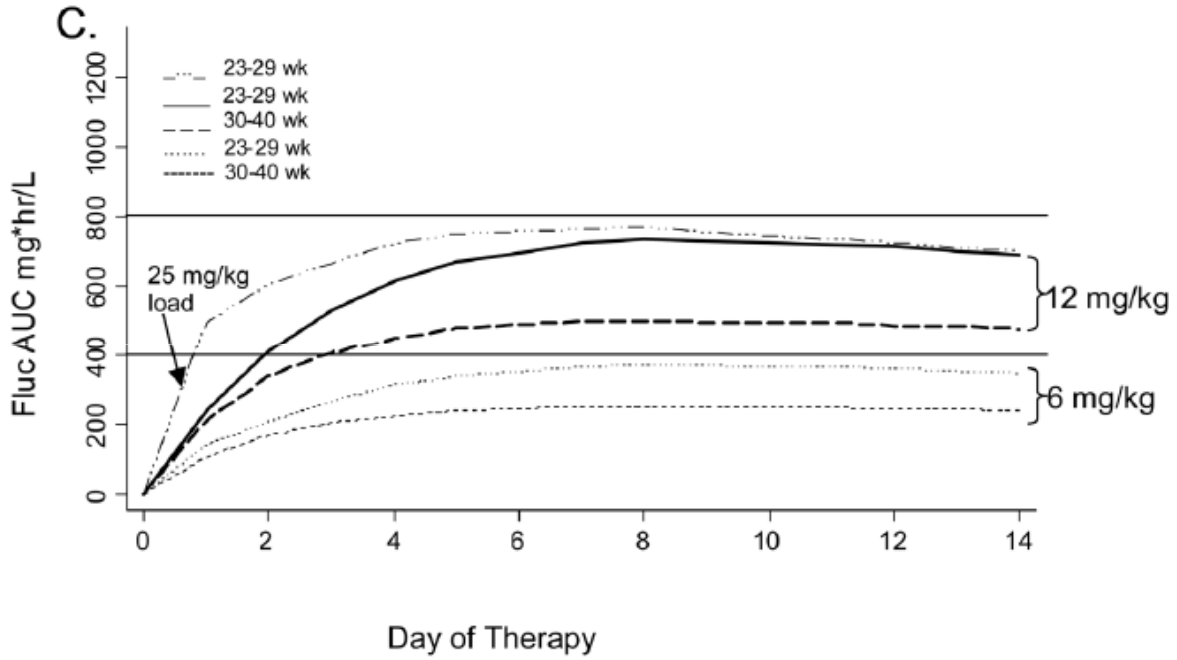
Wade, KC PIDJ 2010

Dosis de Fluconazole para Prvencion y Tratamiento de Candidiasis Invasiva en Infantes jovenes (Niveles en Plasma/Tratamiento)



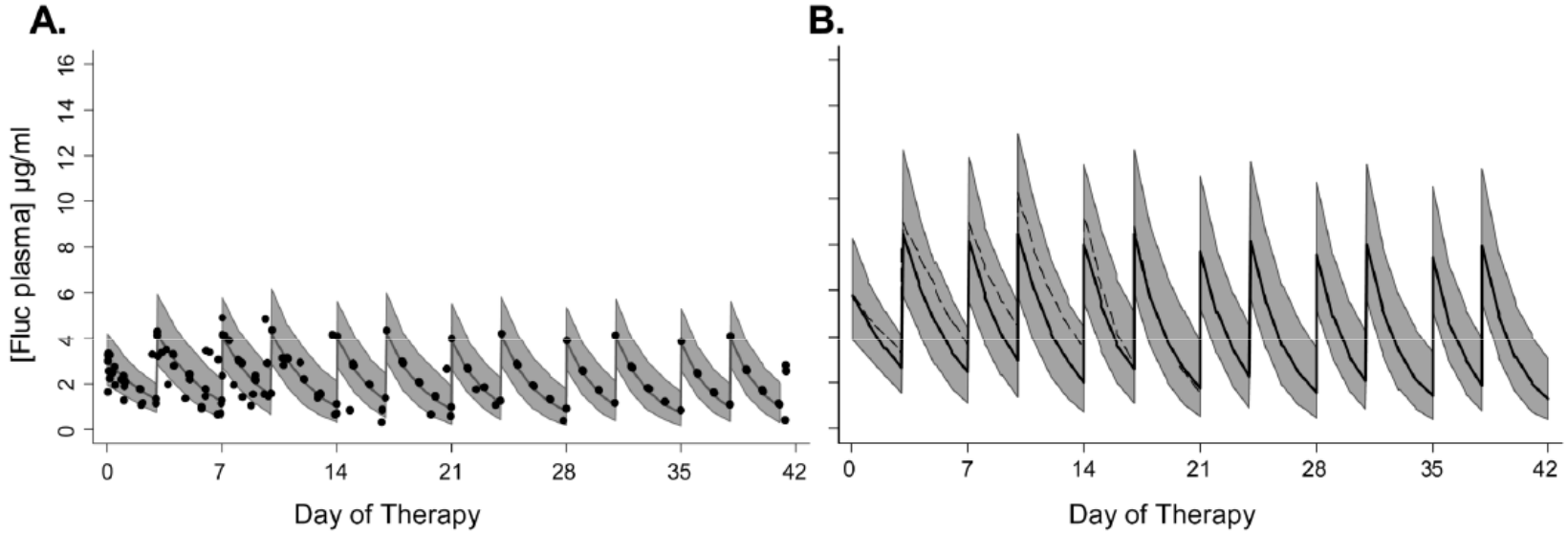
Concentracion en plasma media y rango de variabilidad (10^{th} – 90^{th} percentile) pronosticada de 100 experimentos simulados en niños pre-termino 23 – 29 semanas de gestacion (A) y 30 – 40 semanas de gestacion (B) tratados con 12 mg/kg/dia x 14 dias

Dosis de Fluconazole para Prevencion y Tratamiento de Candidiasis Invasiva en Infantes jovenes (AUC/Tratamiento)



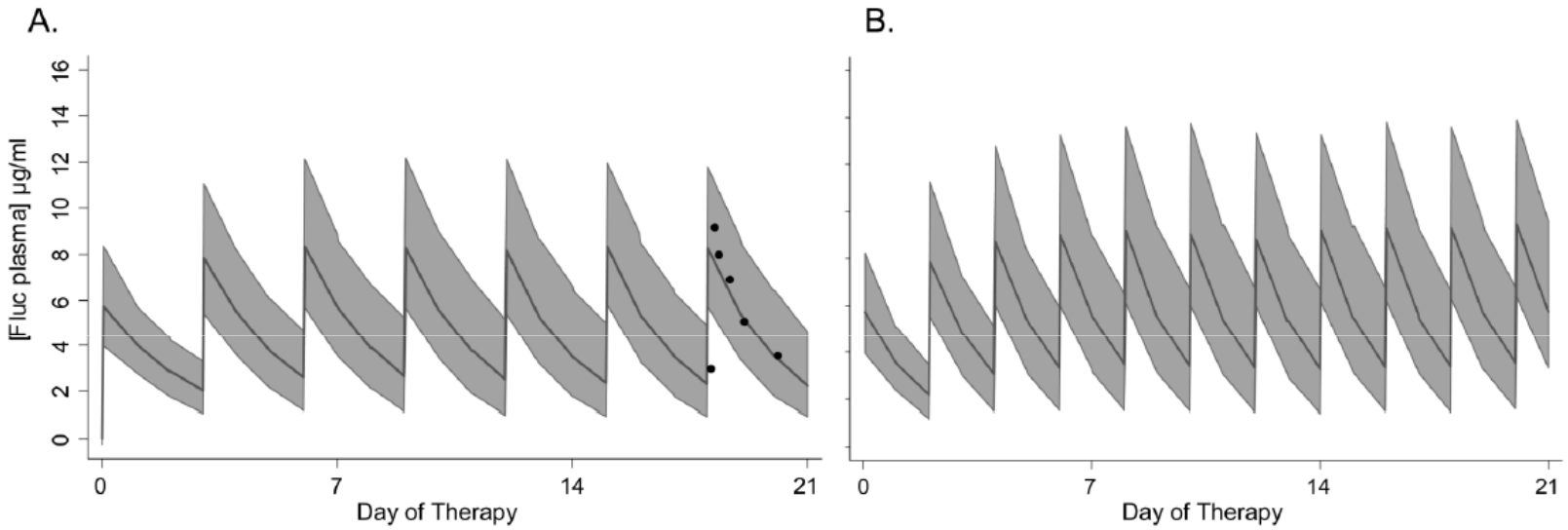
AUC mediana de fluconazole pronosticada para pacientes prematuros de 23 – 29 y 30 – 40 semanas de gestacion recibiendo dosis de 6 y 12 mg/kg/dia. Tambien se muestra la AUC para una dosis de carga de 25 mg/kg/dia en prematuros de 23 – 29 semanas de gestacion

Dosis de Fluconazole para Prvencion y Tratamiento de Candidiasis Invasiva en Infantes jovenes (Niveles en Plasma/Profilaxis)



Concentracion en plasma media y rango de variabilidad (10^{th} – 90^{th} percentile) pronosticada de 100 experimentos simulados en ninos pre-termino 23 – 29 semanas de gestacion tratados con 3 mg/kg (A) y 6 mg/kg (B) dos veces/semana x 45 dias empezando en el dia 5 de vida

Dosis de Fluconazole para Prvencion y Tratamiento de Candidiasis Invasiva en Infantes jovenes (Niveles en Plasma/Profilaxis Tardia)



Concentracion en plasma de fluconazole pronosticada en neonatos de 23 – 29 semanas de gestacion tratados con 6 mg/kg/ cada 72h para aquellos de 7 – 42 dias de edad post natal (A) y 6 mg/kg cada 48h para aquellos de 43 – 80 dias de edad

Conclusiones

- Ninos prematuros con infeccion invasiva por *Candida* requieren un minimo de 12 mg/kg/dia de fluconazole para conseguir los objetivos de AUC24 y el AUC/MIC (MIC < 8 mcg/ml) requeridos.
- Para prevencion temprana de candidiasis, dosis de 3 y 6 mg/kg dos veces por semana mantienen niveles de fluconazole encima de 2 – 4 mcg/ml respectivamente por > 40% intervalo entre dosis (apoyado por resultados de estudios clinicos)
- Para la prevencion de candidiasis tardia, dosis de 6 mg/kg cada 48h – 72h dependiendo de la edad gestacional y edad post natal son razonables para mantener niveles de fluconazole encima de un MIC 4 mcg/ml por > 40% del intervalo entre dosis

Famacokinetica y “Safety” de una Dosis de Carga (loading dose) en Infantes

- Debido al largo $T_{1/2}$ de fluconazole, puede tomar 5 – 7 dias en conseguir los parametros de PK/PD objetivados (AUC > 400 mg*h/L; AUC/MIC $\geq$ 50 for MIC $\leq$ 8 mcg/ml)
- Una dosis de carga inicial de 25 mg/kg puede ser necesaria para conseguir el objetivo en las primeras 24h de tratamiento.

Piper, L 2011 PIDJ

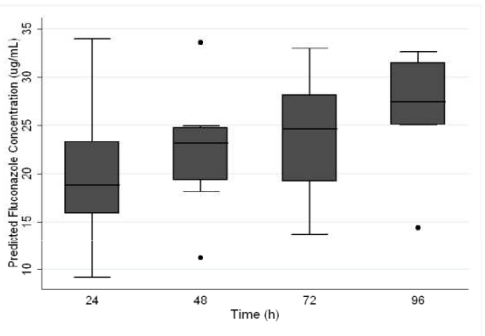
Famacokinetica y “Safety” de una Dosis de Carga (loading dose) en Infantes

TABLE 1

Pharmacokinetic Parameters

Subject	Age (days)	Serum Creatinine	Clearance (mL/kg/h)	Vd (mL/kg)	Half life (h)	Kel (h^{-1})	AUC_{0-24} (mg*hr/L)
1	6	1.0	27	785	19.9	0.050	493
2	13	1.3	14	1441	73.4	0.013	350
3	14	0.8	12	1522	91.4	0.010	338*
4	14	0.5	18	1021	39.1	0.025	466
5	19	1.2	9	1081	79.4	0.012	493
6	36	0.5	21	711	23.8	0.042	598
7	55	0.3	23	882	27.2	0.036	506
8	59	0.2	14	1635	81.2	0.012	271
Median	17	0.7	16	1051	56	0.02	479
(IQR)	(14–41)	(0.4–1.1)	(13–21)	(858–1461)	(26–80)	(0.01–0.03)	(347–496)

* Infant 3 was supported by extracorporeal membrane oxygenation.



Una dosis de carga de fluconazole consiguio un AUC_{24} > 400 mg*h/ en la mayoria de los sujetos estudiados y todos exibieron una concentracion basal > 8 24 h despues de la dosis. Esta dosis fue bien tolerada

Fluconazole Prophylaxis
Simple Questions

- Does fluconazole prevent *Candida* BSI
  - Yes
    - Rate of prevention is dependent on pre-existing risk (~80% reduction)
- Does it decrease mortality in ELBW infants?
  - No
- Is it safe?
  - Yes
- Should we adopt it?
  - Highest risk group

Summary Table Fluconazole Prophylaxis Studies 2001 – 2006

(Adapted Long S. and Stevenson D. J Peds Aug 2005)

	Study Type	Population	Fluc Dose (mg/kg)	Duration	Outcome
Kicklighter (Peds Feb 01)	Pr-R; Pl-C; B	<1500, 53 fluc; 50 plac	6 q 72 h til day 7 then q 24h	Day 28	Rectal colonization in 15 vs 46%; Candida infxn in 2 infants in each group
Kaufman (NEJM Dec 01)	Pr-R; Pl-C; B	<1000 gms if VAD or intubation 50 F vs 50 P	3 q 72h til DOL 14 Q 48h til DOL 28 Q 24	DOL 42 (shorter if IV out)	Colonozation 60% vs 22% Infxn 10 in P vs 0 in F
Kaufman (J Peds Aug 05)	Pr-R; C; B	<1000 gms if VAD or intubation. 41 A vs 40 B	Group A; Same as above Group B; 3 2xs/week	Same as above	Colonization in 10% vs 12 % Infxn 2 (5%) vs 1 (3%)
Bertini (J Peds Aug 05)	L, O, pre/post policy change	All < 1500 gms if IV access	6 til DOL 7 Then qd	DOL 28	Infxn in 9 (7.6%) vs 0 in F period Mortality 12.6% vs 8.1% (NS) Fungal infxn mortality 33% (2.7%)
Healy J Peds (Aug 05)	L,O, pre/post policy change	Discretionary <1000gms VAD	Kaufman's 01	Kaufman's 01	Ifxn 7% vs 2% ICRM 2% vs 0 All cause 17% vs 16%
Manzoni (Peds Jan 06)	L,O, pre/post policy change	<1500gms 240 A vs 225B	6 q72h til DOL 7; Then q 48h	DOL 30 <1500 gms DOL 45 < 1000 gms	Colonization 43.8 vs 24% Multisite 5.8% vs 2.6% HR 9.2% vs 5.8% SFI 16.7% vs 4.4%
Smart (Peds Apr 06)	L,O, pre/post Policy change	<1500 gms (<32w) 206 A vs 178 B Targeted abx > 3fays	3 72h Then q 48h	?	IFI A vsB 6.3% vs 1.1% Decreased exposure to F

Pr = Prospective; R = Randomized; Pl = Placebo; B = Blinded; C = Controlled; L = Longitudinal; O = Observational

Summary Table Fluconazole Prophylaxis Studies 2006 – 2014

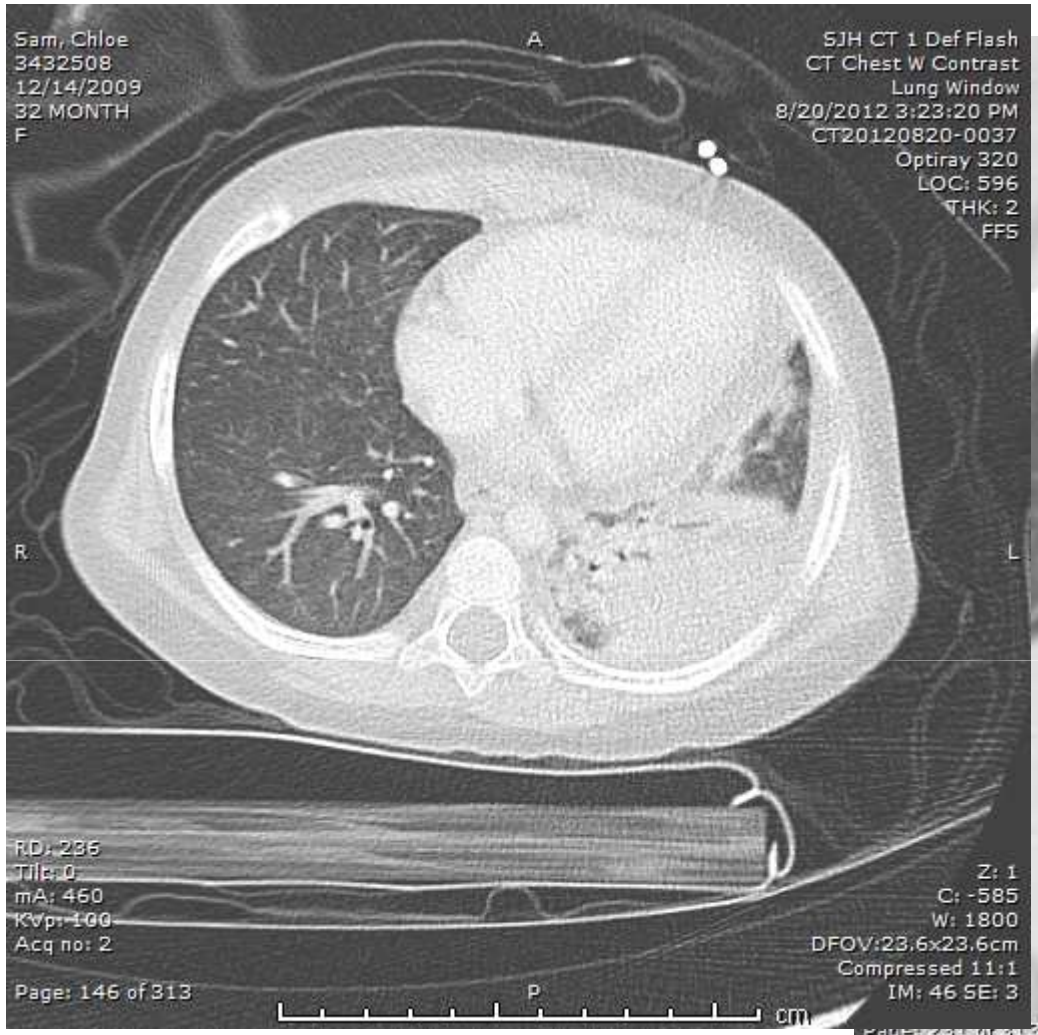
(Adapted from Ericson EJ, Curr Opin Pedistr 2014)

	Study Type	Population	Fluc Dose (mg/kg)	Duration	Outcome
Uko (Peds 06)	Cohort 01-02	<1500 g, or < 32 w + > 3 days of abx	3 mg/kg q 2 – 3 days		Candidiasis F = 1% P = 6% (p=0.007) Mortality 4% vs 5% NS
Manzoni (NEJM 07)	RCT	< 1500 g	6 mg/kg or 3 mg/kg q 2 days (q 3 days x 2 weeks)		Candidiasis F = 3%; P = 13% (p < 0.05) Mortality 8% vs 9% NS
McCrossan (Arch Dis Child 07)	Pr-R; C; B	< 1500 g + 1 RF (abx > 10d, CL, colonization)	6 mg/kg q 1 – 3 days		Candidiasis F = 0; P = 18/% (p = 0.03) Mortality 21% vs 10%
Azis (PIDJ 10)	Cohort (00 – 02)	< 1000 g + CL	3 mg/kg q 1 – 3 days		Candidiasis F = 2%; P = 7% (p = 0.04) Mortality 5% vs 9% NS
Martin (J prinatol 12)	Cohort (05 – 06)	< 1500 g + > 2 days abx + RF	3 mg/kg q 2 – 3 days		Candidiasis F = 6%; P = 15% Mortality 44% vs 37% p = 0.9
Rolnitsky (Eur J Peds)	Cohort (02 – 04)	< 1000g or < 28W + RF	6 mg/kg q 2 days		Candidiasis F = 1%; P = 6% (p = 0.02) Mortality 16% vs 15% NS
Benjamin (JAMA Peds 14)	RCT	< 750 g	6 mg/kg 2 x/week	42 days	Death or Candidiasis F = 16%; P = 21% (p = 0.24) Candidiasis 3% Vs 9% p = 0.02 Neurological impairment not different

Pr = Prospective; R = Randomized; Pl = Placebo; B = Blinded; C = Controlled; L = Longitudinal; O = Observational

Chloe

- Niña de 4 años de edad
- Diagnostico leucemia myelocytica aguda
- Admitida con fiebre y neutropenia
  - Permanece febril despues de 3 dias
    - Micafungin 3.5 mg/kg
  - Permanece febril dia 5
    - Tomografia torax/abdomen/pelvis


Sam, Chloe
3432508
12/14/2009
32 MONTH
F
A
SJH CT 1 Def Flash
CT Chest W Contrast
Lung Window
8/20/2012 3:23:20 PM
CT20120820-0037
Optiray 320
LOC: 596
THK: 2
FFS
R
L
RD: 236
Tilt: 0
mA: 460
KVp: 100
Acq no: 2
Z: 1
C: -585
W: 1800
DFOV:23.6x23.6cm
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IM: 46 SE: 3
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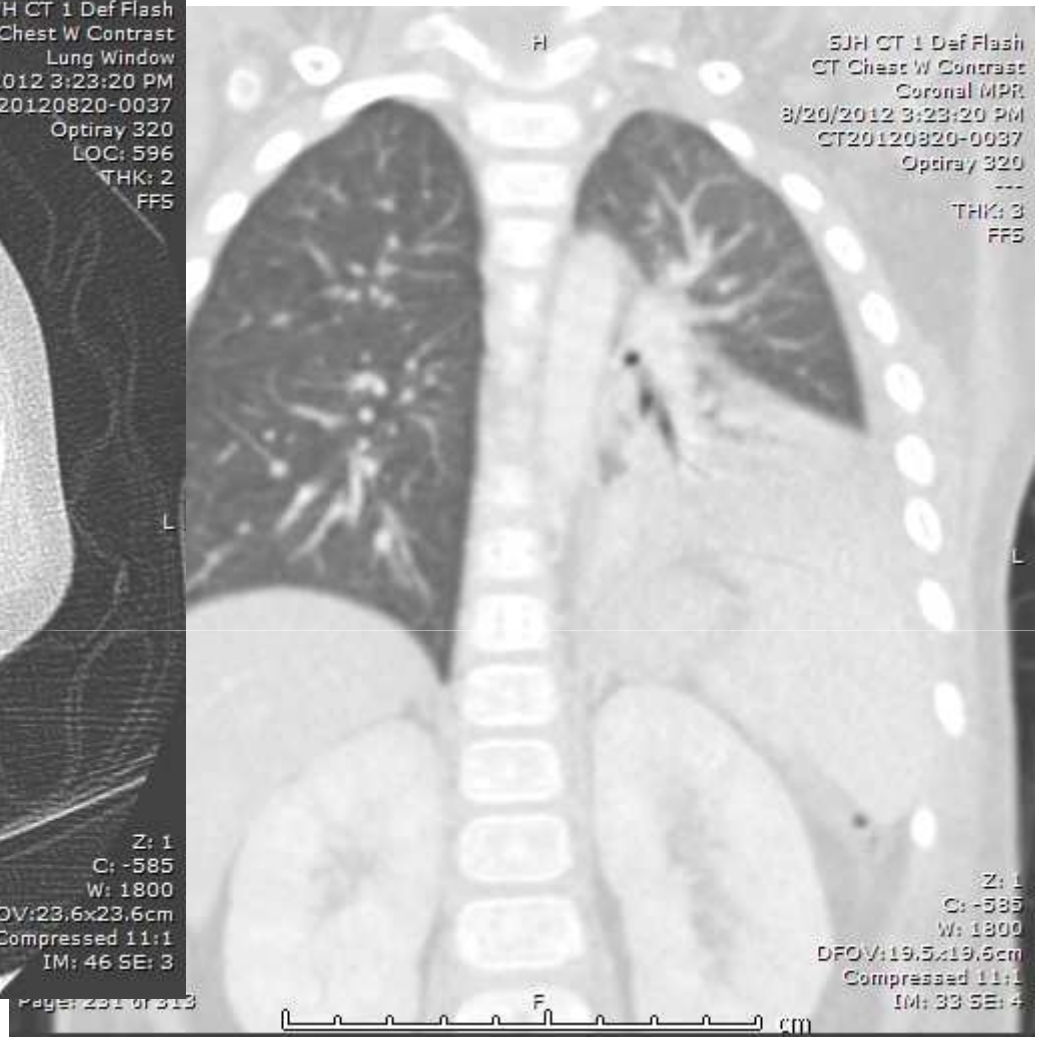
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SJH CT 1 Def Flash
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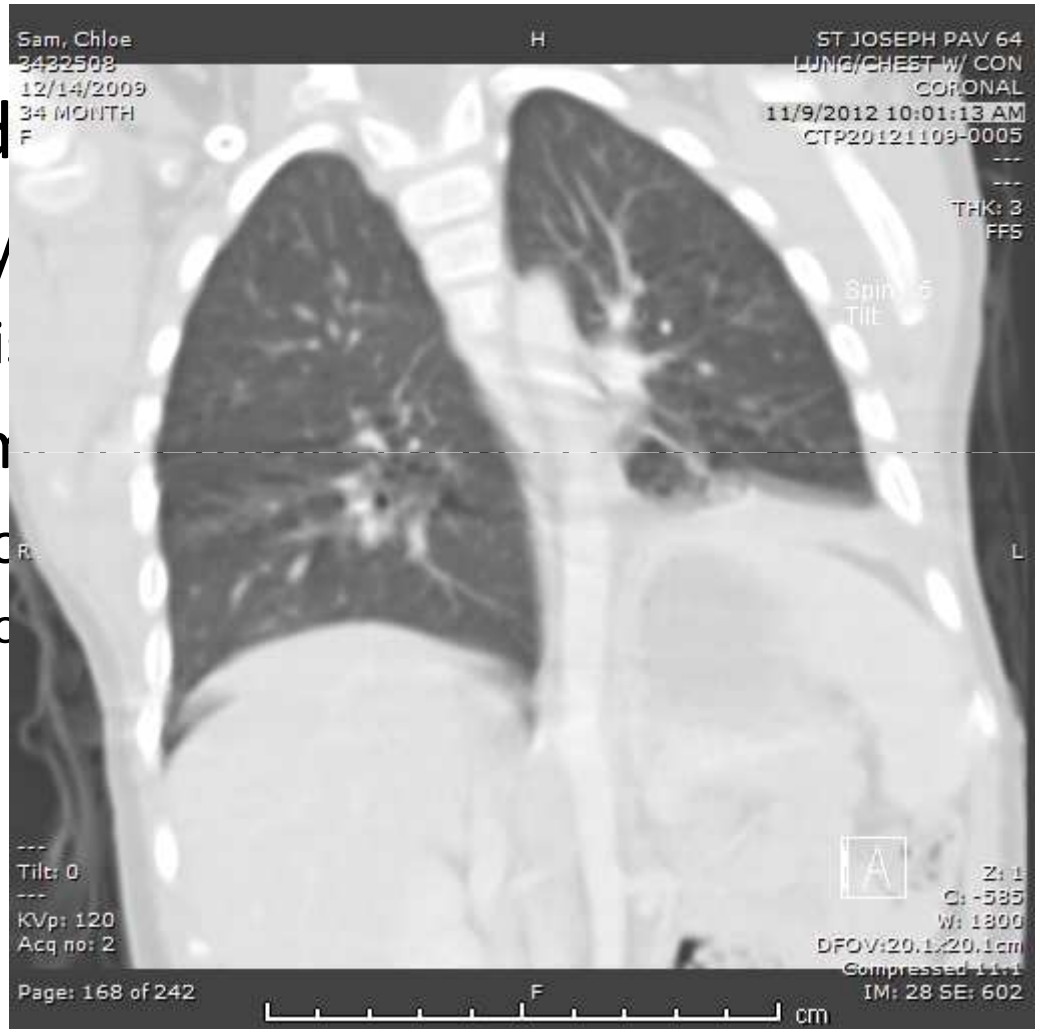
CT20120820-0037
Optiray 320

THK: 3
FFS
L
Z: 1
C: -585
W: 1800
DFOV:19.5x19.5cm
Compressed 11:1
IM: 33 SE: 4
F
cm

Diagnostico y Tratamiento

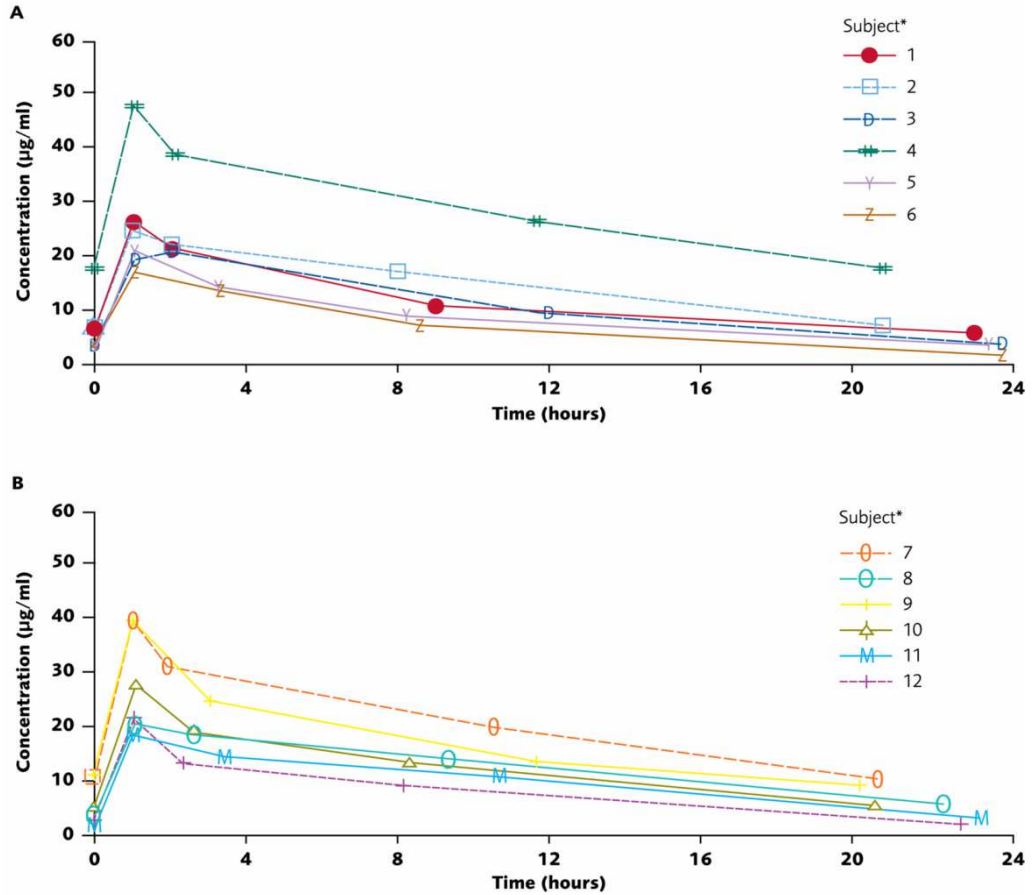
- Biopsia d
  - Zygomy
    - Ambi
  - Especin
    - Rhyzo
      - Po



Echinocandins

- Complete new class of antifungals
  - Interfere with cell wall synthesis
    - Inhibit 1,3-Beta-D-glucan synthase
      - *Aspergillus* sp. : Inhibit hyphal tip and branch point growth
        - » Fungistatic?
    - No CP- 450 metabolism
      - Less drug-drug interaction
    - Highly protein bound
    - Only parenteral
      - Large water soluble molecule (CNS???)

Safety and Pharmacokinetics of Repeat-Dose Micafungin in Young Infants



Micafungin 7 mg/kg (≥ 1000g) and 10 mg/kg (< 1000 g)

Target systemic exposure

$AUC_{0\text{-}24} \geq 166.5$ mg.h/ml

RESULTS (7 and 10 mg/kg)

Cmax 26.6 and 28.1

$AUC_{0\text{-}24}$ 258.1 and 291.2

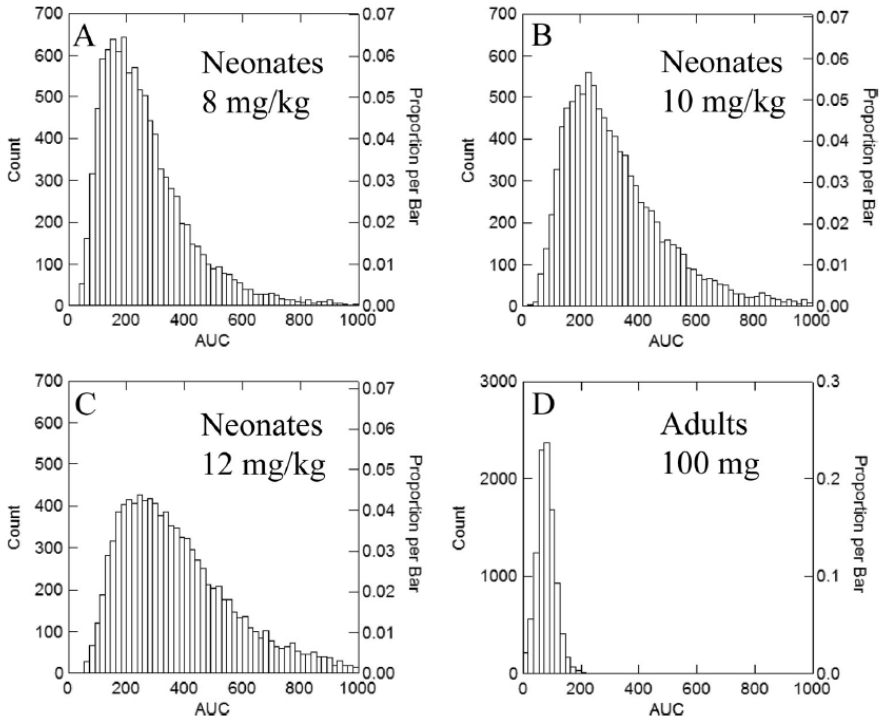
No evidence of renal toxicity, one subject experienced elevated alkaline phosphatase

Micafungin a las dosis estudiadas, alcanza los niveles de PK/PD necesarios para tratar infecciones en infantes prematuros con potencial compromiso del sistema nervioso central.

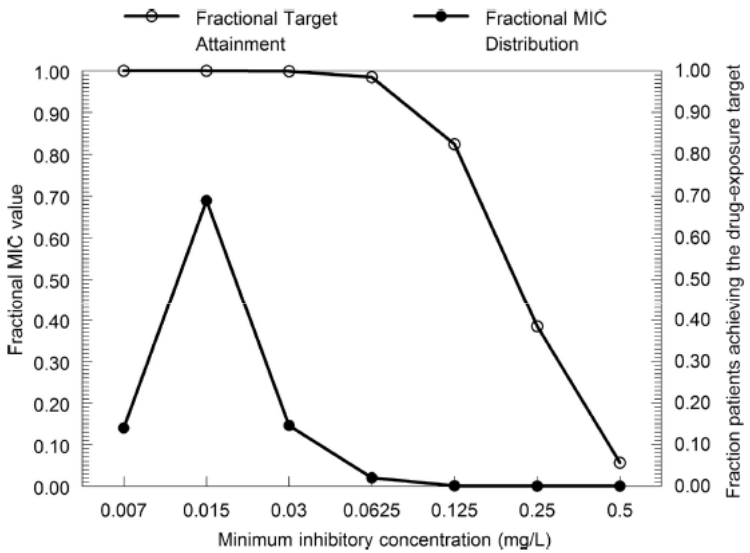
Estas dosis fueron bien toleradas

Benjamin DK Clin Pharm Ther 2010

Population Pharmacokinetics of Micafungin in Neonates and Young Infants



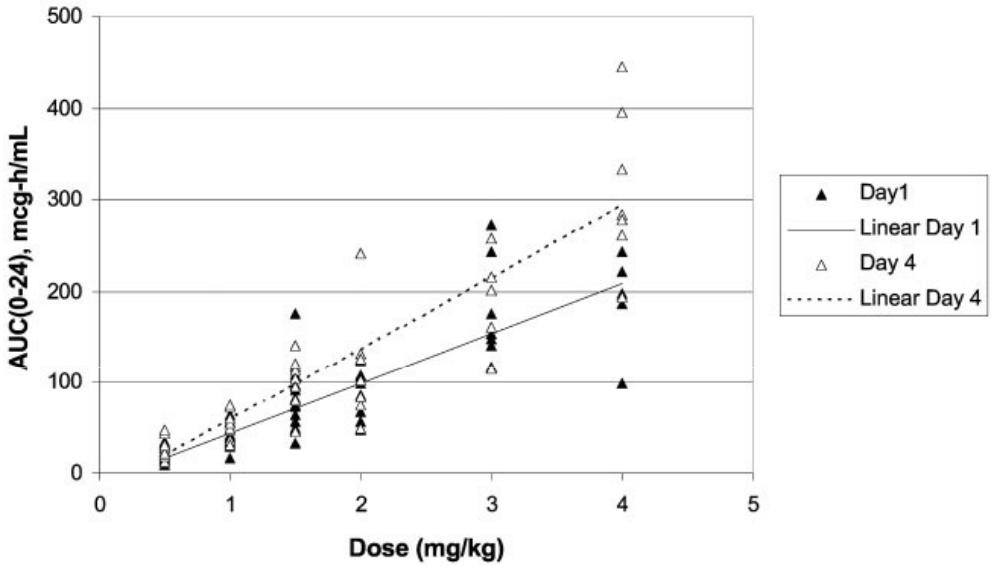
Monte Carlo simulation for 9,999 patients receiving micafungin.
The proportion of simulated patients receiving 8,10, and 12 mg/kg with an AUC < 165 mg.h/L was 29.3%, 17.4% and 10.5%



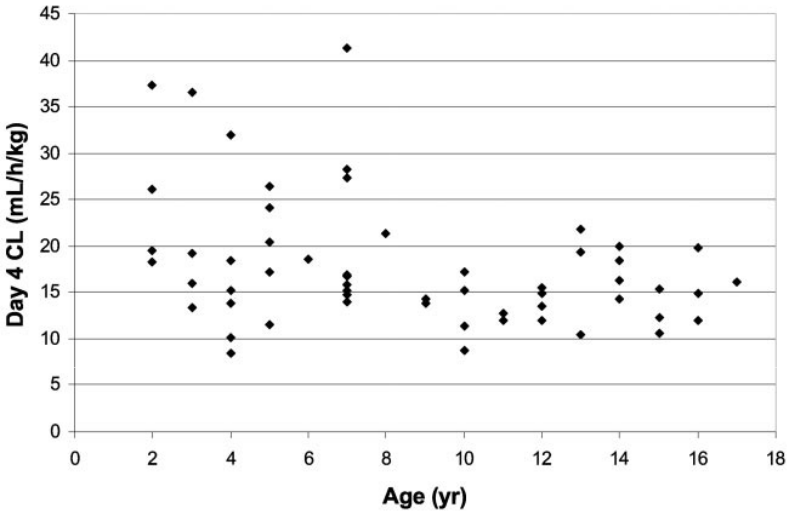
Target attainment rates as a function of MIC
All neonates receiving 10 mg/kg had an AUC/MIC ratio of at least 1,332 for MICs of 0.007 – 0.0625 mg/l.
Progressively fewer neonates achieved the target with isolates with MIC 0.125 mg/L.

Hope, WW AAC 2010

Safety, Tolerability, and Pharmacokinetics of Micafungin (FK463) in Febrile Neutropenic Pediatric Patients



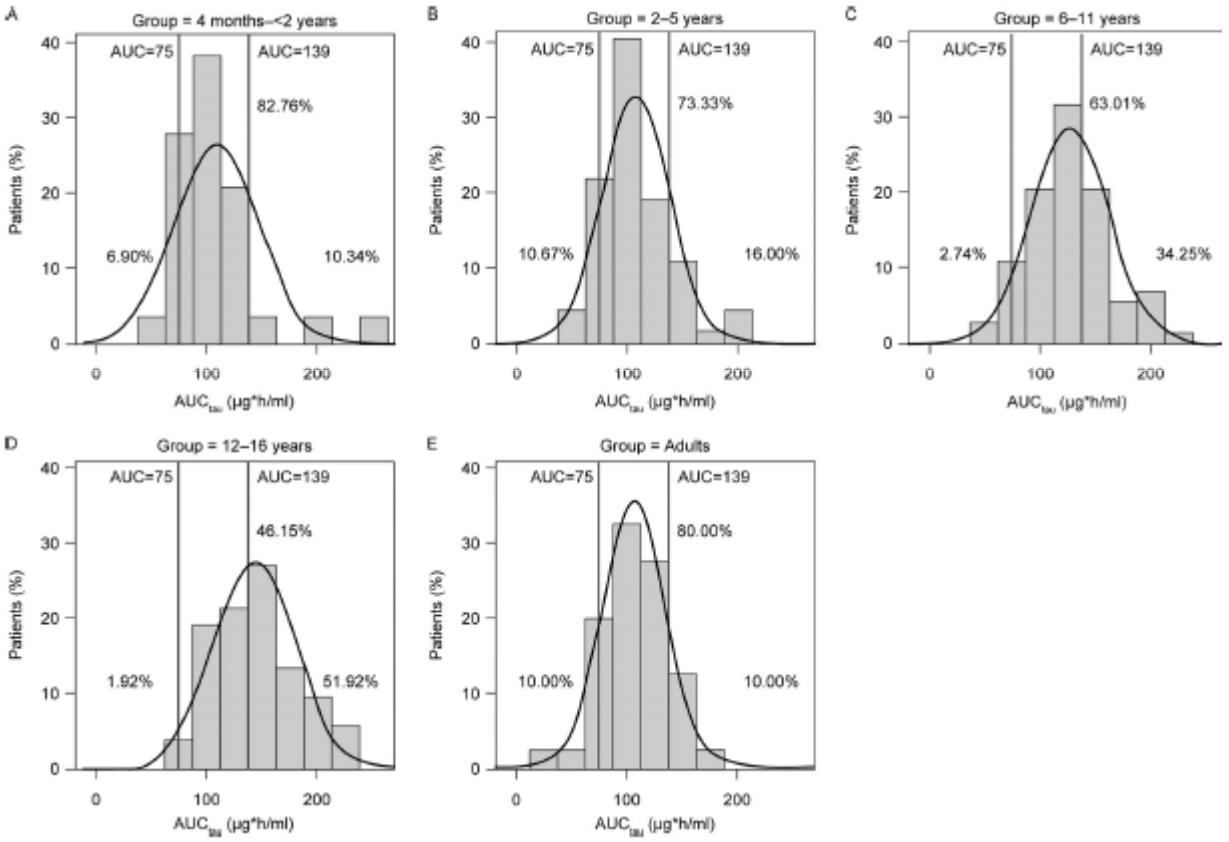
Individual plasma AUC0–24 values of micafungin in neutropenic pediatric patients between 2 and 17 years of age as a function of micafungin dose on days 1 and 4.



Individual plasma clearance values of micafungin in neutropenic pediatric patients as a function of age on day 4 over the micafungin dose range (0.5 to 4.0 mg/kg/day).

Pk profile (0.5 – 4 mg/kg demonstrated dose linearity. An inverse relation was noted between age and clearance (2 – 8 years old clearance was close to 1.5 times that of > 9 years old. So a 2 – 3 mg/kg adult dose equivalent would be 3 – 4.5 mg/kg in younger children

Population Pharmacokinetics of Micafungin in Children and Adolescents

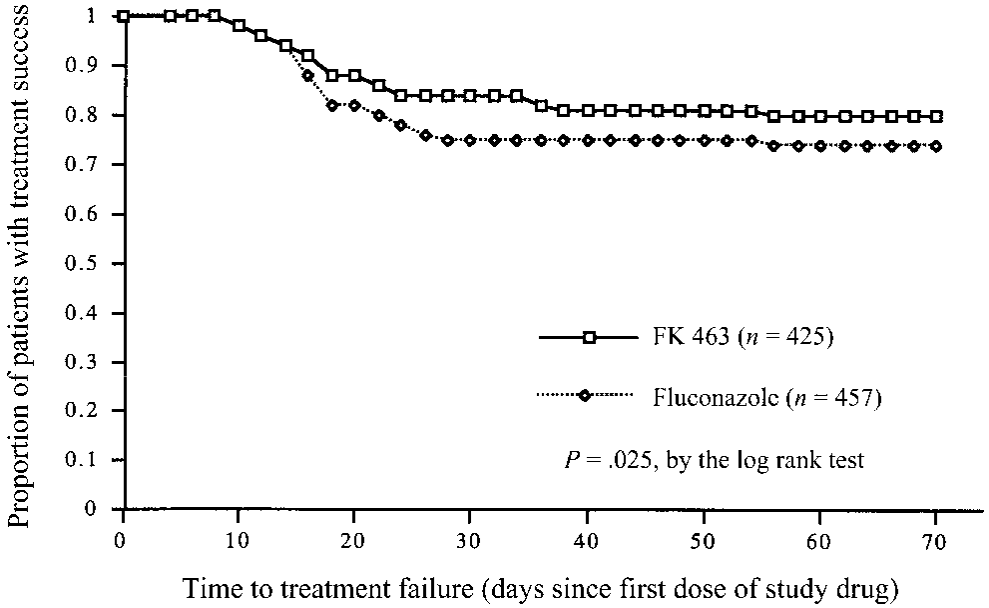


Identificar regimen terapeutico en niños de 4 meses a < 17 años que resulten en la misma exposicion que adultos recibiendo 100 mg/dia
Se simularon dosis de 0.5 – 5 mg/kg

Distribucion simulada en estado estable para una dosis de 2 mg/kg comparada con adultos recibiendo 100 mg

Hope, WW AAC 2015

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



425 patients on Micafungin 1 mg/kg (50 mg)
Vs 457 on fluconazole 8 mg/kg (400 mg)
Until earliest of:

- Engraftment
- Day 42
- Proven, probable, or suspected fungal infection
- Toxicity

•Treatment Success defined as:

"Absence of proven, probable, or suspected systemic fungal infection through the end of prophylactic therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week period after treatment"

van Burik, JA CID 2004

RESULTS:

	Micafungin (80%)	Fluconazole (73.5%) (NS)
Pediatric <16 yrs	69.2% (27/39)	53.3% (24/45)
Adult 16-64 yrs	81.1% (313/386)	75.7% (312/412)
Adult > 64 yrs	97.0% (32/33)	69.6% (16/23)

Micafungin: (7 infections)

- Candidemia in 3 (*parapsilosis, albicans,* and *lusitaniae*) and 1 *glabrata* after treatment.
- *Aspergillus* in 2 (1 proven one probable)
- Fusarium spp 1; Zygomaycosis in1

Fluconazole (11 infections)

- Candidemia in 2 (1 *krusei*, 1 *parapsilosis*
- *Aspergillus* 7 *(*proven4, probable 2*)*
- *Fusarium* 2

A Randomized, Double-blind Trial Comparing Micafungin versus Liposomal Amphotericin B in Pediatric Patients with Invasive Candidiasis

- **Objective**
  - Efficacy and safety of micafungin vs liposomal amphotericin B (Ambisome®, L-AMB) in pediatric patients with invasive candidiasis (IC) or candidemia
- **Design**
  - Multi-center, double-blind, randomized (1:1)
- **Main inclusion criteria**
  - Clinical and microbiological evidence of IC or candidemia (all *Candida* species)
  - Non-neutropenic and neutropenic pediatric patients ≤ 15 years
- **Primary efficacy endpoint**
  - Overall treatment success based on clinical and mycological response at end of therapy (EOT) as determined by investigator

Regimen: Micafungin 2 mg/kg/day i.v.

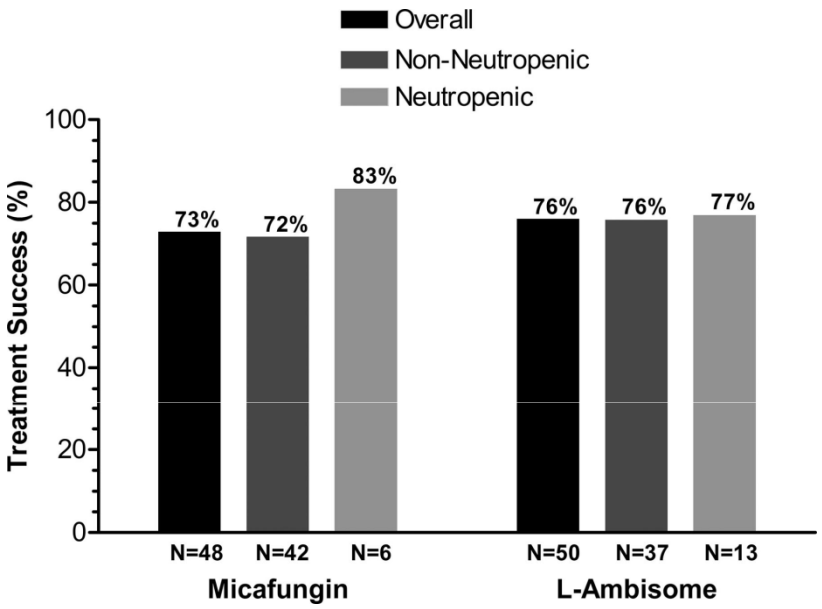
L-AMB 3 mg/kg/day i.v.

Dose adjustments permitted under predefined conditions

- Dose increase to 4 mg/kg/day for micafungin or 5 mg/kg/day for L-AMB
- Dose decrease by 50% due to nephro- toxicity (only for L-AMB)

Queiroz-Tellez, F PIDJ 2008

Micafungin Versus Liposomal Amphotericin B for Pediatric Patients With Invasive Candidiasis



Treatment success in the MITT population.
MITT population: Patients who received at least one dose of study drug and had a confirmed *Candida* infection at baseline.

Micafungin (48 subjects) 2 mg/kg Vs L-AmB (50 subjects)3 mg/kg
Positive blood or sterile site cultures
Similar succes rate for each arm.
More subjects in L-AmB discontinued drug due to Aes (3.8% Vs 16.7%; p = 0.05)

Overall Treatment Success for Candidemia Patients at EOT by Species (MITT)

	Micafungin	L-AMB
Candidemia	33/44 (75.0%)	36/47 (76.6%)
• Most frequent species		
C. albicans	13/16 (81.3%)	14/14 (100%)
C. parapsilosis	8/10 (80.0%)	9/15 (60.0%)
C. tropicalis	6/10 (60.0%)	7/12 (58.3%)
C. krusei	3/4 (75.0%)	-
C. lipolytica	1/2 (50.0%)	2/2 (100%)
C. guilliermondii	2/2 (100%)	1/1 (100%)

Treatment-related Adverse Events (ITT)

	Micafungin n = 52	L-AMB n = 54
Overall	19 (36.5%)	23 (42.6%)
Serious AEs†	2 (3.8%)	5 (9.3%)

Treatment Discontinuation due to adverse Events (ITT)

	Micafungin n = 52	L-AMB n = 54
Overall AEs	2 (3.8%)	9 (16.7%)
Drug-related AEs††	1 (1.9%)	3 (5.6%)

Safety, Efficacy and Pharmacokinetics (PK) of Micafungin (mica) in Pediatric (ped) Patients (pts)

AC Arrieta[1], N. Seibel[2], L. Kovanda[3], J. Keirns[3], D. Facklam[3], D. Buell[3], TJ Walsh[4]
Children's Hospital of Orange County[1], Children's National Medical Center[2], Astellas Pharma US, Inc.[3], NIH, Bethesda, MD[4]

Methods: Meta-analysis of the use of mica in peds from 5 clinical trials.

Demographic and Baseline Characteristics

A total of 244 pediatric patients received at least one dose of micafungin. There were no significant differences between gender or race across age groups.

Age Categories	Number of Patients
0 to 2 years *0 through 27 days* *28 days through <24 months*	60 (24.6%) 10 (16.7%) 50 (83.3%)
3 to 7 years	75 (30.7%)
8 to 12 years	63 (25.8%)
13 to 15 years	46 (18.9%)

Age (years)	0 to 2 (N=60)	3 to 7 (N=75)	8 to 12 (N=63)	13 to 15 (N=46)	Total (N=244)
Underlying Condition					
HIV	0 (0.0%)	3 (4.0%)	1 (1.6%)	2 (4.3%)	6 (2.5%)
Hematologic Malignancy or BMT	16 (26.7%)	61 (81.3%)	53 (84.1%)	36 (78.3%)	166 (68.0%)
Premature Infant	29 (48.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (11.9%)
Other*	15 (25.0%)	11 (14.7%)	9 (14.3%)	8 (17.4%)	43 (17.6%)

* Other includes: Aplastic Anemia, Solid Tumor, Corticosteroid Therapy, and Antibiotic Use

Arrieta A.C. et al. ICAAC, 2006

Overall Summary of Response to Micafungin by Pediatric Age Group

Study Population[1]	No. Pediatric Pts	Treatment Success by Age Group (years)				Total
		0 - 2	3 to 7	8 - 12	13 - 15	
Treatment of Candidemia or Invasive Candidiasis[2]	53	19/28 (67.9%)	7/11 (63.6%)	8/9 (88.9%)	4/5 (80.0%)	38/53 (71.7%)
Treatment of Invasive Aspergillosis[3]	58	2/5 (40.0%)	7/16 (43.8%)	5/18 (27.8%)	12/19 (63.2%)	26/58 (44.8%)
Empirical Treatment of Febrile Neutropenic Patients[4]	69	4/5 (80.0%)	23/30 (76.7%)	13/22 (59.1%)	9/12 (75.0%)	49/69 (71.0%)
Prophylaxis in Hematopoietic Stem Cell Transplant Recipients[5]	Mica 39	6/7 (85.7%)	10/14 (71.4%)	7/12 (58.3)%	4/6 (66.7%)	27/39 (69.2%)
	Fluc 45	6/13 (46.2%)	4/7 (57.1%)	10/19 (52.6%)	4/6 (66.7%)	24/45 (53.3%)

1. Patients who received at least one dose of study drug.

Treatment success defined as:

2. Complete or partial response at the end of therapy
3. Complete or partial response as assessed by the Data Review Panel
4. Absence of systemic fungal infections at the end of therapy
5. The absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study

Treatment of Candidemia [1]
(Complete and Partial Response)

Candida species	No. of Pediatric Pts	Treatment Success
C albicans	11	8/11 (72.7%)
C parapsilosis	6	5/6 (83.3%)
C lusitaniae	1	1/1
C glabrata	1	1/1
C tropicalis	1	0/1

Treatment of Invasive Aspergillosis

Independent Review Panel Assessment	De Novo - monotherapy (N=1)	De Novo- combination (N=3)	Refractory – monotherapy (N=1)	Refractory – combination (N=53)
Overall Treatment Success	1/1 (100%)	1/3 (33.3%)	0/1 (0.0%)	24/53 (45.3%)
Complete Response	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (17.0%)
Partial Response	1 (100.0%)	1 (33.3%)	0 (0.0%)	15 (28.3%)
Overall Treatment Success = 26/58 (44.8%)	Overall De Novo Success = 2/4 (50.0%)		Overall Refractory Success = 24/54 (44.4%)	

Prophylaxis in Hematopoietic Stem Cell Transplant Recipients

Overall Treatment Success	Micafungin	Fluconazole
	27/39 (69.2%)	24/45 (53.3%)

- Four pediatric patients developed proven or probable breakthrough infections in this study: one patient in the micafungin treatment group (proven zygomycosis) and three fluconazole treated patients (proven aspergillosis in two children; C. parapsilosis candidemia in one child).
- The requirement for empirical antifungal therapy was also lower in the micafungin treatment arm 10/39 (25.6%) compared with the fluconazole treatment arm 15/45 (33.3%).

Safety

Incidence of Most Common Micafungin Related Adverse Events (AE)

	0-2 yrs n=60	3-7 yrs n=75	8-12 yrs n=63	13-15 yrs n=46	Total N=244
Overall AE Rate	15 (25%)	12 (16%)	21 (33.3%)	12 (26.1%)	60 (24.6%)
Increased ALT	3 (5.0%)	2 (2.7%)	3 (4.8%)	1 (2.2%)	9 (3.7%)
Bilirubinemia	1 (1.7%)	4 (5.3%)	1 (1.6%)	2 (4.3%)	8 (3.3%)
Hypokalemia	2 (3.3%)	2 (2.7%)	3 (4.8%)	0 (0.0%)	7 (2.9%)
Increased Alkaline Phosphatase	2 (3.3%)	2 (2.7%)	1 (1.6%)	1 (2.2%)	6 (2.5%)
Abnormal Liver Function Tests	3 (5.0%)	1 (1.3%)	1 (1.6%)	1 (2.2%)	6 (2.5%)
Hypertension	0 (0.0%)	0 (0.0%)	4 (6.3%)	2 (4.3%)	6 (2.5%)

- The incidence of AEs in pediatric patients (<16 years) is generally similar to that in adults (>16 years). Most AEs were mild to moderate in intensity and expected given the underlying conditions and co-morbidity.
- Micafungin at doses up to 8.6 mg/kg/day and durations up to 681 days were well tolerated and dose increases were not associated with an increase in the incidence or severity of AEs.
- The incidence of related Serious AEs was very low (4.9%, 12/244) with only 7/244 (2.9%) pediatric patients discontinuing micafungin due to a drug-related adverse event.

Caspofungin vs L-AmB para Tratamiento Empirico Antifungico en Fiebre-Neutropenia (Pediatricos)

Randomized, double-blind (& Sponsor-blind), multicenter study

Caspofungin **vs.** **Liposomal AmB (AmBisome™)**

50 mg/m² day **3 mg/kg/day**

(70 mg/m² on Day 1)

Designed to evaluate the safety and efficacy in pediatric patients (2-17 years) with persistent fever and neutropenia

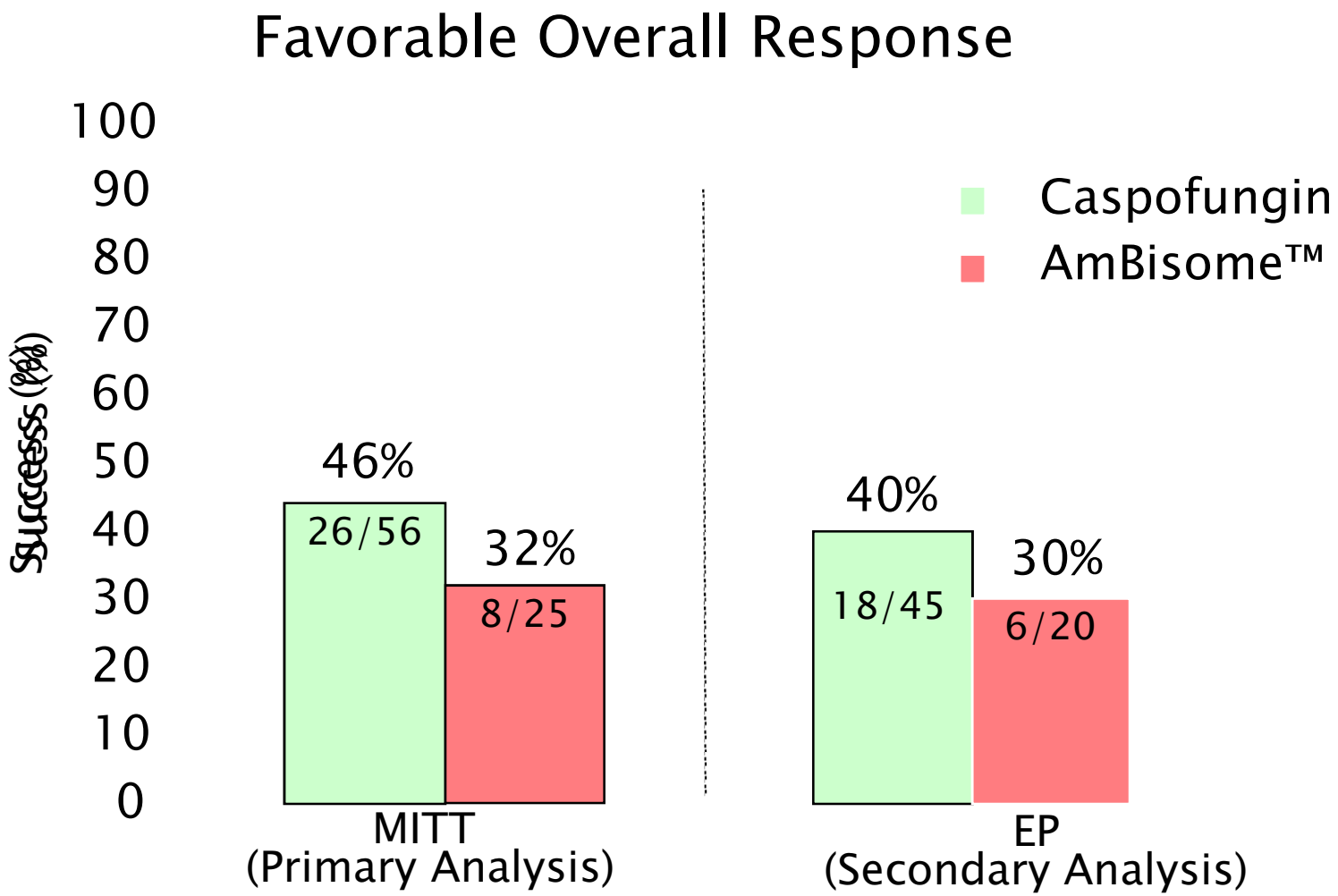
Stratified caspofungin to AmBisome™ at 2:1
Updosing caspofungin 70 mg/m² (maximum 70 mg daily) or AmBisome™5 mg/kg allowed after 5 days

Maertens, JA PIDJ 2010

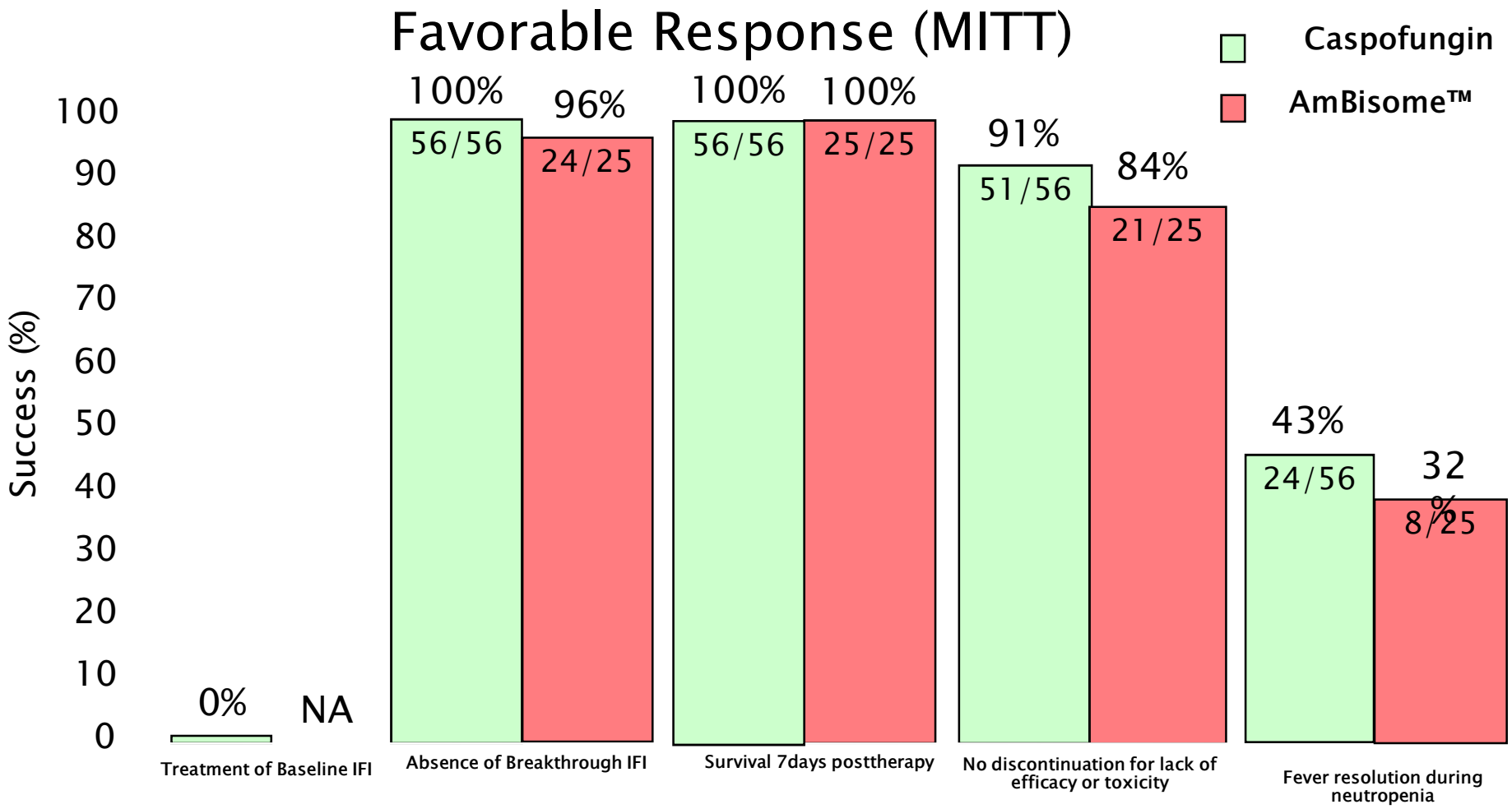
Resultados

- 81 pacientes incluidos en MITT analisis
  - Caracteristicas estuvieron bien balaceadas
  - 60% con diagnostico de leucemia
    - AML y ALL bien distribuidas en los grupos
  - 70% tuvieron ANC < 100

Overall Efficacy Results



Efficacy of Individual Endpoints



Caspofungin y L-AmB tuvieron "safety" y eficacia comparables en el manejo de pacientes pediatricos con neutropenia indicuda por quimoterapia y fiebre prolongada

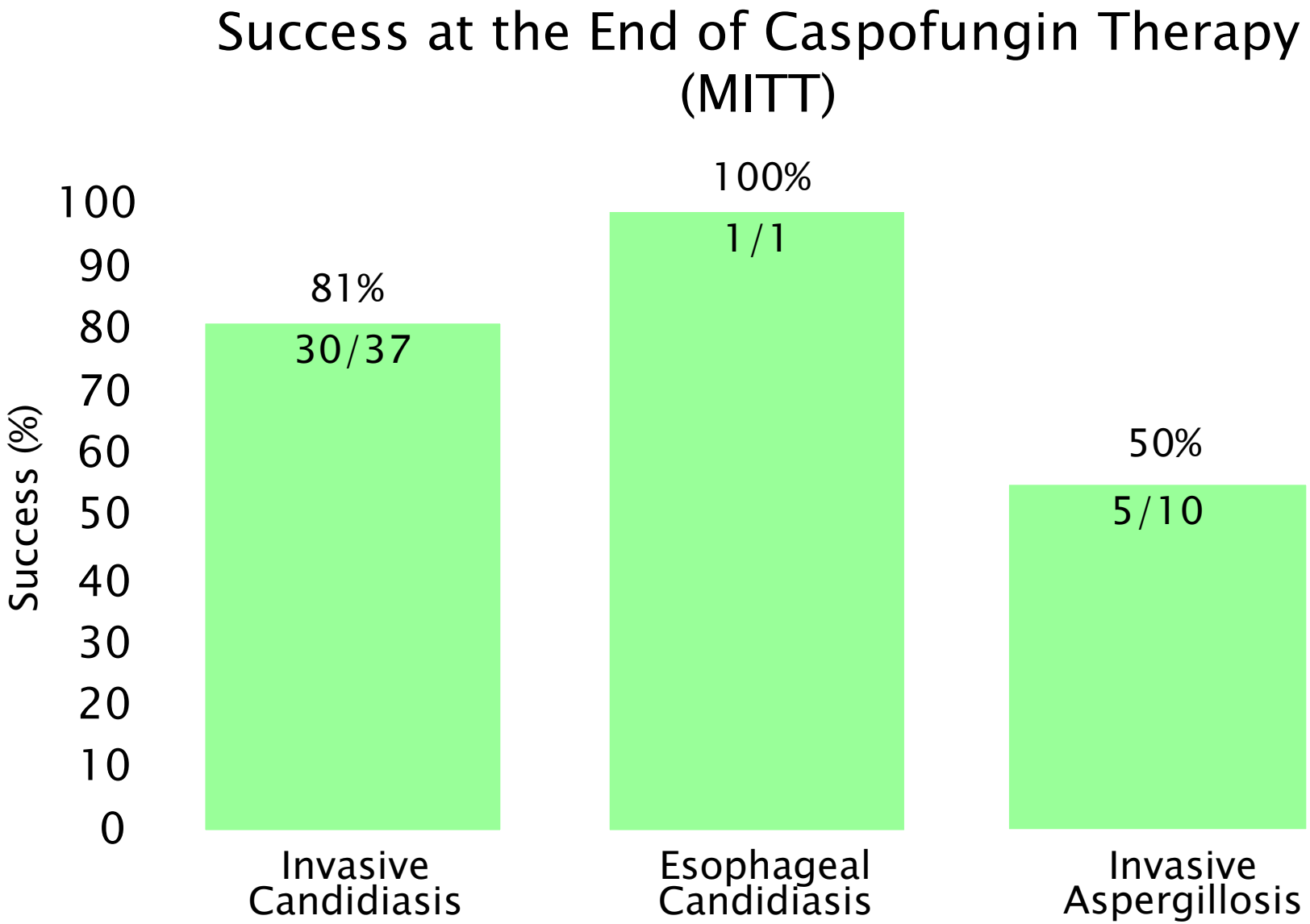
A Prospective Multicenter Study of Documented *Candida* and *Aspergillus* infections in Pediatric Patients

- Open-label, noncomparative study evaluating caspofungin in documented *Candida* or *Aspergillus* infections in patients 3 months to 17 years of age
  - Esophageal candidiasis (1)
  - Invasive candidiasis (37 only 6 neutropenic)
  - Invasive aspergillosis (10 all as salvage therapy only 3 neutropenic)

- Caspofungin dosing at 50 mg/m^2 daily, following 70 mg/m^2 on Day 1 (maximum 70 mg/day)
  - Updosing of caspofungin to 70 mg/m^2 (max 70 mg) allowed in patients not responding

Zaoutis, TE; Pediatrics March 09

Efficacy by Infection Type



Safety and Pharmacokinetics of Anidulafungin in Neutropenic Children

- **Children 2 – 17 years old**
  - **25 patients**
    - **12 in 2-11; 13 in 12-17**
- **0.75 mg/kg (50 mg) / 1.5 mg/kg (100 mg)**
  - **Loading dose of 1.5 and 3 mg/kg respectively (not to exceed 100 and 200 mg)**
- **Sampling before, at completion, and 3, 6, 12 and 24 h after start of infusion**
- **Demonstrated concentration-time profile**
- **Similar to that of adults**
- **Well tolerated**
  - **Red man syndrome?**

Benjamin DK et al. AAC, Feb 2006

TABLE 3. Multiple-dose pharmacokinetic profile of anidulafungin in children with compromised immunity and neutropenia

Parameter	Value for group with dose				Value for all patients (n = 24)	
	0.75 mg/kg/day (n = 12)		1.50 mg/kg/day (n = 12)			
	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	0.75 mg/kg/day (n = 12)	1.5 mg/kg/day (n = 12)
C_{max} (mg/ml)						
Mean (SD)	3.32 (1.66)	4.35 (0.98)	7.57 (2.59)	6.88 (1.67)	3.83 (1.32)	7.23 (2.13)
Range	0.91–5.98	3.1–5.57	5.22–12.3	3.71–8.66	0.91–5.98	3.71–12.3
AUC_{ss} (mg·h/ml)						
Mean (SD)	41.1 (15.8)	56.2 (15.6)	96.1 (38.0)	102.9 (29.0)	48.6 (15.7)	99.5 (33.5)
Range	16.5–57.8	31.8–79.8	43.2–155.7	50.3–134.1	16.5–79.8	43.2–155.7
$t_{1/2}$ (h)						
Mean (SD)	20.3 (7.9)	26.0 (10.2)	18.9 (3.5)	21.1 (5.2)	23.1 (9.0)	19.9 (4.3)
Range	13.9–35.1	12.0–38.9	13.6–24.1	15.0–27.8	12.0–38.9	13.6–27.8
CL/kg (liters/h/kg)						
Mean (SD)	0.0217 (0.0123)	0.0133 (0.0031)	0.0163 (0.0048)	0.0156 (0.0079)	0.0175 (0.0077)	0.0159 (0.0063)
Range	0.0113–0.0446	0.0095–0.018	0.0094–0.0231	0.0096–0.0311	0.0095–0.0446	0.0094–0.0311
V_{ss} (liters/kg)						
Mean (SD)	0.575 (0.243)	0.499 (0.231)	0.419 (0.066)	0.449 (0.166)	0.537 (0.237)	0.434 (0.116)
Range	0.337–0.962	0.163–0.803	0.319–0.5	0.314–0.73	0.163–0.962	0.314–0.730

TABLE 2. Single-dose pharmacokinetic profile of anidulafungin in children with compromised immunity and neutropenia

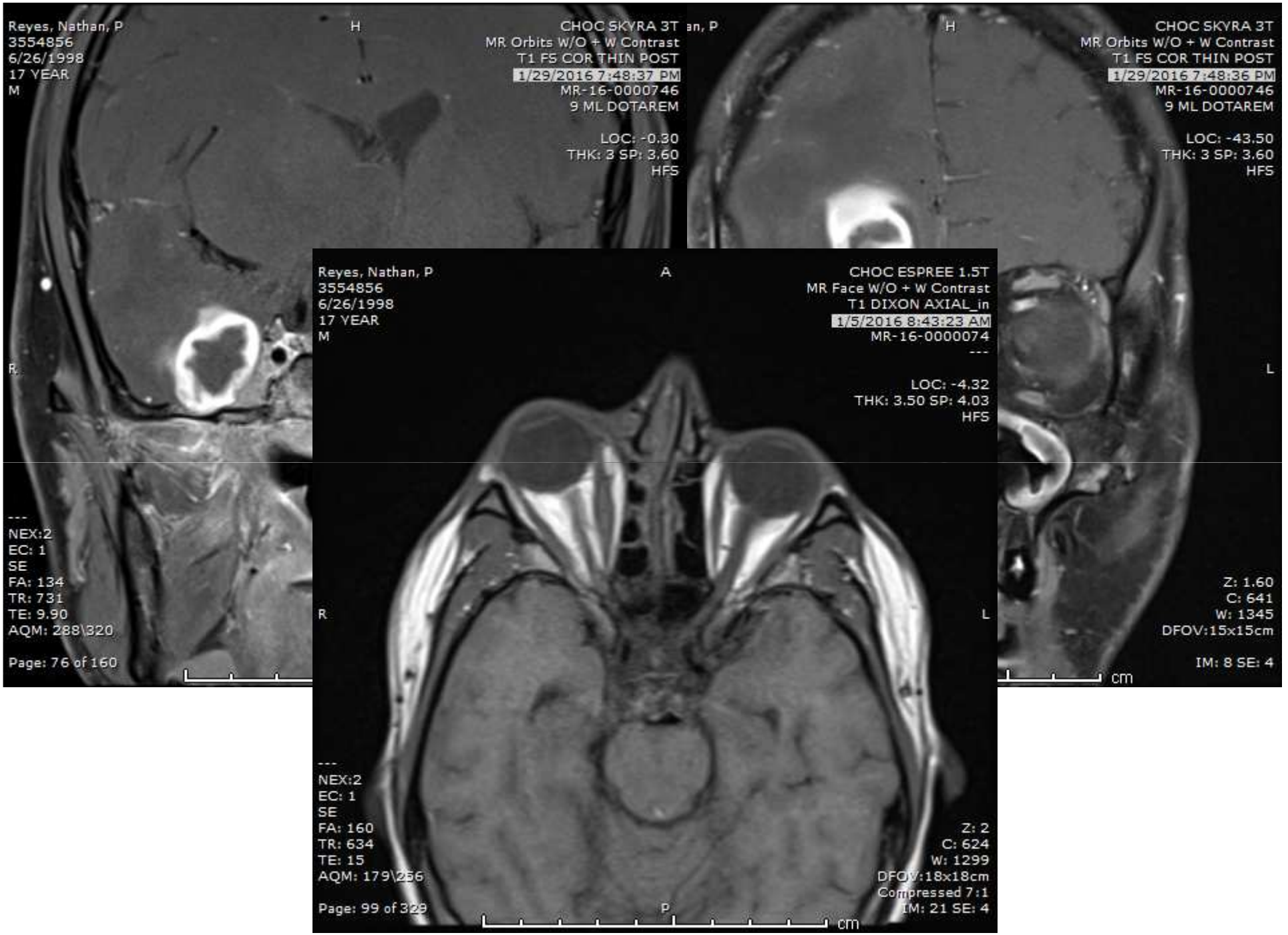
Parameter	Value for group with dose				Value for all patients (n = 24)	
	1.5 mg/kg (n = 12)		3.0 mg/kg (n = 12)			
	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	Ages 2–11 yr (n = 6)	Ages 12–17 yr (n = 6)	1.5 mg/kg (n = 12)	3.0 mg/kg (n = 12)
C_{max} (mg/ml)						
Mean (SD)	3.95 (0.74)	4.10 (1.11)	7.80 (0.76)	5.99 (1.50)	4.02 (0.9)	6.90 (1.13)
Range	3.04–4.91	2.98–6.08	6.93–8.97	4.06–7.88	2.98–6.08	4.06–8.97
AUC_{0-24} (mg·h/ml)						
Mean (SD)	46.3 (8.70)	49.6 (14.6)	92.3 (11.9)	87.2 (23.6)	48.0 (11.6)	89.7 (18.0)
Range	34.7–54.1	40.0–78.7	77.4–107.5	56.1–119.2	34.7–78.7	56.1–119.2
$t_{1/2}$ (h)						
Mean (SD)	17.3 (3.7)	24.3 (8.7)	18.3 (6.7)	20.8 (4.8)	20.8 (6.2)	19.5 (5.8)
Range	14.7–24.7	13.3–36.0	14.2–31.8	17.4–29.3	13.3–36	14.2–31.8
CL/kg (liters/h/kg)						
Mean (SD)	0.0208 (0.0052)	0.0143 (0.0062)	0.0200 (0.0058)	0.0181 (0.0078)	0.0175 (0.0057)	0.0191 (0.0068)
Range	0.0145–0.0275	0.0054–0.0199	0.0102–0.0266	0.0116–0.0316	0.0054–0.0275	0.0102–0.0316
V_{ss} (liters/kg)						
Mean (SD)	0.488 (0.086)	0.430 (0.133)	0.474 (0.036)	0.523 (0.193)	0.459 (0.110)	0.499 (0.115)
Range	0.399–0.602	0.267–0.610	0.421–0.529	0.375–0.857	0.267–0.610	0.375–0.857

Voriconazole

- **Second generation triazole**
  - **Synthetic derivative of fluconazole**
  - **Hepatic metabolism**
  - **90% oral bio-availability**
  - **Major role in metabolism of P-450-2C19**
    - **Poor and extensive metabolizers**
      - **5 – 7% Caucasians deficient ~ 15 – 20% Japanese**
  - **45-65% plasma bound, good CNS penetration**
    - **½ life 6 h**
  - **Children require higher doses than adults**
    - **Less saturation of liver metabolic sites (Walsh AAC 48:2166)**

Nathan

- Muchacho de 18 años
- Diagnostico leucemia mieloide aguda
  - Transplante de medula osea alogeneico no relacionado
  - Profilaxis con fluconazole 400 mg/dia
  - Desarrolla hinchazon y proptosis ojo derecho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Page: 99 of 329
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Diagnostico y Tratamiento

- Rhinoorbital mucormycosis con extension a lobulos frontal y temporal
- Enucleacion del ojo y L-AmB 8 – 10 mg/kg
  - Deferazirox (debate)
  - Posaconazole (debate)
- Transferido a USC
  - Isavuconazole

Pharmacokinetics and Safety of Intravenous Voriconazole in Children after Single- or Multiple-Dose Administration

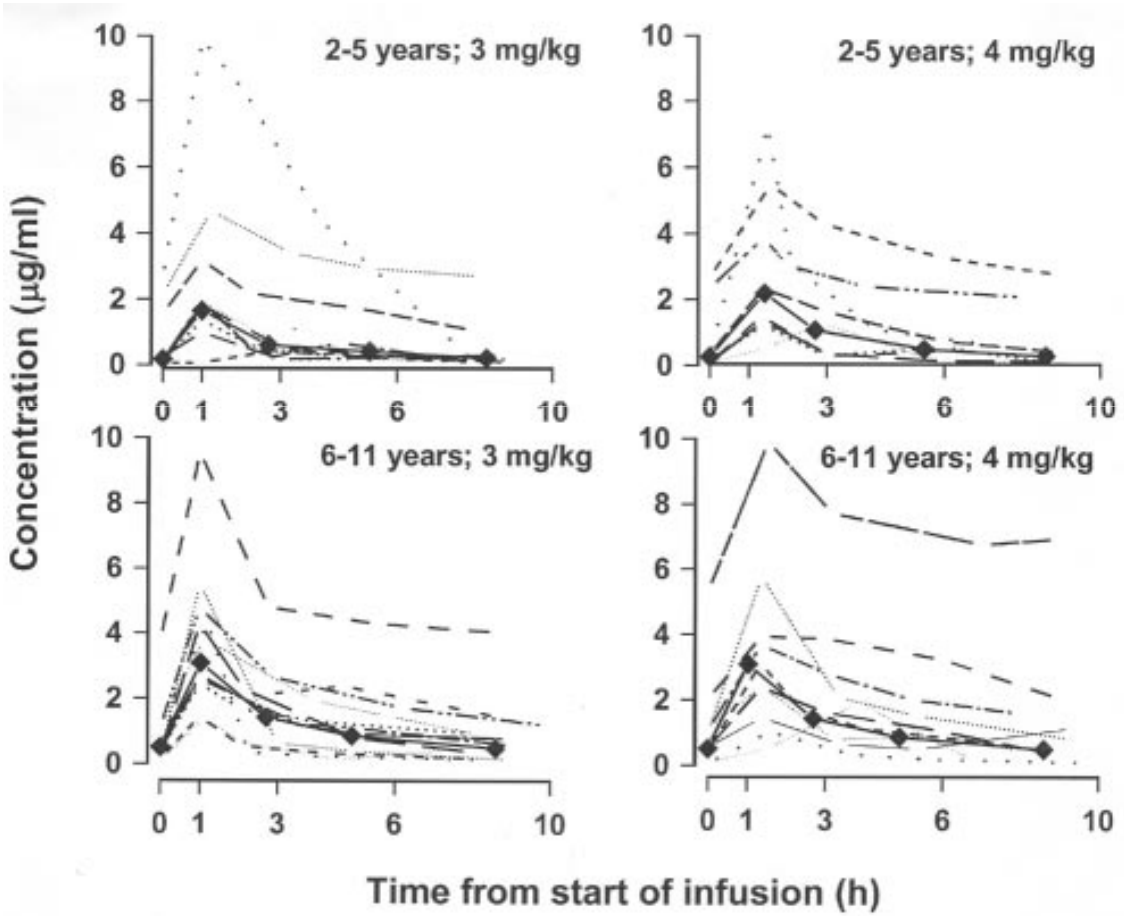


TABLE 3.

Simulated pharmacokinetic data for pediatric and adult populations

Parameter	Value[a]			
	Pediatric		Adult	
	3[b]	4	3	4
AUC_T (ng · h/ml)	10,670	14,227	13,855	38,605
C_{mean} (ng/ml)	889	1,186	1,155	3,217

[a]Data are reported as medians following 6 mg/kg 12 every h on day 1 and maintenance dose 3. The values are derived from population pharmacokinetic analyses of 236 healthy volunteers.
[b]Dosage (milligrams per kilogram).

TABLE 4.

Extrapolated plasma pharmacokinetic parameters for pediatric population

Dosage (mg/kg)	AUC (ng · h/ml)	C_{mean}
Pediatrics		
5	17,783	1,482
6	21,340	1,778
7	24,897	2,075
8	28,453	2,371
9	32,010	2,668
10	35,567	2,964
11	39,123	3,260
12	42,680	3,557
Adult		
4	38,605	3,217

Documentation of Low Voriconazole Blood Levels Followed by Dose Adjustment in Patients with Invasive Fungal Infections not Responding to Therapy.

	<1 mg/L (n=9)	>1 mg/L (n=28)
Aspergillosis	67%	68%
Candidiasis	22%	25%
Other IFI	11%	7%
Median VRC dose (mg/kg/d)	7 (2.2 to 11.7)	8 (4.6 to 8)
I.v. / orally	44% / 56%	50% / 50%
Failure of therapy	6/9 (67%) *	2/28 (7%)
Median days to failure	21 (9 to 34)	18 (15 to 21)

* P=0.008

Among 6 Pts with VRC failure and trough levels ≤1 mg/L, 4 had proven (MIC of VRC <0.5 mg/L) and 1 probable aspergillosis; 1 had probable candidiasis. VRC dose was increased in the 6 cases: median follow-up VRC trough level was 2.1 mg/L (0.8 to 3.1). All Pts had partial or complete response.

Pascual, AA; ICAAC 06

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation

- Subjects ≥ 2 yO HCT; myeloablative; ≥ 5 HLA match
  - Serum galactomanan collected twice weekly until day 60, weekly until day 100
    - If GM positive or clinical suspicion imaging was done and if positive BAL or Bx was done
      - Ampho-B or caspofungin was permitted during evaluation
- Subjects were randomized to vori 200 mg PO BID or fluc 400 mg q day from day 0 - 100
- Primary efficacy endpoint was FFS at 180 days post transplant
  - Secondary enpoints included incidence of IFI, time to IFI, SAEs, and GVHD

Wingard, JR Blood 2010

Results

Table 2. Number of patients with invasive fungal infection (IFI) through day 365

IFI category	Days 0-180		Days 0-365	
	FLU	VORI	FLU	VORI
Proven				
Aspergillus	3	0	5	2
Candida	3	3	3	6
Zygomycetes	1	1	2	3
Other*	0	1	1	3
Multiple†	2	0	2	1
Subtotal	9	5	13	15
Probable				
Aspergillus	14	9	16	15
Other‡	1	0	2	0
Subtotal	15	9	18	15
Presumptive	9	8	10	8
Total IFIs (proven/probable/presumptive)§	33	22	41	38

FFS at 180 days 75% vs 78% p = 0.49
Trend in favor of Voriconazole for fewer IFIs at 180 days (11.2% V 7.3%) and at 1 year (13.7% V 12.7%); Fewer Aspergillus infections (9 vs 17 p = 0.09); and less frequent empiric AF-Rx (24.1 vs 30.2 p = 0.11)

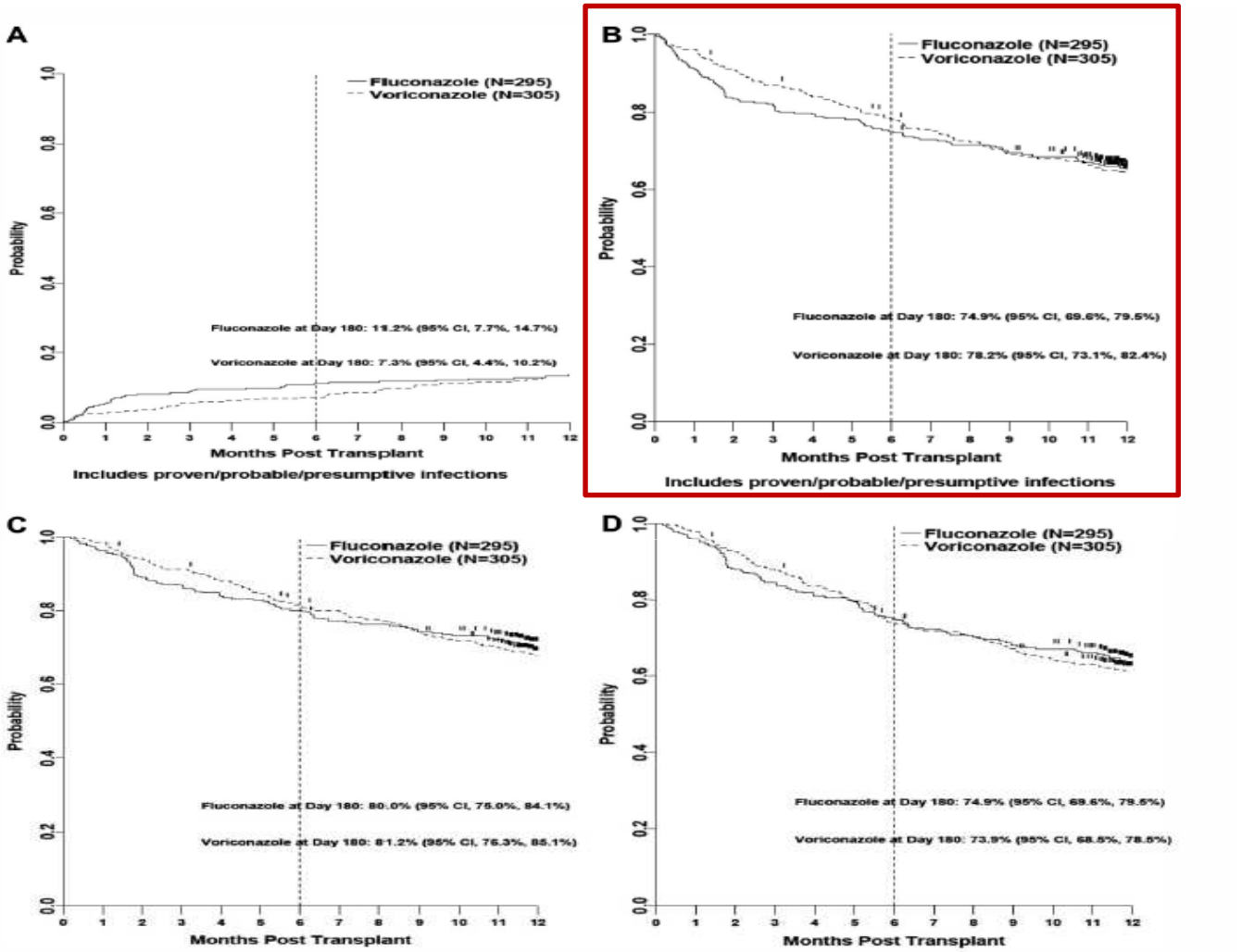


Figure 1. Kaplan-Meier estimates. (A) Cumulative incidence of presumptive, probable, and proven invasive fungal infection. (B) Fungal-free survival (include proven/probable/presumptive infections) by treatment arm. (C) Overall survival by treatment arm. (D) Relapse-free survival by treatment arm.

In the context of intense monitoring and structured empiric antifungal therapy, 6 m FFS
And overall survival did not differ in ALLO-BMT recipients given prophylactic fluc or vori

Posaconazole

- Traizole de segunda generacion
  - Derivado de itraconazole
  - Inhibe CYP-450 dependiente 14-alphademethylase en la via del ergosterol
- Farmocokinetica proporcional a dosis entre 50 y 800 mg
  - Saturacion de absorcion encima de 800 mg
  - Alcanza estado estable en 7 – 10 dias
- Inhibe cytochrome P3A4
  - Menor interaccion con otras drogas

Posaconazole Prophylaxis in Severe GVHD

(Ullman AJ; NEJM, Jan 07)

- **Posaconazole 301 (200mg TID) Vs fluconazole 299 (400mg q D)**
  - **GVHD II – IV or Chronic**
  - **High dose steroids; ATG; ≥ 2 agents**
    - **Excluded if receiving drugs known to interact with azoles**
- **As good as fluconazole for overall fungal infxn (5.3% Vs 9.0%)**
  - **Superior for**
    - ***Aspergillus* (2.3% Vs 7%; p = 0.006)**
    - **Overall fungal during exposure (7 days post randomization) (2.4% Vs 7.6%; p = 0.004)**
    - **Aspergillus during exposure (1.0% Vs 5.9%; p = 0.001)**
- **Similar overall mortality; superior fungal related mortality (1% Vs 4%; p = 0.046)**

Posaconazole Prophylaxis

(Cornely OA; NEJM, Jan 07)

- **Posaconazole 304; (200mg PO TID) Vs fluconazaole 298; (400mg PO qD) or itraconazole 58; (200mg PO BID)**

Table 2. Proven or Probable Invasive Fungal Infection during the Treatment Phase.*

Invasive Fungal Infection	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	Fluconazole (N=240)	Itraconazole (N=58)	P Value	95% CI
			number (percent)			
Proven or probable†	7 (2)	25 (8)	19 (8)	6 (10)	<0.001	−9.7 to −2.5
Mold						
Invasive aspergillosis	2 (1)	20 (7)	15 (6)	5 (9)	<0.001	−9.1 to −3.1
Aspergillus fumigatus	0	2	1	1		
A. flavus	0	2	2	0		
Aspergillus species‡	2	16	12	4		
Rhizopus species	0	1	1	0		
Pseudallescheria boydii	0	1	1	0		
Mold, not otherwise specified	1	0	0	0		
Yeast						
Invasive candidiasis	3 (1)	2 (<1)	2 (<1)	0		
Candida glabrata	2	1	1	0		
C. krusei	0	1§	1§	0		
C. parapsilosis	0	1§	1§	0		
C. tropicalis	1	0	0	0		
Other						
Pneumocystis jirovecii¶	1	1	0	1		

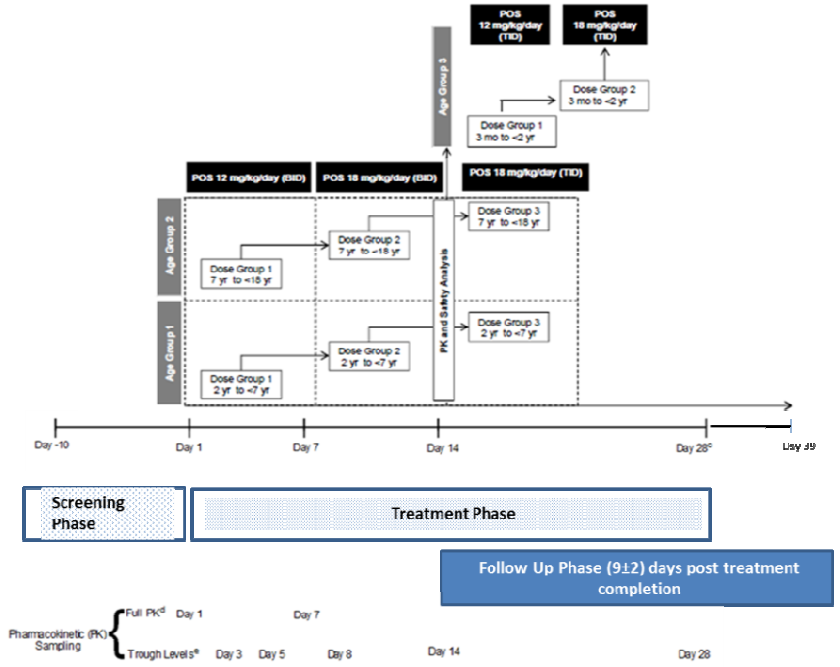
Post Rx phase 14 (5%) Vs 33 (11%) developed fungal infxn (p=0.003)
SAE 19 (6%) Vs 6 (2%); fungal infxn related mortality 5(2%) Vs 16 (5%) (p=0.01)

Estudio Tolerabilidad y Farmacokinetico de Posaconazole Suspension Oral en Niños Immuno Comprometidos y Neutropenicos

- Prospectivo no-randomizado, abierto,multicentrico de dosis secuencialmente incrementada
- Tres grupos etareos y

  3 cohortes de dosis

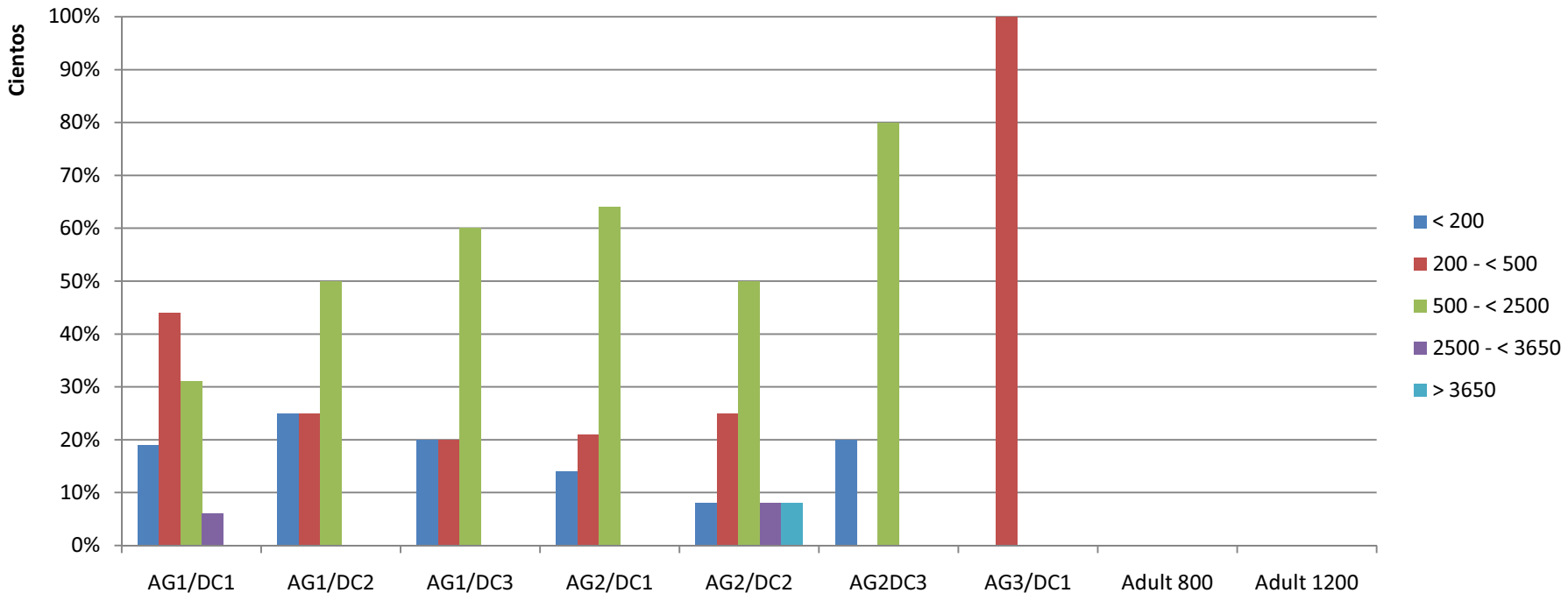
  – 2 – 7; 7 – 15 y 3 meses a 2 años
- Pk completo dias 1 y 7
- Objetivo:
  - C_{avg} exposure 1200 ng/ml
  - 90% with C_{avg} 500 – 2500 ng/ml



Distribucion de C_{AVG}:Grupo Etareo y Cohorte de Dosis

			Cavg (ng/ml)				
AG	DC	N	< 200	200 - < 500	500 - < 2500	2500 - < 3650	>3650
1 (2 - < 7)	1 (12/kg/d BID)	16	19%	44%	31%	6%	0
	2 (18/kg/d BID)	12	25%	25%	50%	0	0
	3 (18/kg/d TID)	5	20%	20%	60%	0	0
2 (7 - < 19)	1 (12/kg/d BID)	14	14%	21%	64%	0	0
	2 (18/kg/d BID)	12	8%	25%	50%	8%	8%
	3 (18/kg/d TID)	10	20%	0	80%	0	0
3 (3 m - < 2)	1 (12 mg/kg/d TID	1	0	100%	0	0	0

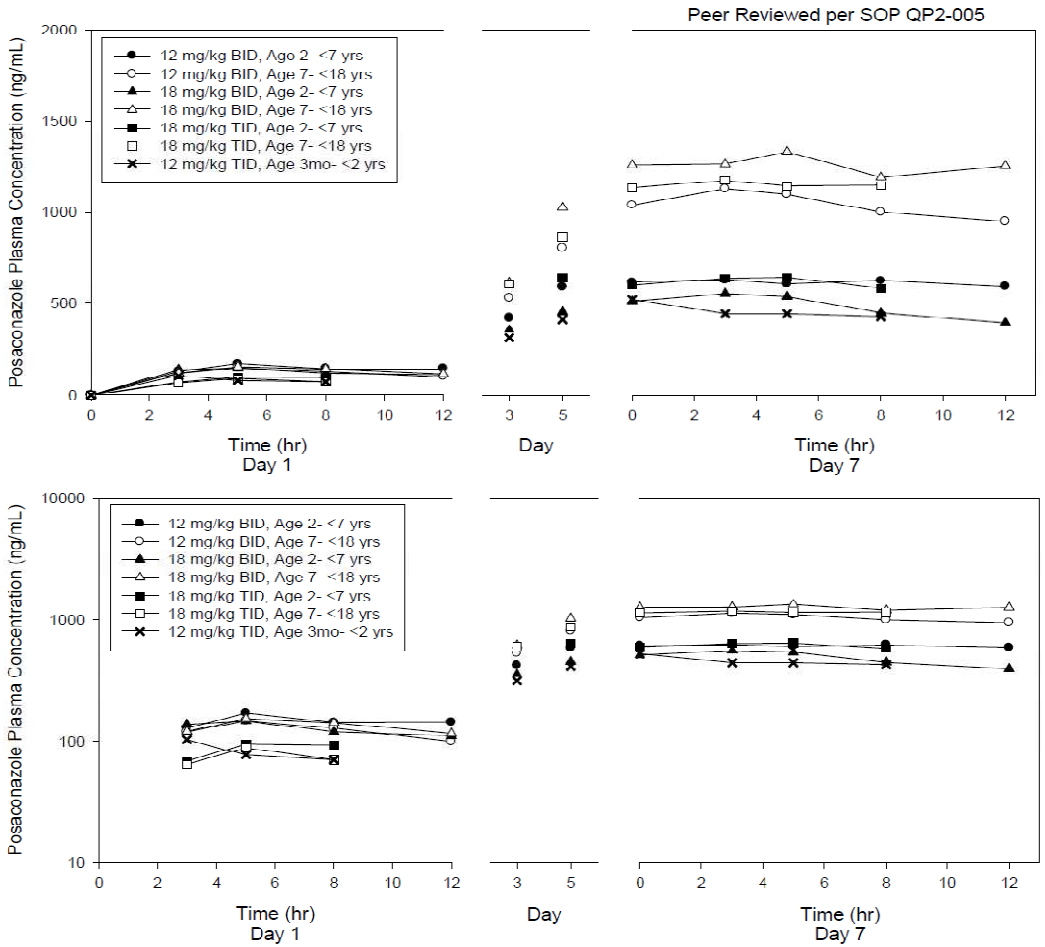
Distribucion de C_{AVG}:Grupo Etareo y Cohorte de Dosis



El objetivo farmacokinetico (90% the pacientes con Cavg entre 500 ng – 2500 ng/ml) no se cumplio a las dosis estudiadas.

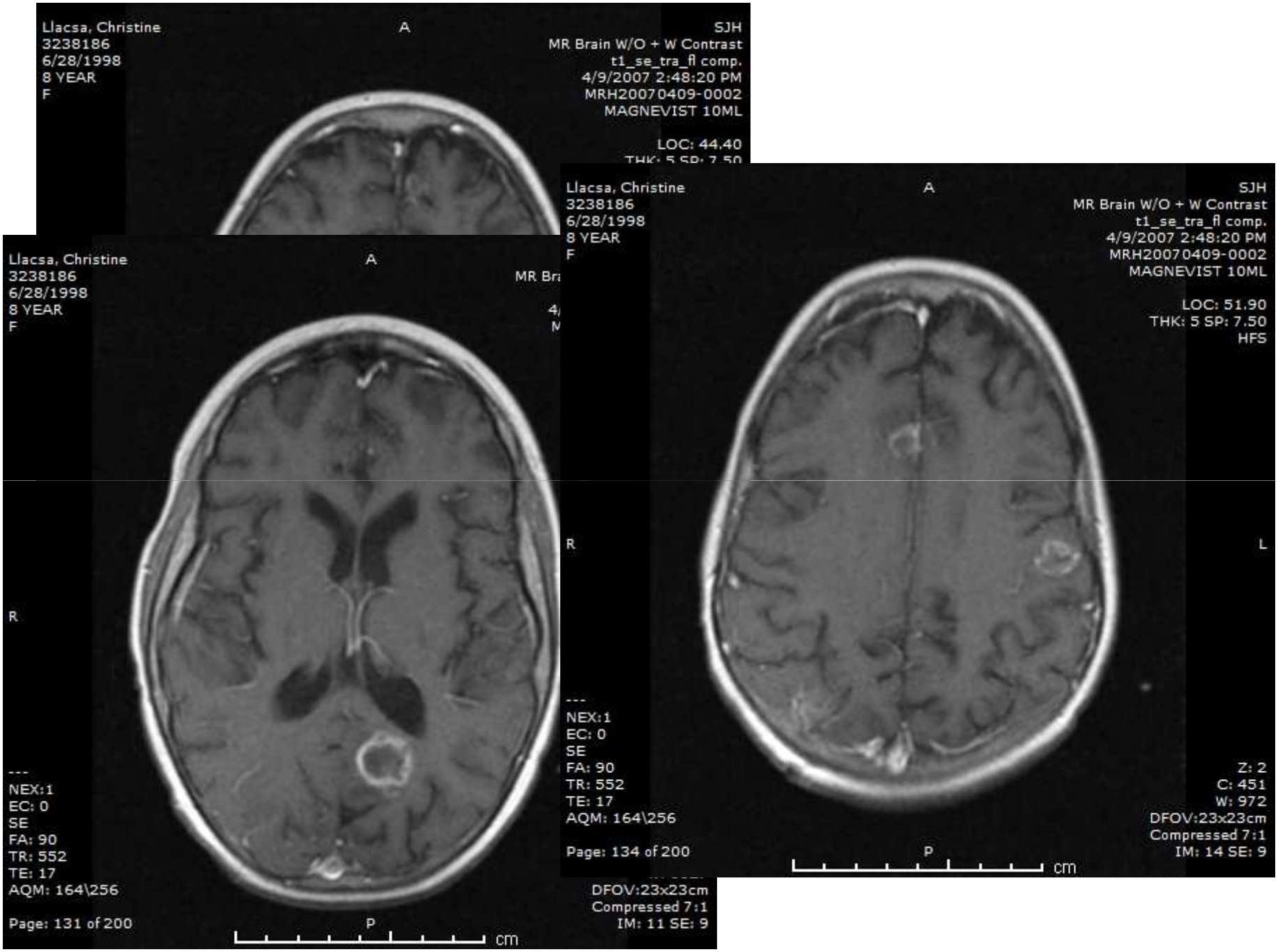
Posaconazole fue bien tolerado por ninos de 2 – 18 anos

Perfil Combinado de Concentracion Media en Plasma por Grupo Etareo y Cohorte de Primera Dosis (Dia 1) y a Estado Estable (Dia 7)



Christine

- Nina de 13 años
- Diagnostico ALL alto riesgo
- Se presenta en la emergencia con convulsiones
  - ANC 0


Llacsa, Christine
3238186
6/28/1998
8 YEAR
F
A
SJH
MR Brain W/O + W Contrast
t1_se_tra_fl comp.
4/9/2007 2:48:20 PM
MRH20070409-0002
MAGNEVIST 10ML
LOC: 44.40
Llacsa, Christine
3238186
6/28/1998
8 YEAR
F
A
R

NEX:1
EC: 0
SE
FA: 90
TR: 552
TE: 17
AQM: 164\256
Page: 131 of 200
P
cm
DFOV:23x23cm
Compressed 7:1
IM: 11 SE: 9
Llacsa, Christine
3238186
6/28/1998
8 YEAR
F
A
SJH
MR Brain W/O + W Contrast
t1_se_tra_fl comp.
4/9/2007 2:48:20 PM
MRH20070409-0002
MAGNEVIST 10ML
LOC: 51.90
THK: 5 SP: 7.50
HFS
R
L

NEX:1
EC: 0
SE
FA: 90
TR: 552
TE: 17
AQM: 164\256
Page: 134 of 200
P
cm
Z: 2
C: 451
W: 972
DFOV:23x23cm
Compressed 7:1
IM: 14 SE: 9

Diagnostico y Tratamiento

- 13 abscesos intracraneanos por *Aspergillus fumigatus*
- *Voriconazole 13 mg/kg/dose 2 veces al dia x 6 meses*
  - *Niveles "trough" entre 1 y 5*
  - *Monitoreo de enzymas hepaticas*
- *Micafungin 200 mg q 24 x 2 meses*

Recomendaciones
(No Necesariamente Iguales a las Guias)

- Candidiasis
  - Neonato < 1000g BW:
    - Micafungin 10 mg/kg/dia
    - Fluconazole 25 mg/kg dia 1 seguido por 12 mg/kg/dia
    - Micafungin 10 mg/kg/dia + Fluconazole 12 mg/kg/dia x 3 dias
      - Candida albicans o parapsilosis; parar micafungin
      - Candida non albicans (krusei o glabrata); parar fluconazole
  - Neonato $\geq$ 1000 g BW
    - Micafungin 7.5 mg/kg/dia
    - Alternativas igual que arriba pero con dosis de micafungin de 7.5 mg/kg si se escoge combinacion

- Candidiasis
  - > 3 meses de edad
    - Neutropenico o immuno comprometido
      - Micafungin 2 mg/kg/day (considerar 3.5 mg/kg en menores de 5 años) dosis Max 200 mg (150 si es mayor de 13 años)
      - En caso de compromiso urinario añadir fluconazole (excepto *C krusei o C glabrata* MIC $\geq$ 8)
    - No neutropenico con infeccion de compromiso vital
      - Micafungin igual que arriba
      - Fluconazole 24 mg/kg/dia div q 6h x 4 luego 12 mg/kg/dia div q 12h (*C krusei o C glabrata* MIC $\geq$ 8 use micafungin)
    - No Neutropenico con infeccion leve a moderada
      - Fluconazole 24 mg/kg/dia div q 6h x 4 luego 12 mg/kg/dia div q 12h (*C krusei o C glabrata* MIC $\geq$ 8 use micafungin)

- Prophylaxis
  - Neonato < 750g BW (< 1000g BW si mas de 72h de antibioticos de amplio espectro)
    - Fluconazole 6 mg/kg dos veces por semana x 6 semanas
  - Allo SCT (bone marrow, cordon)
    - Micafungin 2 mg/kg/dia (max 100 mg/dia) si menos de 13 años
    - Fluconazole 6 mg/kg q 12h (400 mg /day si > 60Kg) en niños y adultos
      - Monitoreo intenso de galactomannan; no esteroides para GVHD
    - Voriconazole 200 mg q 12h (mayores de 13 años)
      - Vigilar interacciones
    - Posaconazole (mayor de 13 años) 200 mg q 8h

- Aspergillosis
  - Voriconazole 8 mg/kg IV q 12 (Menores de 13 anos)
    - Voriconazole 6 mg/kg q 12h x 2 loading followed by 4 mg/kg BID maintenance (≥ 13 años)
  - Voriconazole 200 mg/dia via oral(independiente del peso)
    - Monitorear enzimas hepaticas
    - TDM trough level 1 – 5 mcg/ml
    - Considerar añadir micafungin (o caspofungin o anidulafungin) durante neutropenia
  - Posaconazole 18 mg/kg/day div q 8h
    - TDM trough level > 0.75 ng/ml
    - Considerar añadir micafungin (o caspofungin o anidulafungin) durante neutropenia
  - Isavuconazole (No hay datos en pediatria)

- Zygomycosis (Tratar de identificar specie)
  - Empirico
    - L-AmB 5 – 8 mg /kg/day
      - Monitorear funcion renal
      - Especie susceptible a triazole
    - Posaconazole 18 mg/kg/dia div q 8h
      - TDM Trough > 0.75 – 1 ng/ml
      - Considerar añadir echinocandina
    - Isavuconazole 200 mg q 8h x 3 doses luego 200 mg/dia
      - No existe informacion en pediatria
  - Debatible el uso de deferasirox, contraindicado el uso de deferoxamina

- *Fusarium spp*
  - L-AmB 8 – 15 mg/kg
    - Monitorear funcion renal
  - Voriconazole 8 mg/kg IV inicial, seguido por 200 mg/dia via oral (independiente del peso)
    - TDM trough level 1 – 5 mcg/ml
    - Considerar añadir terbinafine