



Profilaxia em Imunossuprimidos: bactérias, vírus e fungos: Quais são as evidências?

Marcia Garnica, MD, PhD

Infectologista

Professora Adjunta de Clínica Médica

Universidade Federal do Rio de Janeiro

Interventions in Infection Diseases

- All approaches have consequences...
 - Prophylaxis also...

but in this case, we are treating someone that is not ill..

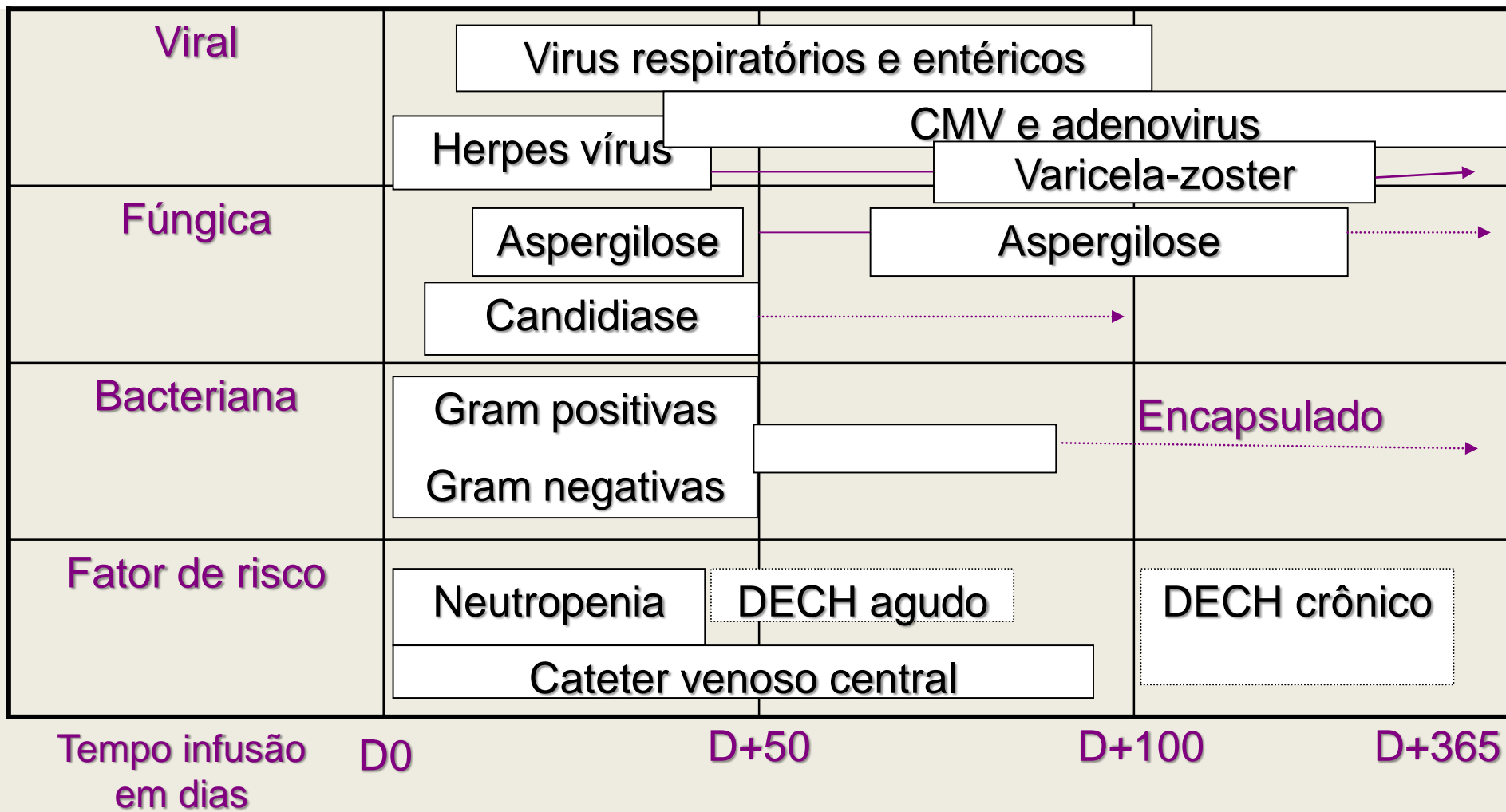
Important points to analysis before the indication of prophylaxis

- ❑ Is the event frequent?
- ❑ Is the event serious ?
- ❑ Is there an effective prophylaxis approach?
 - ❑ Number needed to treat <20
- ❑ Is prophylaxis safe?
 - ❑ Resistance, toxicity, and costs

Difficults in prophylaxis

- Definition of the period of risk
 - When does it start and end??
- What is the agent I am trying to prevent?

Distribuição dos tipos de infecção em relação ao tempo pós TCTH Alogénico

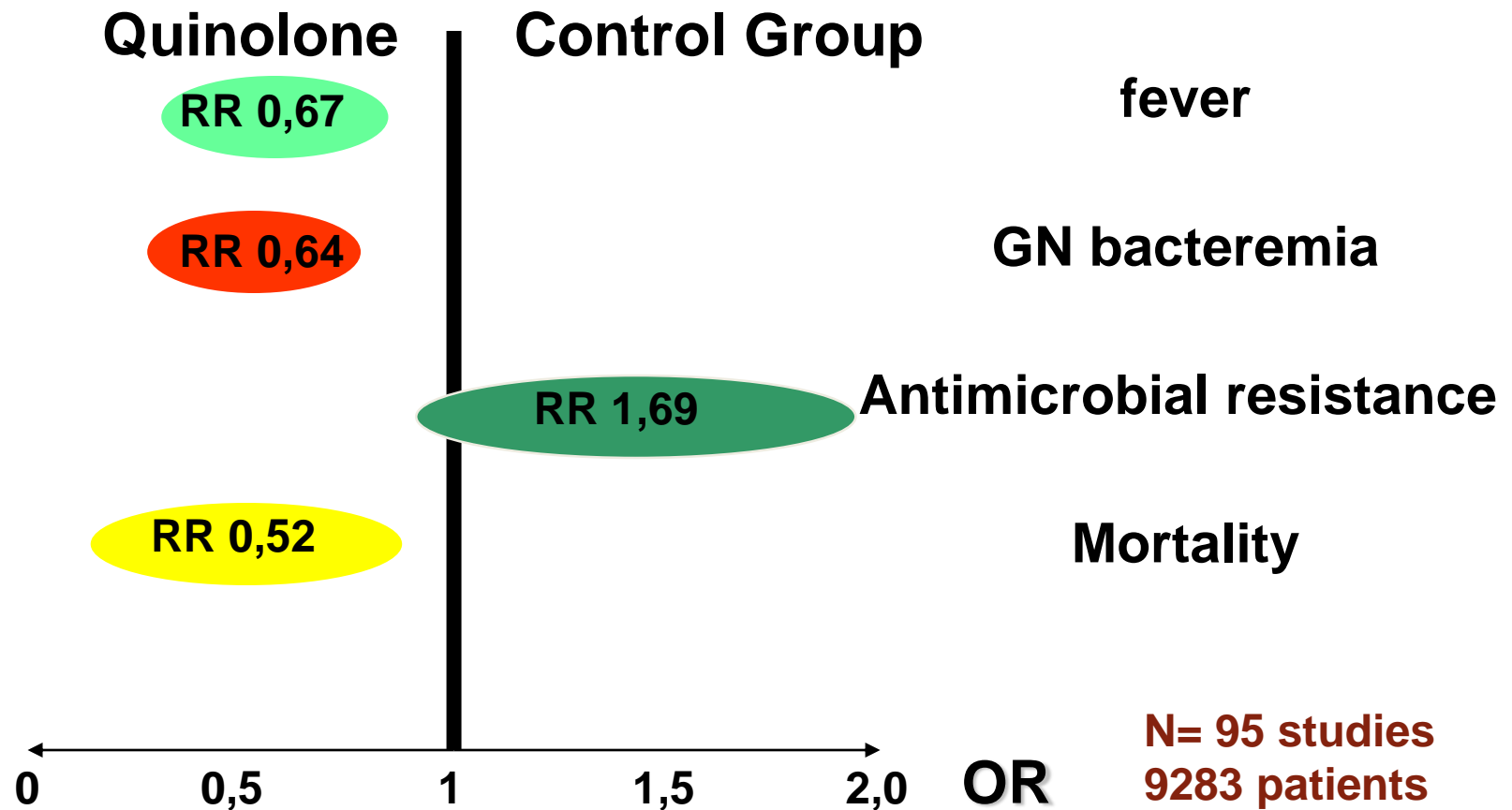


- profilaxia antibacteriana

Why antibacterial prophylaxis in neutropenic and stem cell transplant?

- ❑ Bacterial infection is frequent in neutropenia
 - ❑ 20 – 30% of FN have bacteremia
- ❑ Most important etiology in the first fever
- ❑ Severe infections and high rates of infection related mortality

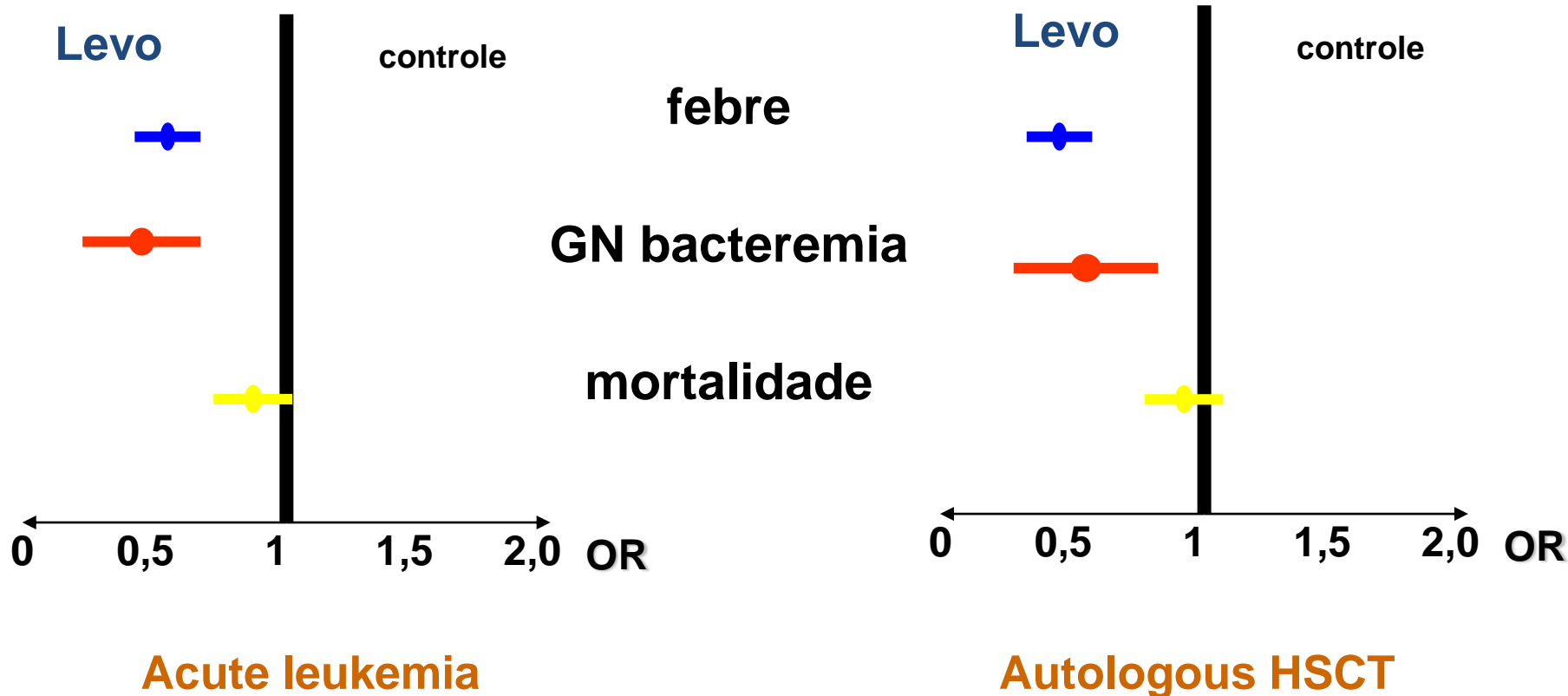
Meta- analysis of prophylaxis in neutropenic patients -



Quinolones in prophylaxis practices ...

	Favorable	Unfavorable
Norfloxacin	Cost +	↓↓systemic distribution Low spectrum
Ciprofloxacin	Cost ++ Good option for Pseudomonas Few adverse events	No spectrum for Streptococcus viridans GN resistance
Levofloxacin	spectrum for Streptococcus viridans Few adverse events	Cost +++ ↑ Pneumococcal Resistance
Moxifloxacin	Anaerobic spectrum	Cost +++ ↑ C. difficile (colitis)

Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia



5 patients received levo for 1 case of FN prevention

Other studies in Acute leukemia and SCT patients

	Population	Design	N	Quinolone	Outcomes
Solano, 2005	AutoHSCT	Cohort (matched control)	51 x 51	Pip-Tazo x norfloxa	↑ anfoB, ↑ duration of antibiotics
Graig, 2007	AL e HSCT	Cohort (before and after)	217 x 326	Levo x No	↓ GN bacteremia, GP =
Eleutherakis-Paparakovou, 2010	LA, AutoHSCT	Clinical trial	89 x 68	Cipro + vanco x No	↓ NF, ↓ bacteremia
Sohn, 2011	AutoHSCT	Retrospective	144 x 118	Cipro X No	↓ NF, ↓ FOO,
Garnica et al, 2012	LA, Auto HSCT	Cohort (before and after)	144 x 79	Cipro x No	↓ NF, ↓ bacteremia. ↓ hospitalization

✓ Improvement in outcomes: FN, bacteremia, time free of fever, duration of hospitalization

✓ No improvement in mortality rates

Antibacterial Prophylaxis after Chemotherapy for Solid Tumors and Lymphomas

Levofloxacin

Ca mama/ Tu pulmão/ linfoma/ Tu testicular

- ✓ ↓ episódios febris ($p < 0.001$)
- ✓ ↓ número de internações ($p = 0.004$)
- ✓ benefício apenas se NF no 1º ciclo
- ✓ principalmente no 1º e 2º ciclos

20.000 doses de leva para prevenir 35 NF !!

Cullen et al. NEJM 2005; 353 (10):989-998

Cullen et al. JCO 2007; 25 (30):4821-4828

Baden L. NEJM, 2005 (10): 1052 - 54

RESEARCH ARTICLE

Open Access

Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance

Marcia Garnica¹, Simone A Nouér¹, Flávia LPC Pellegrino^{1,2}, Beatriz M Moreira², Angelo Maiolino¹ and Marcio Nucci^{1*}

Variable	Ciprofloxacin group N=219	Control group N=110	<i>p</i> value
Underlying disease			
Acute myeloid leukemia	48 (22)	22 (20)	0.69
Acute lymphoid leukemia	48 (22)	24 (22)	0.98
Multiple myeloma	56 (26)	31 (28)	0.61
Non-Hodgkin lymphoma	40 (18)	8 (7)	0.008
Hodgkin lymphoma	18 (8)	15 (14)	0.12
Other*	9 (4)	10 (9)	-
Autologous HCT	89 (41)	53 (48)	0.19
Allogeneic HCT	30 (14)	14 (13)	0.81

Variable	Ciprofloxacin group N=219	Control group N=110	<i>p</i> value
→ Fever	159 (73)	102 (93)	<0.001
Fever of unknown origin	86 (39)	52 (47)	0.16
→ Bacteremia	49 (22)	36 (33)	0.04
due to a single Gram-negative	19 (9)	13 (12)	0.36
due to a single Gram-positive	22 (10)	18 (16)	0.10
Polymicrobial	8 (4)	5 (4.5)	0.77
Microbiologically documented without bacteremia	3 (1)	1 (1)	1.00
Clinically documented	21 (10)	12 (11)	0.71
→ Duration of hospitalization (days), mean ±SD (range)	22 ± 13.9 (4 – 97)	24 ± 10.4 (5 – 57)	0.002
→ Duration of antimicrobial treatment (days) , mean ±SD (range)	8 ± 7.6 (0 – 40)	11 ± 7.0 (0 – 33)	<0.001
→ Receipt of carbapenem**	79 (36)	15 (14)	<0.001
Receipt of glycopeptide	26 (24)	14 (13)	0.82
Death	20 (9)	12 (11)	0.61

Important points to analysis before indication of prophylaxis

- ☐ Is the event frequent? ☐ Yes
- ☐ Is the event serious ? ☐ Yes
- ☐ Is there effective prophylaxis approach? ☐ Yes
 - ☐ Number needed to treat <20 ☐ (few data, but it is in High risk FN)
- ☐ Is prophylaxis safe?
 - ☐ Resistance, toxicity, and costs

Resistance and Prophylaxis

- ❑ Quinolones:

- ❑ Selection of quinolone resistant isolates

- ❑ Selection of isolates with resistance to other antimicrobial classes

Studies in Acute leukemia and SCT

	População	Desenho	N	Quinolona	Desfechos	Resistência
Solano, 2005	AutoHSCT	Cohort (matched control)	51 x 51	Pip-Tazo x norfloxa	↑ anfoB, ↑ duration of antibiotics	Reduction of resistance#
Graig, 2007	AL e HSCT	Cohort (before and after)	217 x 326	Levo x No	↓ GN bacteremia, GP =	↑ VRE
Eleutherakis-Paparakovou, 2010	LA, AutoHSCT	Clinical trial	89 x 68	Cipro + vanco x No	↓ NF, ↓ bacteremia	↑ Empirical therapy failure
Sohn, 2011	AutoHSCT	Retrospective	144 x 118	Cipro X No	↓ NF, ↓ FOO,	↑ R quinolona, ↑ MRSA
Garnica et al, 2012	LA, Auto HSCT	Cohort (before and after)	144 x 79	Cipro x No	↓ NF, ↓ bacteremia. ↓ hospitalization	↑ R quinolona and ↑ ESBL

✓ Increase in:

✓ Resistant pathogens (*C. difficile*);

✓ Resistance to quinolone

✓ Resistance to other classes: MRSA, VRE, ESBL...

Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance

Table 3 Incidence rates (per 1,000 patients-day) of resistant bacteria

	Period 1 (2005)	Period 2 (2006–2008)	<i>p</i> value
Cohort patients			
Bacteremia due to Cip-R organisms*	3.02	6.77	0.03
Cip-R enterobacteria	0.38	2.12	0.06
Cip-R <i>Pseudomonas aeruginosa</i>	0.38	0.63	0.71
ESBL production	0.38	1.27	0.26
Cip-R <i>Staphylococcus aureus</i>	0	0.63	0.26
Cip-R CONS	2.27	2.75	0.72

Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance

Table 3 Incidence rates (per 1,000 patients-day) of resistant bacteria

	Period 1 (2005)	Period 2 (2006–2008)	<i>p</i> value
Non-cohort patients in the hematology unit			
Cip-R enterobacteria	0.53	2.54	0.004
Cip-R <i>Pseudomonas aeruginosa</i>	0.70	0.32	0.39
ESBL production	0.52	1.59	0.08
Cip-R <i>Staphylococcus aureus</i>	0	0.16	0.52
Cip-R CONS	2.64	2.23	0.65
Hospital			
Cip-R enterobacteria	0.76	0.64	0.15
Cip-R <i>Pseudomonas aeruginosa</i>	0.22	0.21	0.78
ESBL production	0.56	0.53	0.74
Cip-R <i>Staphylococcus aureus</i>	0.33	0.23	0.06
Cip-R CONS	0.68	0.60	0.33

Discontinuation of Prophylaxis and Resistance

- Spanish study
- After discontinuation:
 - Similar Bacteremia rates
 - No difference in mortality
 - Return to Quinolone susceptibility

TABLE 2
Microbiologic Findings

Variable	No. of patients (%)		P value
	Ciprofloxacin prophylaxis (n = 43 patients)	No antibiotic prophylaxis (n = 101 patients)	
Positive blood cultures	12 (28) ^a	26 (26) ^a	0.8
Gram positive bacteria	2 (5)	12 (12)	0.2
CNS	2	9	—
<i>S. aureus</i>	0	2	—
viridans streptococci	0	1	—
Gram negative bacteria	11 (26)	15 (15)	0.1
<i>Escherichia coli</i> cip-S	1	7	—
<i>Escherichia coli</i> cip-R	7	2	0.02
<i>Enterobacter aerogenes</i>	0	1	—
<i>Enterobacter cloacae</i>	1	0	—
<i>Pseudomonas</i> spp	1	3	—
<i>Klebsiella</i> spp	1	2	—

CNS: coagulase negative staphylococci; cip-S: ciprofloxacin susceptible; cip-R: ciprofloxacin resistant.

^a One patient had polymicrobial bacteremia.

Discontinuation of Prophylaxis and Resistance

- Study in Japan
 - prophylaxis (2003 -2005) X No (2006 - 2009)

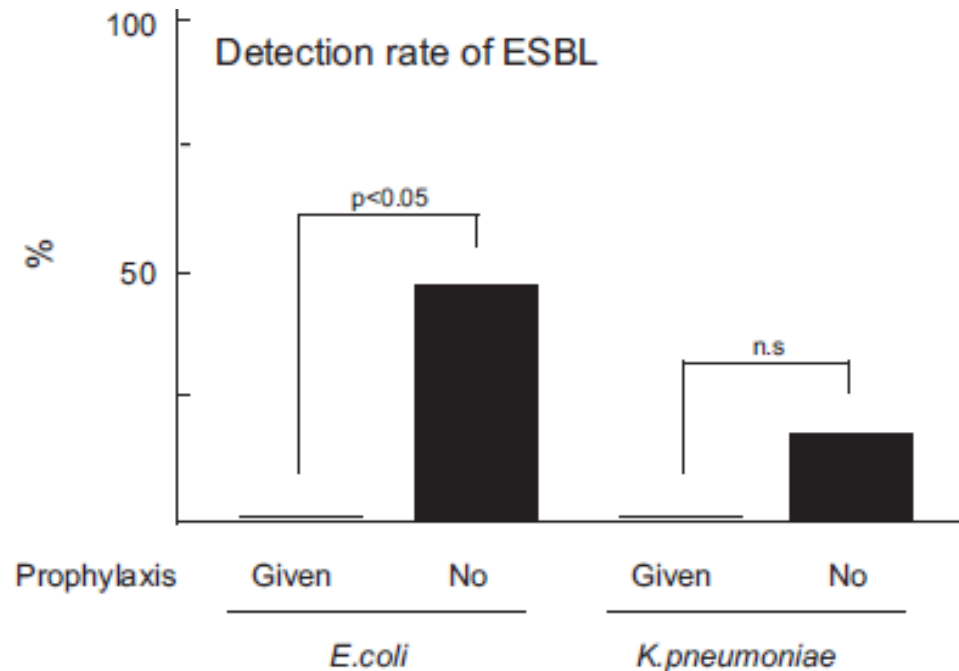


Figure 1. Frequencies of ESBL-producing strains in bacteremic isolates obtained from patients with febrile neutropenia (n.s., not significant).

More recent data...

- Probable the discontinuation will not return the epidemiology
- Increasing in ESBL isolates is a disseminated problem
- Selection of mutant isolates
 - High frequency of quinolone prescription in all scenarios;
 - Most prescribed antimicrobials class

Bow EJ. Curr Opin Inf Dis, 2011

Baden L. NEJM, 2005 (10): 1052 – 54

Wingard et al. Curr Opin Hematol, 2012, 19:21-26

Recomendações IDSA 2010

- **Leucemia aguda ou fase neutropênica do TMO:**
 - Deve ser oferecido profilaxia durante a neutropenia (ciprofloxacin ou levofloxacin)
 - Avaliar o subgrupo de maior benefício
 - Manter avaliação de Resistência

Benefício se R < 20 – 30% !!!

- ❑ **Neutropenia com expectativa de duração < 7 dias:**
 - ❑ Não deve ser oferecido rotineiramente
 - ❑ Avaliar o uso de quinolona com terapia empírica

Resumindo as evidencias...

- Para pacientes de alto risco:
 - Tempo neutropenia > 7 dias
 - Redução de NF, bacteremia e óbito (?) foi demonstrado
- Para pacientes com tempo de neutropenia curto / MASCC escore > 21:
 - Benefício??
 - Perda da oportunidade de tratar a NF empiricamente com Amox-Clav + Quinolona

Bow EJ. Curr Opin Inf Dis, 2011

Baden L. NEJM, 2005 (10): 1052 – 54

Wingard et al. Curr Opin Hematol, 2012, 19:21-26

- **profilaxia antifúngica**

Invasive Fungal Infection (IFI) – Background

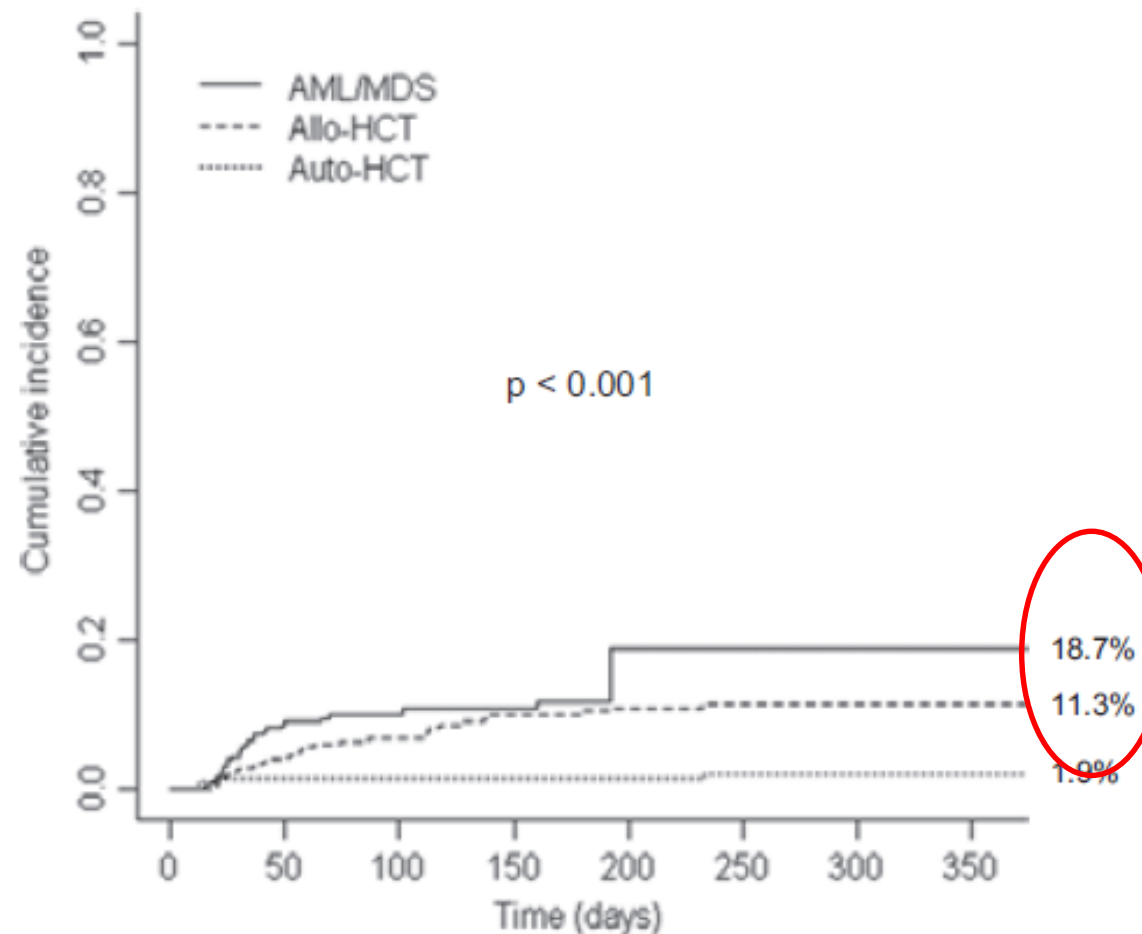
- Important problem during induction remission therapy and consolidation in AML patients
- Major cause of infection related mortality in allogeneic HSCT
- Increase incidences in other settings (myeloma, monoclonal AntB)
- IFI association with:
 - Delays treatment schedules
 - Severe Morbidity
 - High mortality

Maertens et al. Mycoses 2007; 50:2-17

Marr et al CID 2002;34:909-17

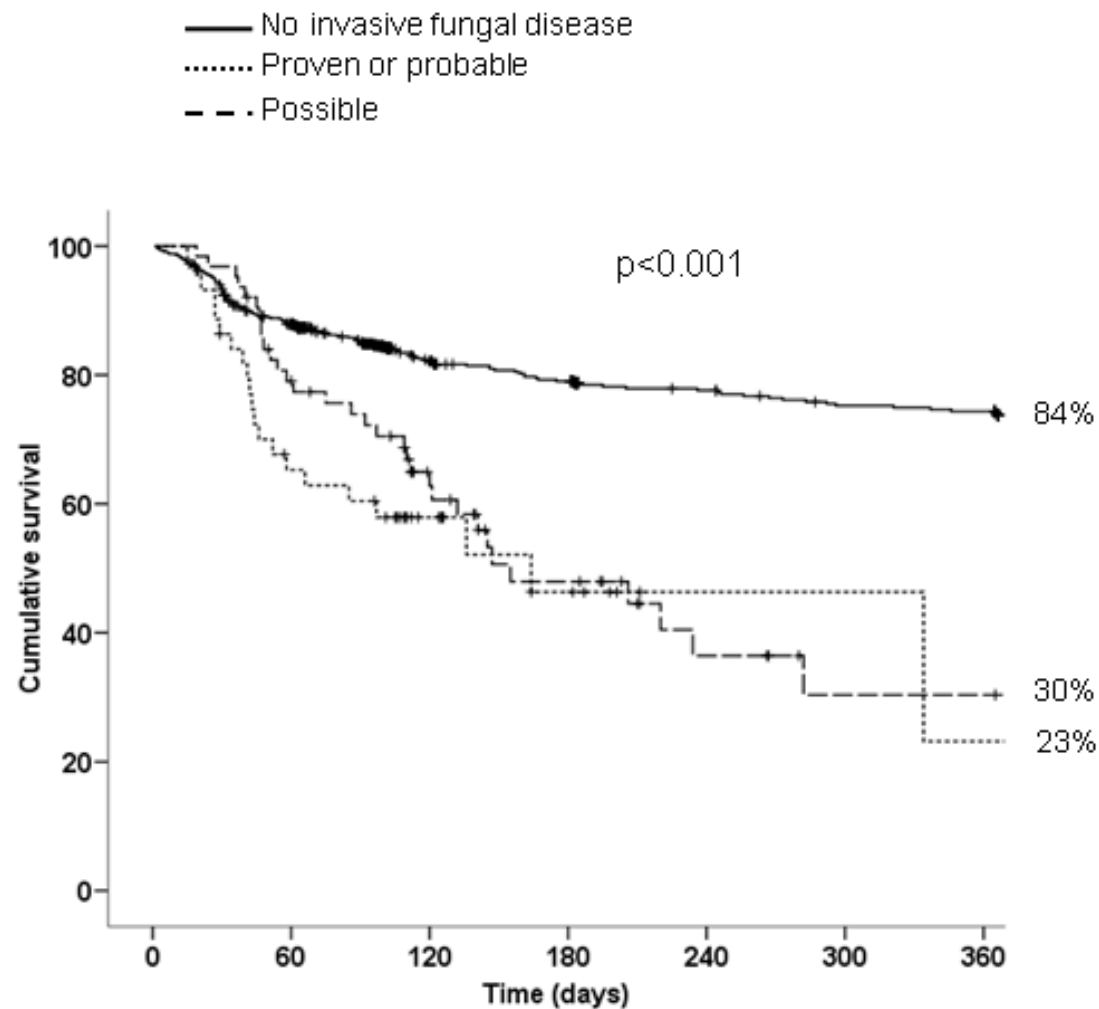
Acosta J et al. Eur J Clin Microb Infect Dis 2011

Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil



Nucci et al. Clin Microb and Inf 2012;

Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil



Approaches to decrease IFI mortality

- Antifungal Therapy

- Empirically
- Preemptive

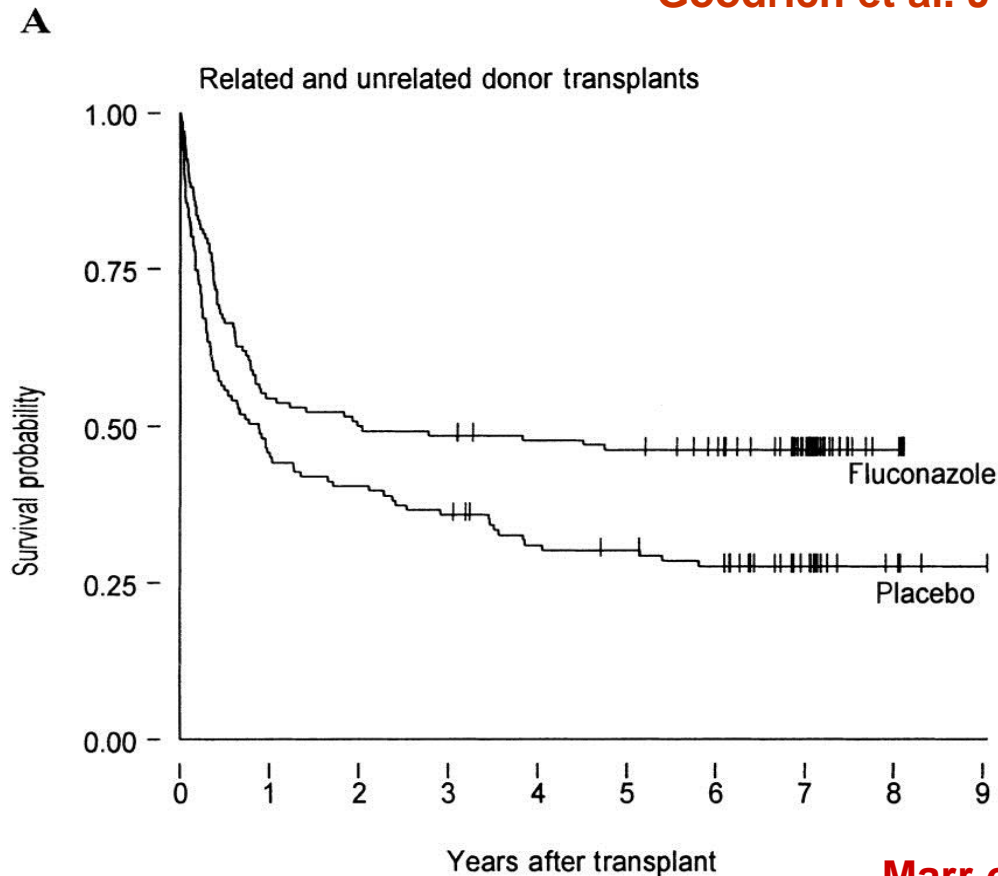
- Prophylaxis

- Ambient measures – HEPA Filter

Fluconazole in Stem Cell Transplant

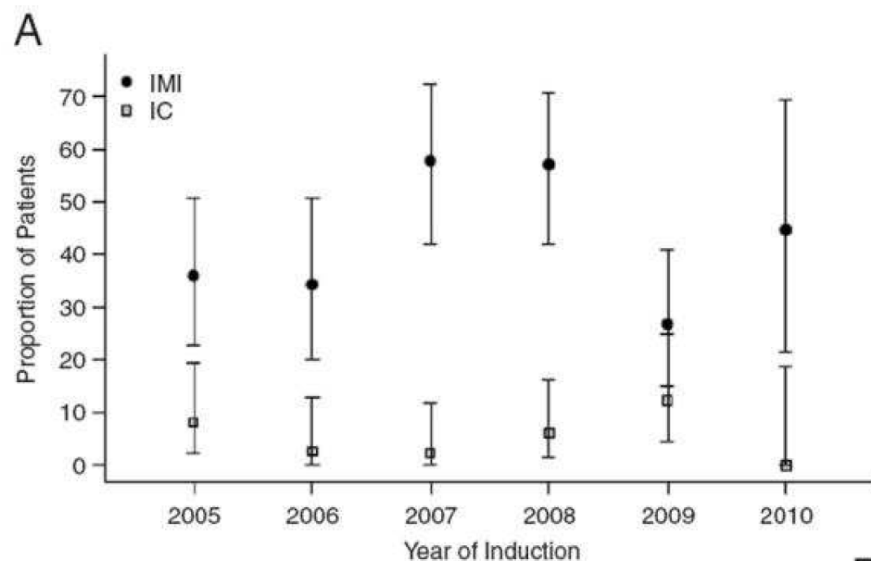
- 80': invasive candidiasis - 10-15%
- Mortality ~30-40%

Goodrich et al. J Infect Dis 1991;164:731-40



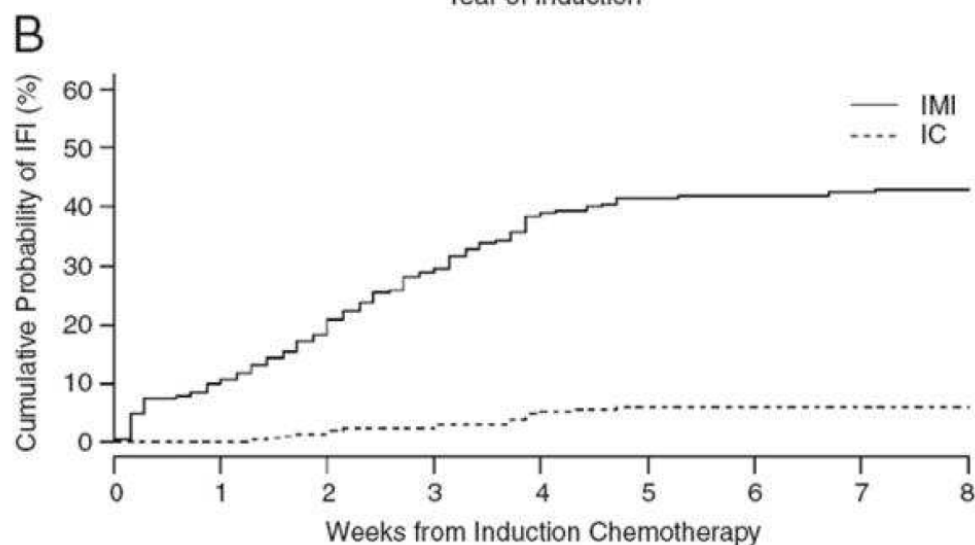
Marr et al. Blood 2000;96:2055-61

Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy☆☆☆☆,☆☆

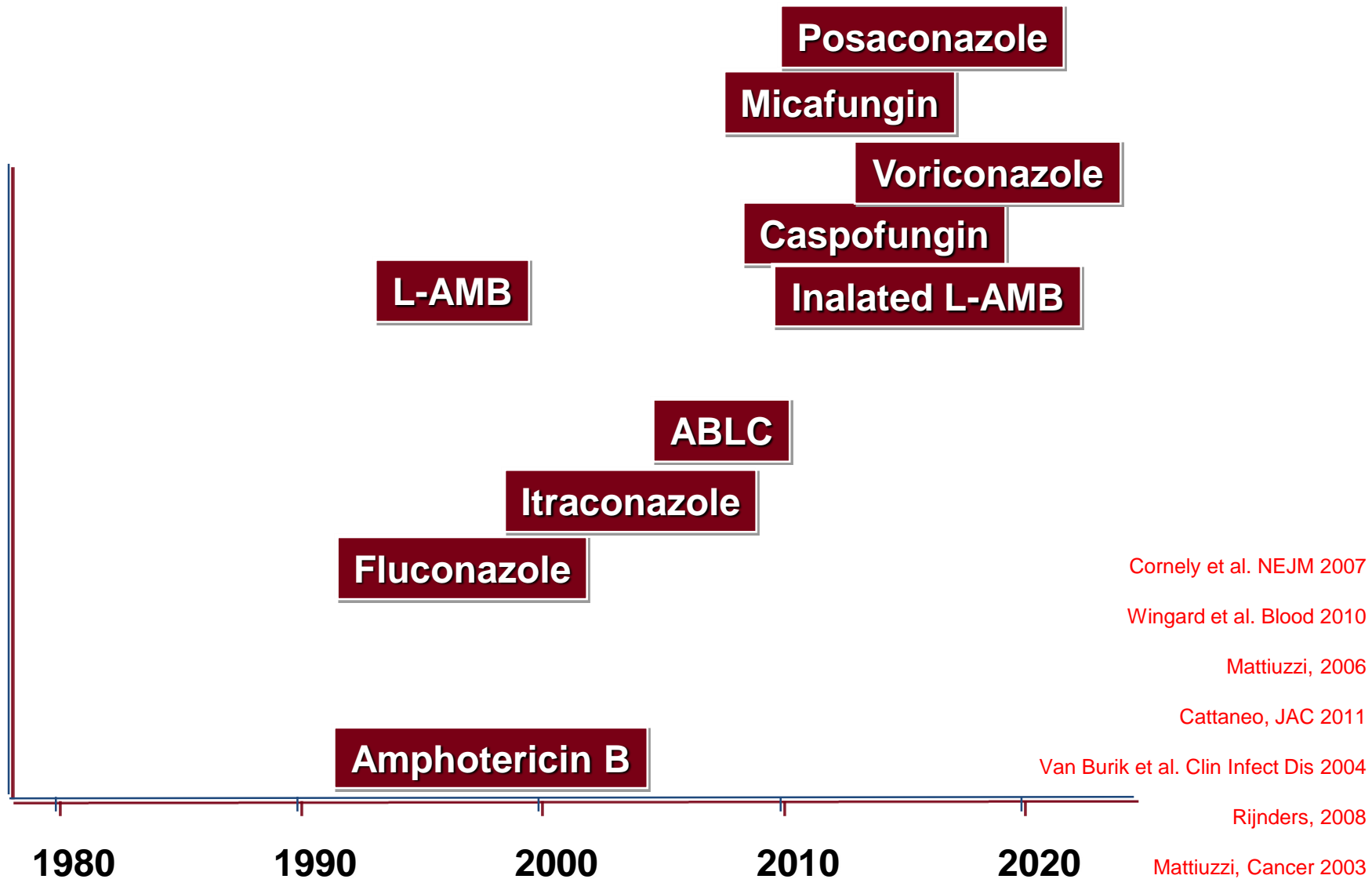


Virtually invasive candidiasis disappeared in High Risk in prophylaxis;

But there is an increase in Mold infections!!



Antifungal Drugs for Prophylaxis in AML or HSCT patients



Prophylaxis trials in AML patients

- New azoles:
 - Posaconazole and Voriconazole*
- Echinocandins:
 - Caspofungin and Mica 50mg x fluco*
- L-Amphotericin
 - Inalted (plus oral flu) or Intravenous

Cornely et al. NEJM 2007

Wingard et al. Blood 2010

Mattiuzzi, 2006

Cattaneo, JAC 2011

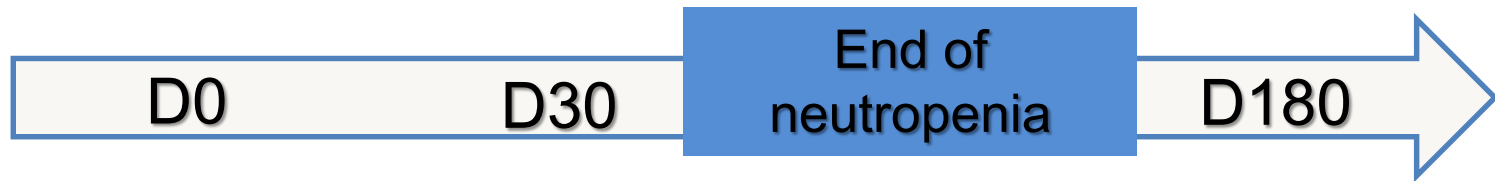
Van Burik et al. Clin Infect Dis 2004

Rijnders, 2008

Mattiuzzi, Cancer 2003

*HSCT patients, including
neutropenic phase

Prophylaxis in AML patients



Posaconazol

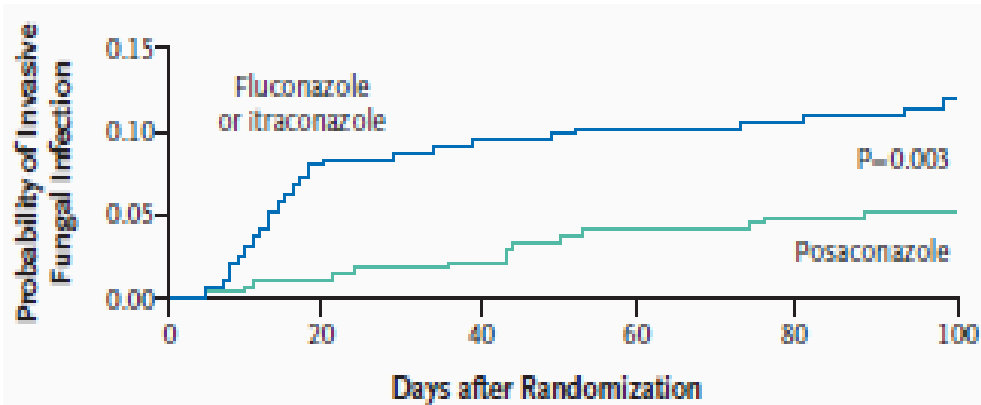
Caspofungin

Itraconazol

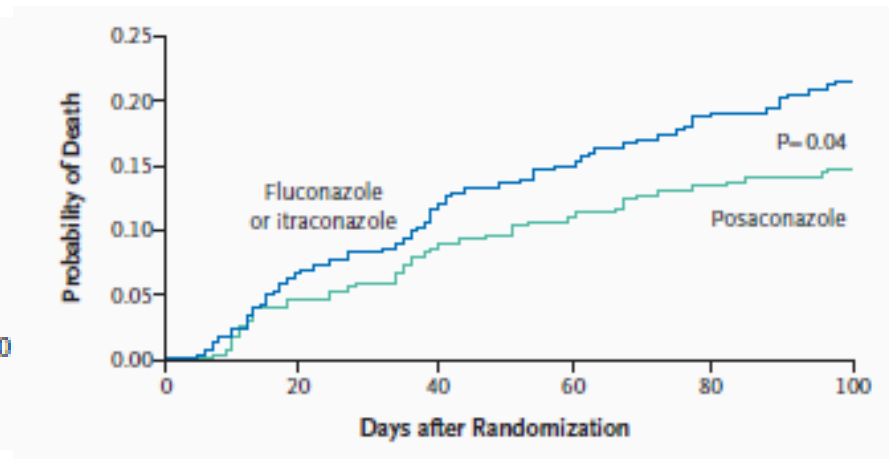
No symptoms at the beginning of drug, only risk!

Posaconazole vs. Fluconazole/Itraconazole in AML/SMD IR

Probability of IFI



Probability of Death

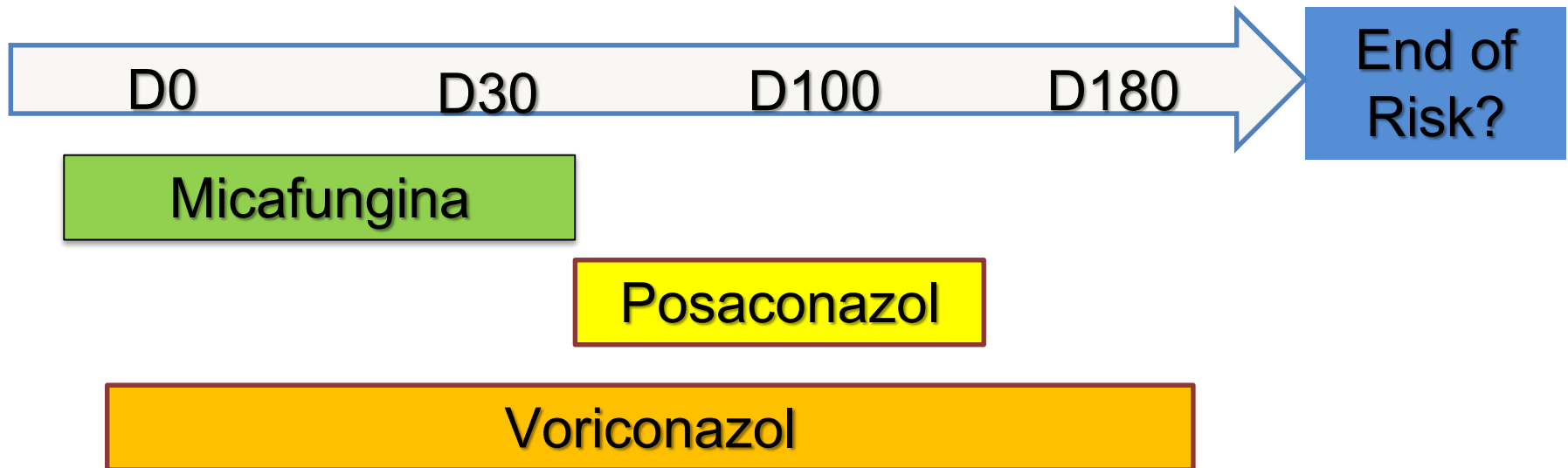


Caspofungin vs. Antifungal Prophylaxis in Acute Leukemia

- Profil-C
- Randomized 1:1 (caspofungin vs. Standard prophylaxis)
- AML (N=138) and ALL (N=37) IR

	Caspo N=93 (%)	SP N=82 (%)	P
IFI	15 (16)	17 (21)	NS
IFI proved/probable	7 (7.5)	3(3.7)	NS

Prophylaxis in HSCT patients



Van Burik et al. Clin Infect Dis 2004

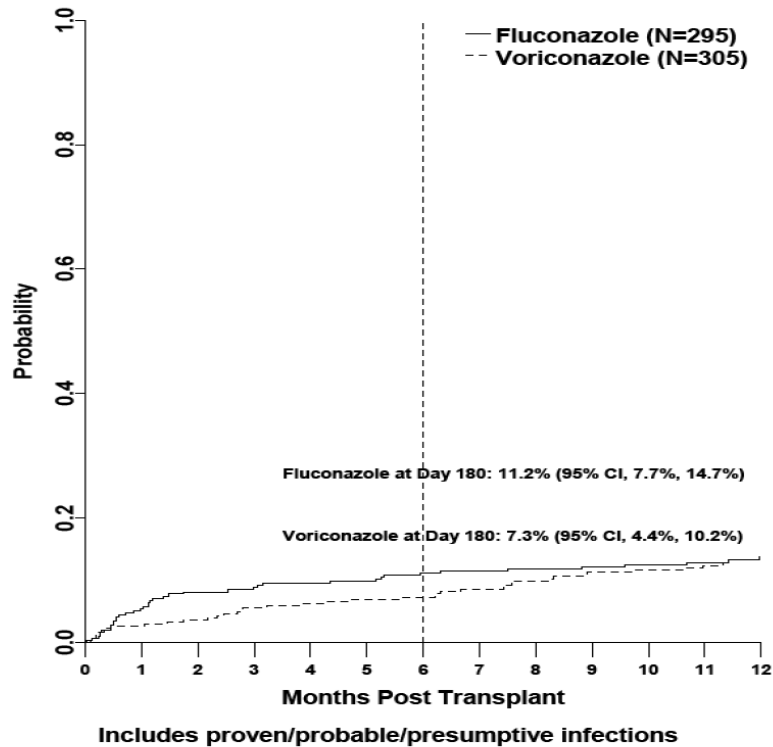
Hiramatsu et al. Int J Hematol 2008; 88: 588 – 595;

Ullmann et al. NEJM 2007; 356(4): 335-347

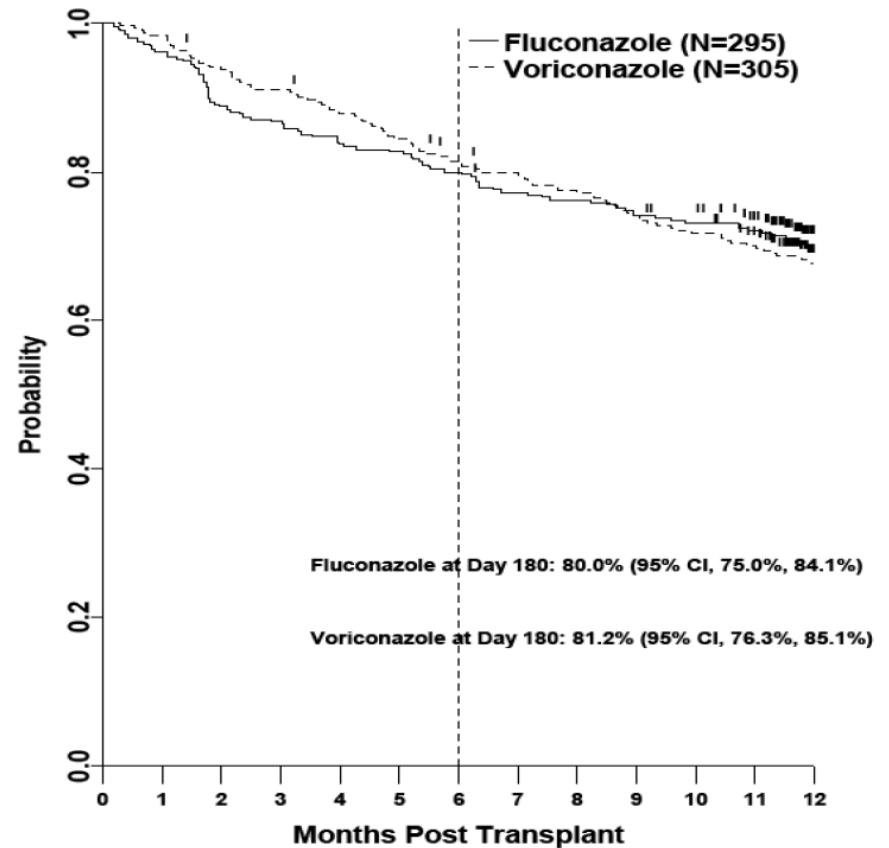
Marr et al. Blood 2003;103:1527-33

Wingard et al. Blood 2010

Voriconazole vs. Fluco + Preemptive in HSCT patients



Cumulative incidence of fungal infection.



Overall survival, by treatment arm.

Wingard, J et al. Blood, 2010

Mica vs. fluconazol during neutropenic phase of autologous and allogeneic HSCT

- 72 centers
- N=889

	Micafungina n=425	Fluconazol n=457	P
Aspergilose	0,2%	1,5%	0,07
Candidíase	0,9%	0,4%	0,44
Total IFI	1,2%	2%	0,35
Terapia AF empírica	15%	21%	0,02

Options Summary of Prophylaxis

Antifungal Agent	Advantages	Disadvantages	Recommendation from Guidelines
Posaconazole	Extended espectrum (including Zigomycosis) - Benefits in OS (for AML)	-PO only -interaction	ECIL 3: AI IDSA: AI
Voriconazole	- PO and IV	- drug Interaction - toxicity -pharmacokinetics	ECIL 3: AI (HSCT) IDSA: NA
Fluconazole	-Cust, -Few interactions	No mold action	ECIL 3: AI for IC; CI for AML (with GMI + HEPA)
LAMB aerosolized	-Few interactions - Local activity	- methods -- No action in yeast prevention (Flu association)	ECIL 3: BI
Micafungin/ Caspo	-Cust	--IV -- low concentration in gut	CI

Hicheri Y. CMI 2012

Maertens et al. BMT 2010

Freifeld et al. CID 2011

Options Summary of Prophylaxis

Antifungal Agent	Advantages	Disadvantages	Recommendation from Guidelines
Posaconazole	Extended espectrum (including Zigomycosis) - Benefits in OS (for AML)	-PO only -interaction	ECIL 3: AI IDSA: AI
Voriconazole	- PO and IV	- drug Interaction	ECIL 3: AI (HSCT)
Fluconazole			I for AML)
LAMB aerosolized	-Few interactions - Local activity	- methods -- No action in yeast	ECIL 3: BI
Micafungin/ Caspo	-Cust	--IV -- low concentration in gut	CI

AML – Evidence level AI
Posaconazole

HSCT – Evidence level BI – CI

Hicheri Y. CMI 2012

Maertens et al. BMT 2010

Freifeld et al. CID 2011

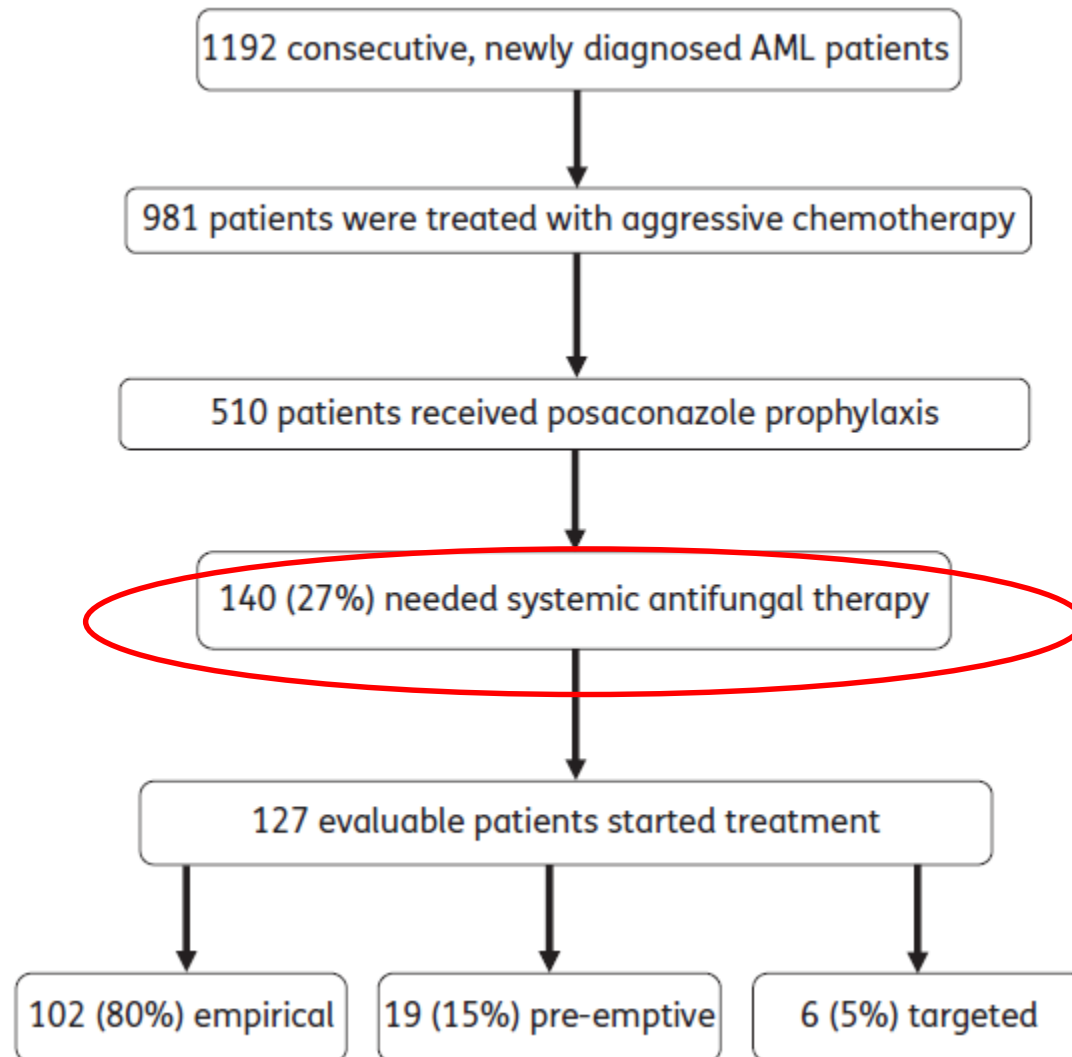
But, we can not prevent all ...

Breakthrough infection in use of prophylaxis

	Posaconazole (AML/MDS)	Voriconazole (HSCT)	Caspofungin (AML)	L-Amb innalted
<i>C krusei</i>	0	} 7	1 (Candida sp.)	
<i>C. glabrata</i>	2			
<i>Aspergillus</i>	2	2 (Pv) + 15 (Pb) + 8 (pres)	5	6
Zigomicetos		4* (flu arm)		
<i>Other Fungi</i>	1	2	1	

Candida Flu R and Molds Breakthrough infections

Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey



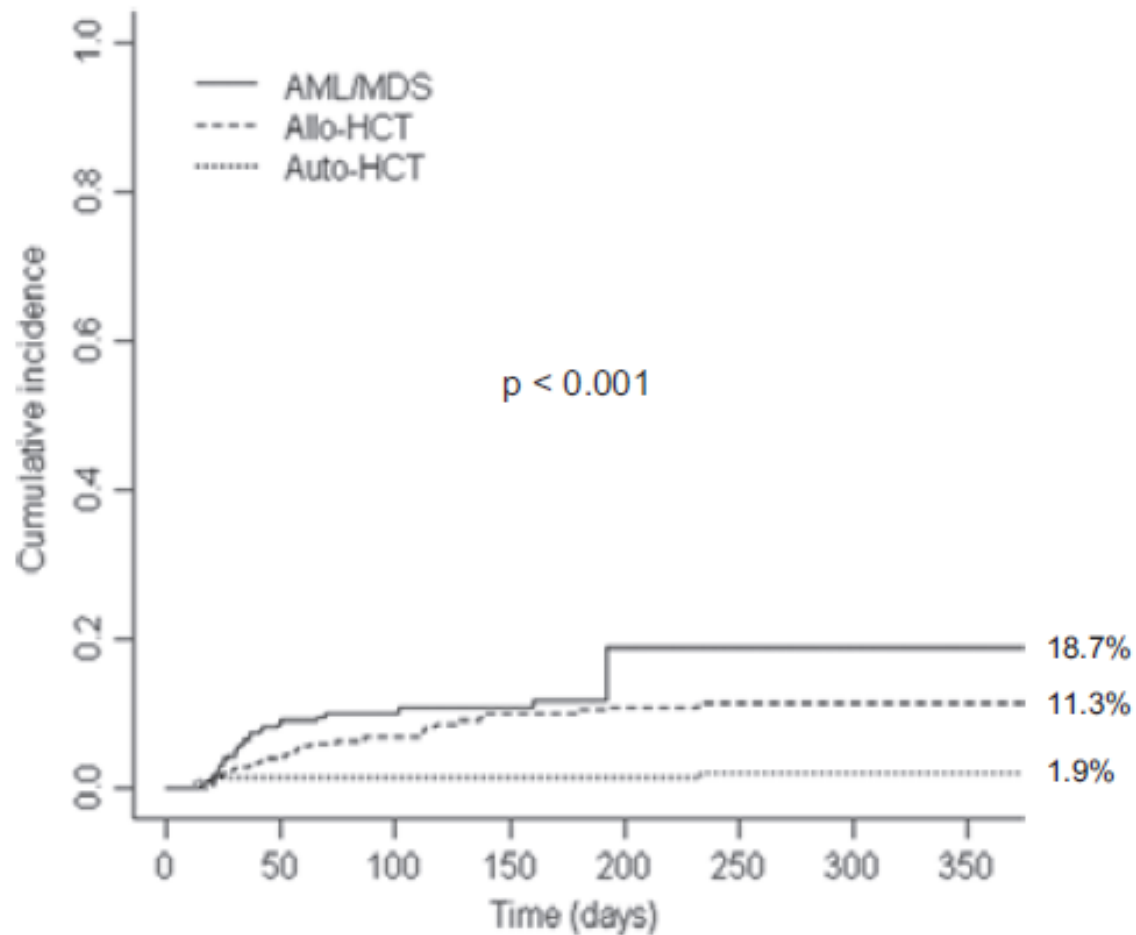
Prophylaxis

- Reduce incidences of IFI
- A special selection of group is necessary
 - AML
 - Allo ? at the time of GVHD? When the risk stops?
- The consumption of antifungal is high

In terms of drug selection...

- Posaconazole .. Will be evaluable next year in Brazil
- Voriconazole ... Only one well designed trial in HCT
 - Erratic concentration
 - Interaction
 - Adverse effects of chronic use.. (skin cancer)
- Equinocandins
 - Low concentration in GUT (Candida escapes)
 - Isolates with high MIC

Risk Assessment



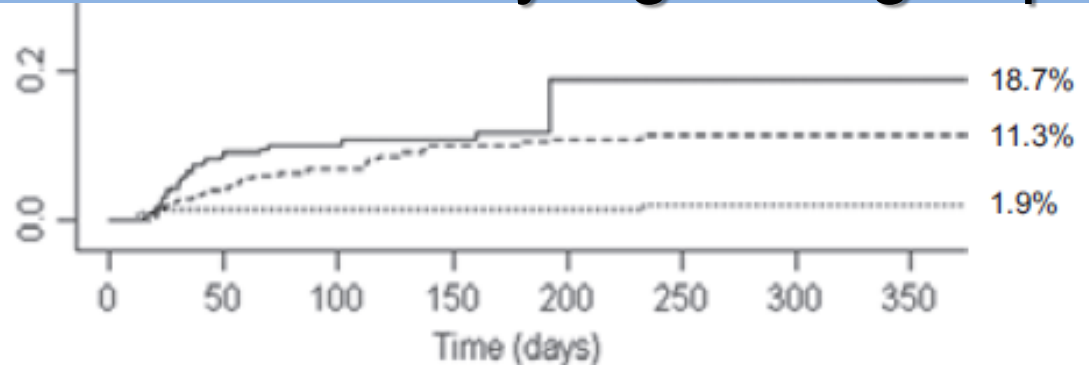
Nucci et al. Clin Micr and Inf 2012;

Risk Assessment



Low risk group – very low incidence of IFI!!

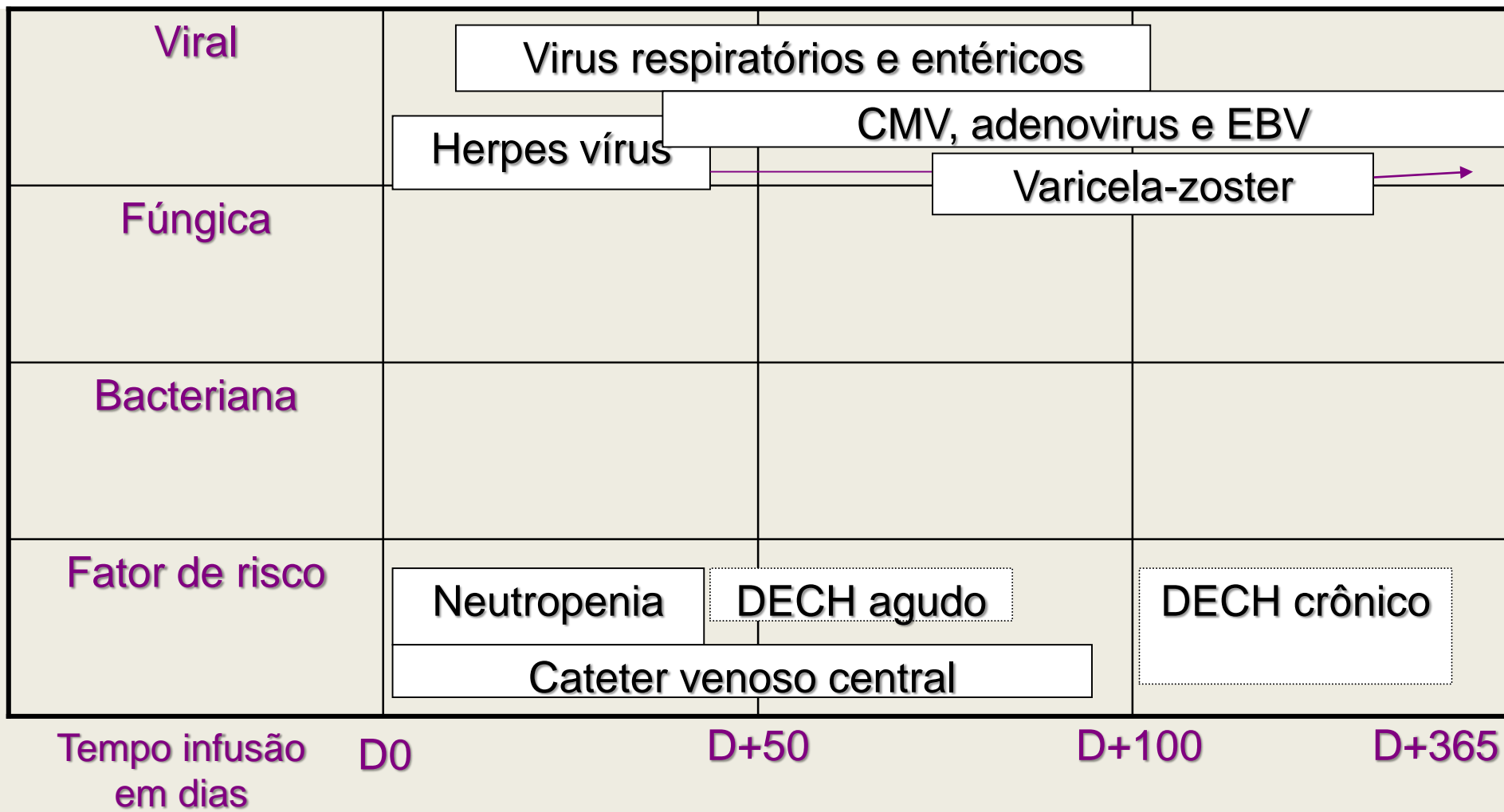
But there is a very high risk group!!



Nucci et al. Clin Microb and Inf 2012;

- **profilaxia antiviral**

Distribuição dos tipos de infecção em relação ao tempo pós TCTH Alogénico



Profilaxia Viral

- Altas taxas de reativação viral (HSV, VZV, CMV) em pacientes hematológicos
 - Durante a neutropenia: Reativação de HSV!!!
-
- ❑ Profilaxia com aciclovir para Leucemia Aguda:
 - ❑ Reduz incidência e severidade da infecção
 - ❑ Não reduz duração de febre
 - ❑ Não reduz uso de antimicrobiano
 - ❑ Não reduz bacteremia

Herpes Simplex em TMO

- ❑ Fase pré-pegã:
 - ❑ quadros graves e até fatais
 - ❑ reativação > 70% dos casos (IgG+).
- ❑ Fase pós-pegã:
 - ❑ reativação >70%: quadros menos graves.

Profilaxia Viral

Pacientes em Risco

LA em IR

Autólogo

Alogênico

HSV	Sem nível de recomendação	Recomendado (condicionamento até D+30)	Recomendado (condicionament o até D+30)
-----	---------------------------	---	---

CMV prophylaxis

- High frequency of reactivation:
 - Allo SCT
 - Fludarabine schedules
 - Monoclonal antibodies??
- Problem:
 - High toxicity related to evaluable drugs
 - Good performance of preemptive approach

Abordagens de CMV em Alo TMO

Transplante



Profilaxia



Reativação CMV



**Terapia
preemptiva**

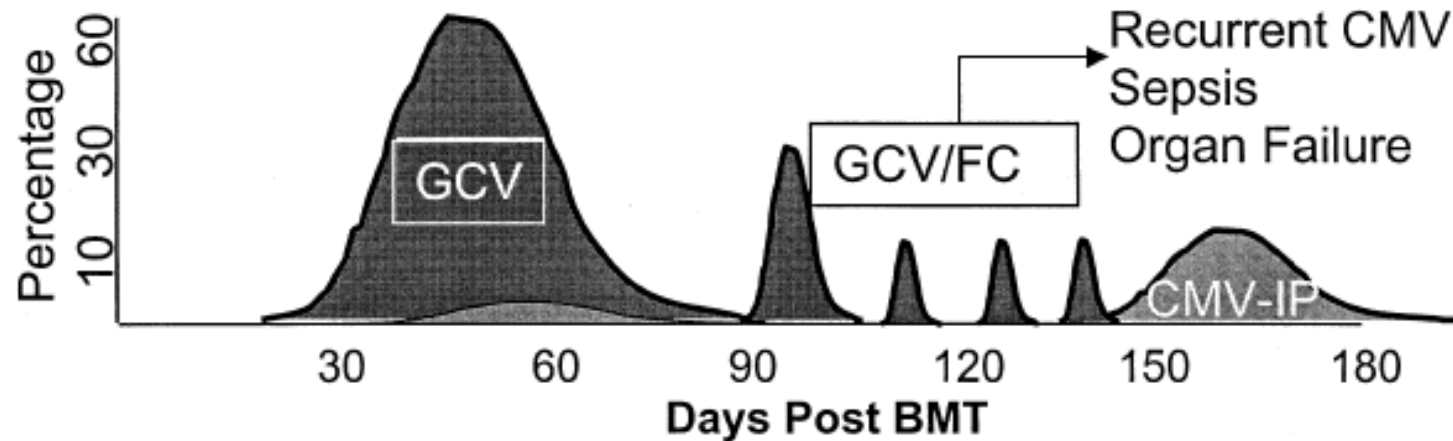


Adoecimento



Tratamento

Reativação de CMV no TCTH- Era Preemptiva



GCV: ganciclovir

CMV-IP: pneumonite intersticial

Estudos randomizados de profilaxia com ganciclovir

Variáveis / Autor	Winston et al	Goodrich et al	Boeckh et al
N	45 P / 40 G	31 P / 33 G	114 PE / 112 G
Duração	-7 a -1 até +120	até d+100	até d+100
Infecção Ativa (reativação)	43% x 20% P=0,008	45% x 3%	79% x 41%
Doença CMV	18% x 9% P=0,20	29% x 0%	14,1% x 2,7%
Impacto sobrevida D+100	Não 64%P x 70%G	Não 81%P x 88%G	Não N pequeno
Outras	Altas taxas de neutropenia	> inc de IFI e bact Doença tardia	> incidencia de IFI Doença tardia

Estudos randomizados de profilaxia com ganciclovir

Variáveis / Autor	Winston et al	Goodrich et al	Boeckh et al
N	45 P / 40 G	31 P / 33 G	114 PE / 112 G
Duração	-7 a -1 até +120	até d+100	até d+100
Infecção Ativa (reativação)	43% x 20% P=0,008	45% x 3%	79% x 41%
Doença CMV	18% x 9% P=0,20	29% x 0%	14,1% x 2,7%
Impacto sobrevida D+100	Não 64%P x 70%G	Não 81%P x 88%G	Não N pequeno
Outras	Altas taxas de neutropenia	> inc de IFI e bact Doença tardia	> incidencia de IFI Doença tardia

Efeitos adversos na hematopoese – fator limitante!!

Preemptivo X Profilático

- Possibilita exposição ao vírus e reconstituição de resposta imune adequada
- Altas taxas de reativação viral após suspensão da profilaxia
- Única droga disponível é ganciclovir IV (estudos randomizados com valganciclovir – mantendo toxicidade hematológica)

New drugs in antiviral scenario...



Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial.

Lancet Infect Dis 2011;
11: 284-92

*Francisco M Marty, Per Ljungman, Genovefa A Papanicolaou, Drew J Winston, Roy F Chemaly, Lynne Strasfeld, Jo-Anne H Young, Tulio Rodriguez, Johan Maertens, Michael Schmitt, Hermann Einsele, Augustin Ferrant, Jeffrey H Lipton, Stephen A Villano, Hongzi Chen, Michael Boeckh, for the Maribavir 1263-300 Clinical Study Group**

ORIGINAL ARTICLE

CMX001 to Prevent Cytomegalovirus Disease in Hematopoietic-Cell Transplantation

Francisco M. Marty, M.D., Drew J. Winston, M.D., Scott D. Rowley, M.D., Estil Vance, M.D., Genovefa A. Papanicolaou, M.D., Kathleen M. Mullane, D.O., Thomas M. Brundage, M.S., Alice T. Robertson, Ph.D., Susan Godkin, R.Ph., Hervé Momméja-Marin, M.D., and Michael Boeckh, M.D.,
for the CMX001-201 Clinical Study Group*

Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation

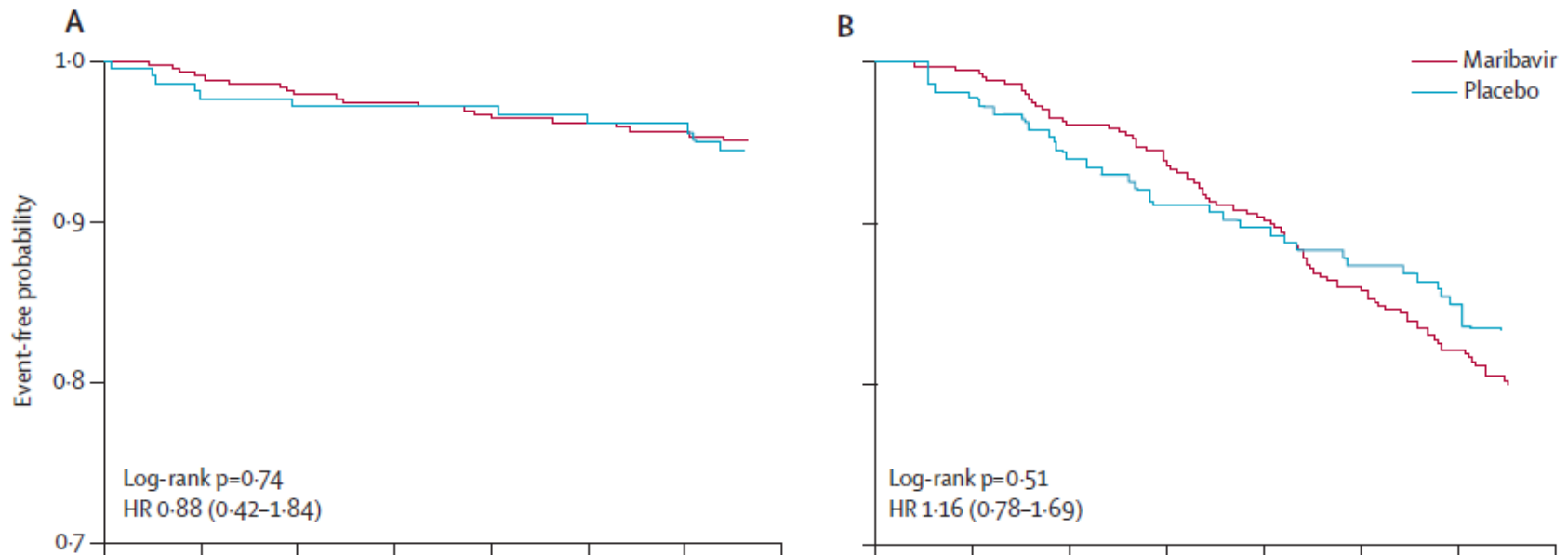
Roy F. Chemaly, M.D., Andrew J. Ullmann, M.D., Susanne Stoelben, M.D., Marie Paule Richard, M.D., Martin Bornhäuser, M.D., Christoph Groth, M.D., Hermann Einsele, M.D., Margarida Silverman, M.D., Kathleen M. Mullane, M.D., Janice Brown, M.D., Horst Nowak, Ph.D., Katrin Kölling, M.Sc., Hans P. Stobernack, D.V.M., Peter Lischka, Ph.D., Holger Zimmermann, Ph.D., Helga Rübsamen-Schaeff, Ph.D., Richard E. Champlin, M.D., and Gerhard Ehninger, M.D., for the AIC246 Study Team*



Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial

Francisco M Marty, Per Ljungman, Genovefa A Papanicolaou, Drew J Winston, Roy F Chemaly, Lynne Strasfeld, Jo-Anne H Young, Tulio Rodriguez, Johan Maertens, Michael Schmitt, Hermann Einsele, Augustin Ferrant, Jeffrey H Lipton, Stephen A Villano, Hongzi Chen, Michael Boeckh, for the Maribavir 1263-300 Clinical Study Group*

- Oral drug, CMV specific
- Tested in prophylaxis after engraftment



Baseline patients with CMV reactivation

CMX001 to Prevent Cytomegalovirus Disease in Hematopoietic-Cell Transplantation

Francisco M. Marty, M.D., Drew J. Winston, M.D., Scott D. Rowley, M.D.,
Estil Vance, M.D., Genovefa A. Papanicolaou, M.D., Kathleen M. Mullane, D.O.,
Thomas M. Brundage, M.S., Alice T. Robertson, Ph.D., Susan Godkin, R.Ph.,
Hervé Momméja-Marin, M.D., and Michael Boeckh, M.D.,
for the CMX001-201 Clinical Study Group*

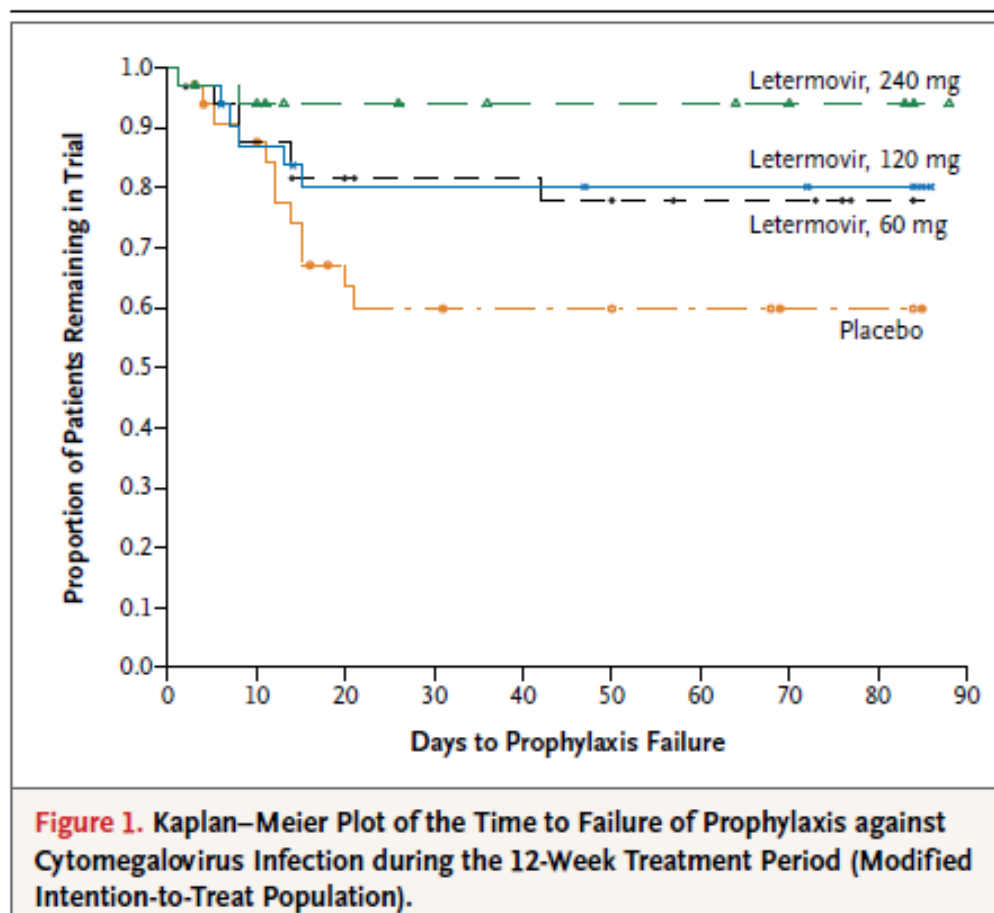
Table 1. Primary Efficacy End Point in the CMX001 Dose Groups as Compared with the Placebo Group (Intention-to-Treat Population).*

Study Group	Patients with CMV Events <i>no./total no. (%)</i>	Absolute Risk Difference <i>percentage points (95% CI)</i>	P Value†
Placebo	22/59 (37)	—	—
CMX001			
40 mg weekly	13/25 (52)	15 (–8 to 38)	0.23
100 mg weekly	6/27 (22)	–15 (–35 to 5)	0.22
200 mg weekly	12/39 (31)	–6 (–26 to 13)	0.53
200 mg twice weekly	7/30 (23)	–14 (–34 to 6)	0.24
100 mg twice weekly	5/50 (10)	–27 (–42 to –12)	0.002

Baseline patients with CMV reactivation

Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation

Roy F. Chemaly, M.D., Andrew J. Ullmann, M.D., Susanne Stoelben, M.D., Marie Paule Richard, M.D., Martin Bornhäuser, M.D., Christoph Groth, M.D., Hermann Einsele, M.D., Margarida Silverman, M.D., Kathleen M. Mullane, M.D., Janice Brown, M.D., Horst Nowak, Ph.D., Katrin Kölling, M.Sc., Hans P. Stobernack, D.V.M., Peter Lischka, Ph.D., Holger Zimmermann, Ph.D., Helga Rübsamen-Schaeff, Ph.D., Richard E. Champlin, M.D., and Gerhard Ehninger, M.D., for the AIC246 Study Team*



Initial data from new anti CMV drugs

	Action	Study	Results	Adverse events
Maribavir	Encapsulation and virus cell egress	Phase 3 on prophylaxis	Negative in efficacy	Few
CMX001	Cidofuvir intracellular	Safety (phase 2)	Positive in prevention (high doses)	Diarrhea – neutropenia
Letermovir	New mechanism (subunit pUL56)	Safety (phase 2)	Positive in prevention (high doses)	Few

Letermovir and Maribavir – CMV specific (HSV prophylaxis necessary)

CMX001 – HSV, VZV and other DNA virus

Conclusões

- Profilaxias têm um grande impacto clínico, porém:
 - Devem ser guiadas pelo risco do paciente
 - Atentar a fase de risco – difícil saber quando parar!!
 - Sempre haverá uma reação:
 - Deve-se identificá-la e maneja-la
 - Avaliar sempre risco-benefício

- Obrigada!

marciagarnica@hucff.ufrj.br