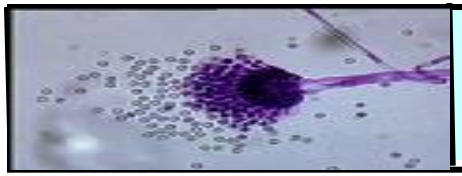
El huésped en la infección por *Aspergillus*

Carolina Garcia-Vidal

Servicio de Enfermedades Infecciosas

Hospital Clínic

Barcelona



VI Reunión científica del GEMICOMED

17 Marzo 2017

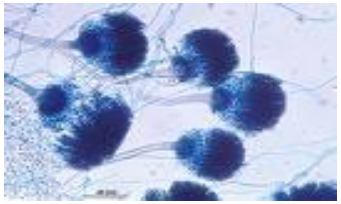
- **Fisiopatogenia de la aspergilosis invasora**
- **Factores de riesgo de la aspergilosis invasora**

- **Fisiopatogenia de la aspergilosis invasora**

- **Factores de riesgo de la aspergilosis invasora**

Video

Defensa del húesped frente a la infección fúngica

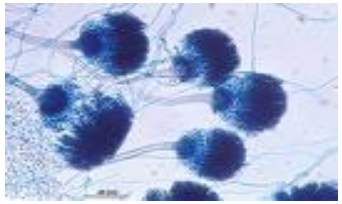


ACTIVACIÓN SISTEMA INMUNE:

- **Sistema inmune INNATO**
- **Sistema inmune ADAPTATIVO**

Garcia-Vidal C, et al
Enf Infecc Microb Clin 2012

Defensa del húesped frente a la infección fúngica



ACTIVACIÓN SISTEMA INMUNE:

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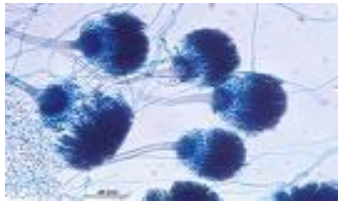
PROTECCIÓN

INFLAMACIÓN

Garcia-Vidal C, et al
Enf Infecc Microb Clin 2012

Defensa del húesped frente a la infección fúngica



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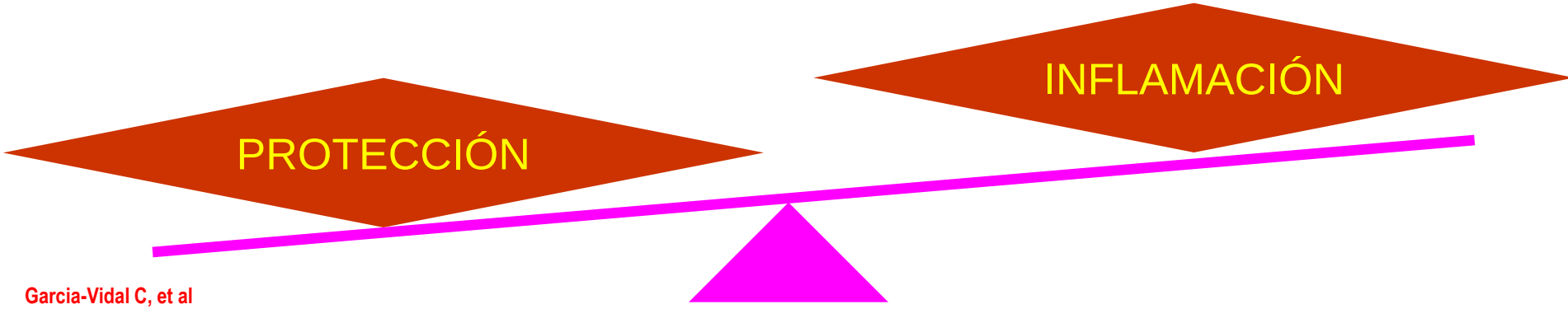
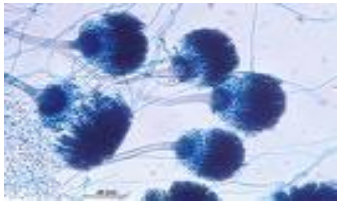


Garcia-Vidal C, et al
Enf Infecc Microb Clin 2012

Defensa del húesped frente a la infección fúngica



ACTIVACIÓN SISTEMA INMUNE:

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- **Sistema inmune ADAPTATIVO**

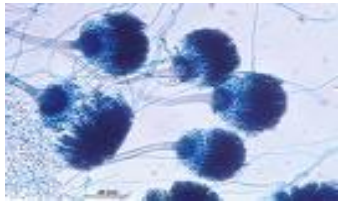
PROTECCIÓN

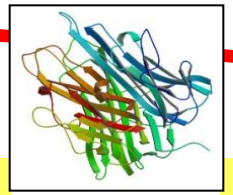
INFLAMACIÓN

Garcia-Vidal C, et al
Enf Infecc Microb Clin 2012

Defensa del húesped frente a la infección fúngica

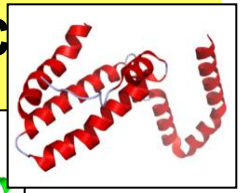
Receptores del sistema inmune innato



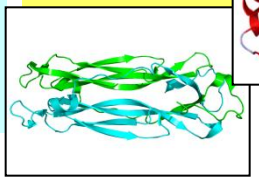


TNF-alpha

Respuesta citoc



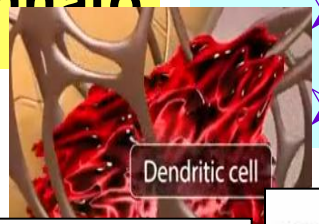
IL-10

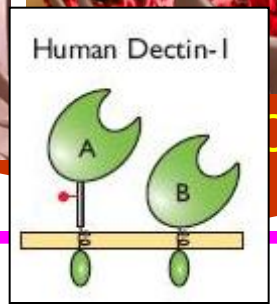


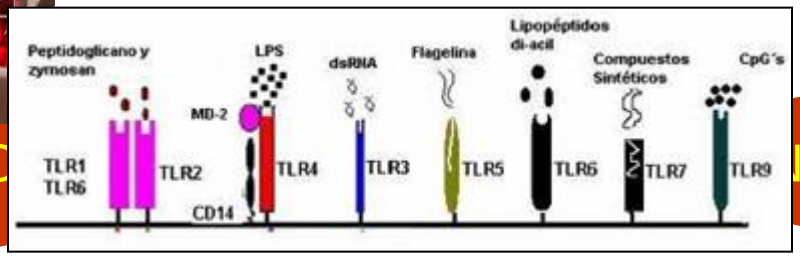
IL-17

ACTIVACIÓN SISTEMA INMUNE:

- Sistema inmune INNATO
- Sistema inmune ADAPTATIVO





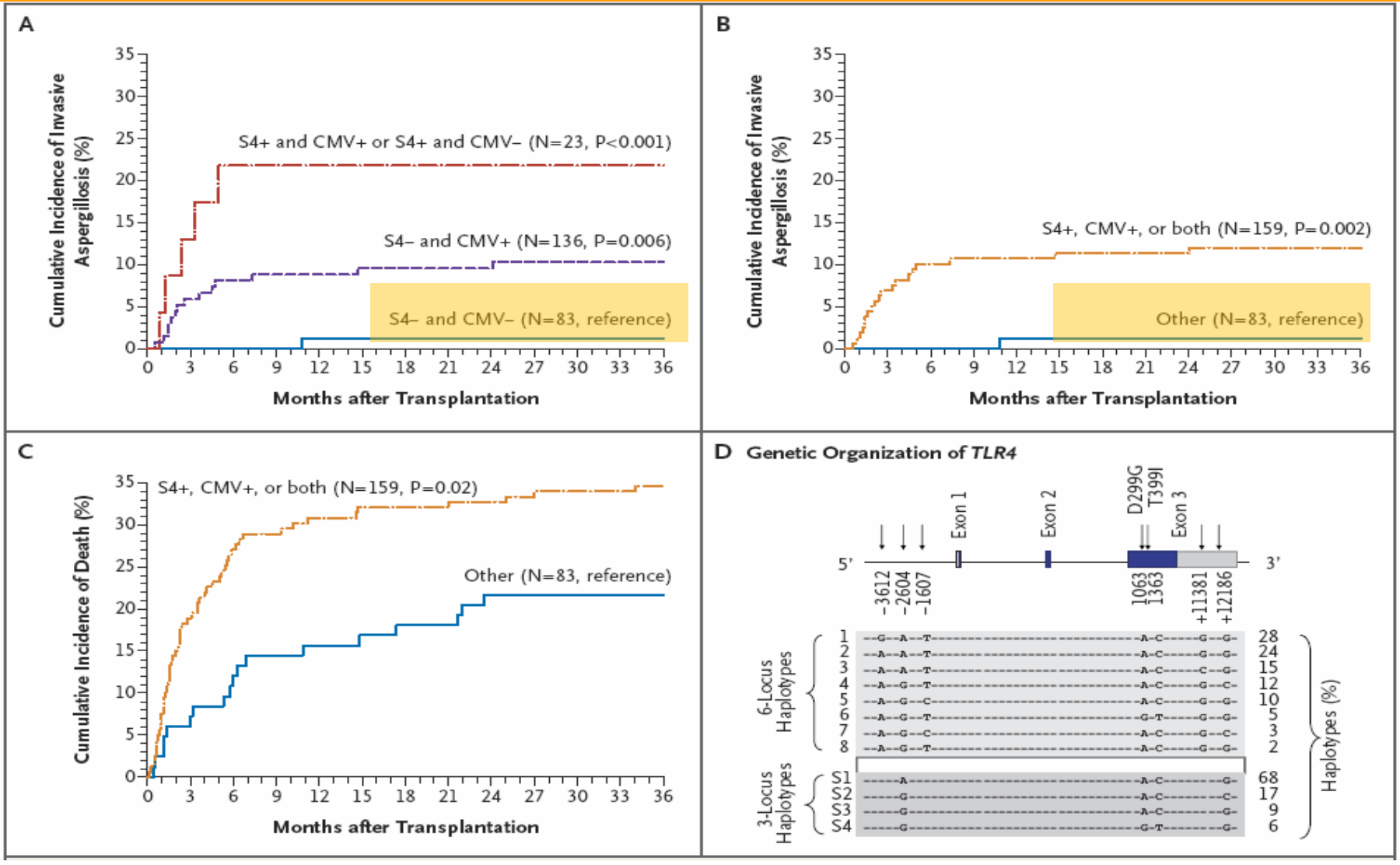


IFLAMACIÓN

Garcia-Vidal C, et al
Enf Infecc Microb Clin 2012

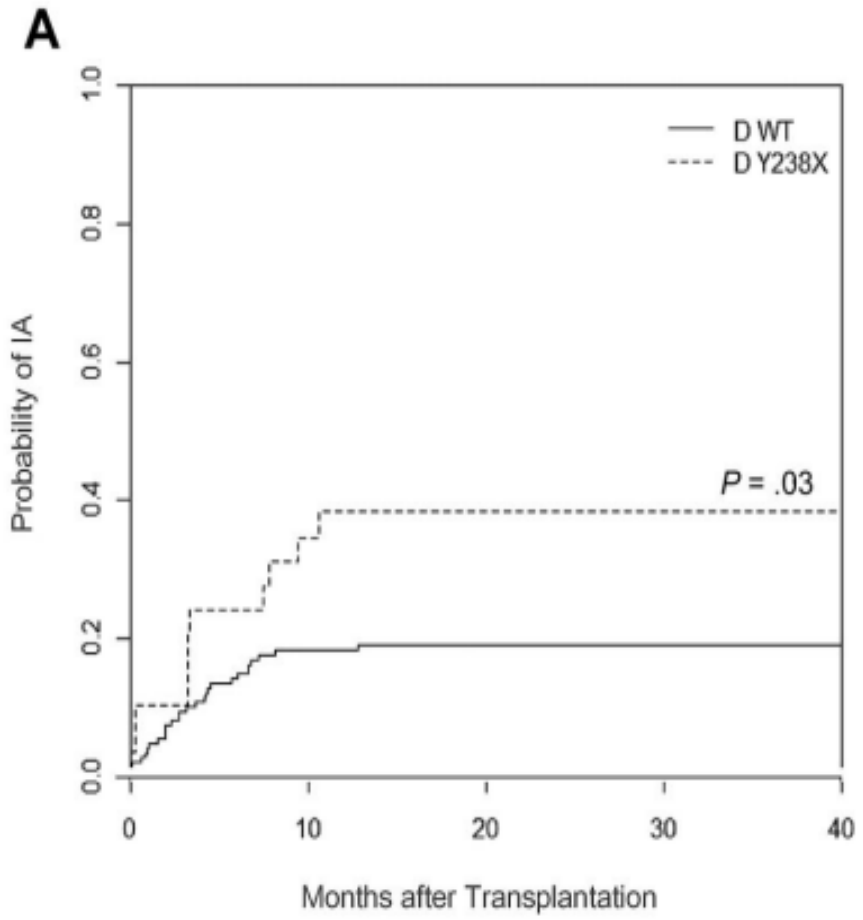
Boychud PY et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation

New england J Med 2008; 359: 1766-77

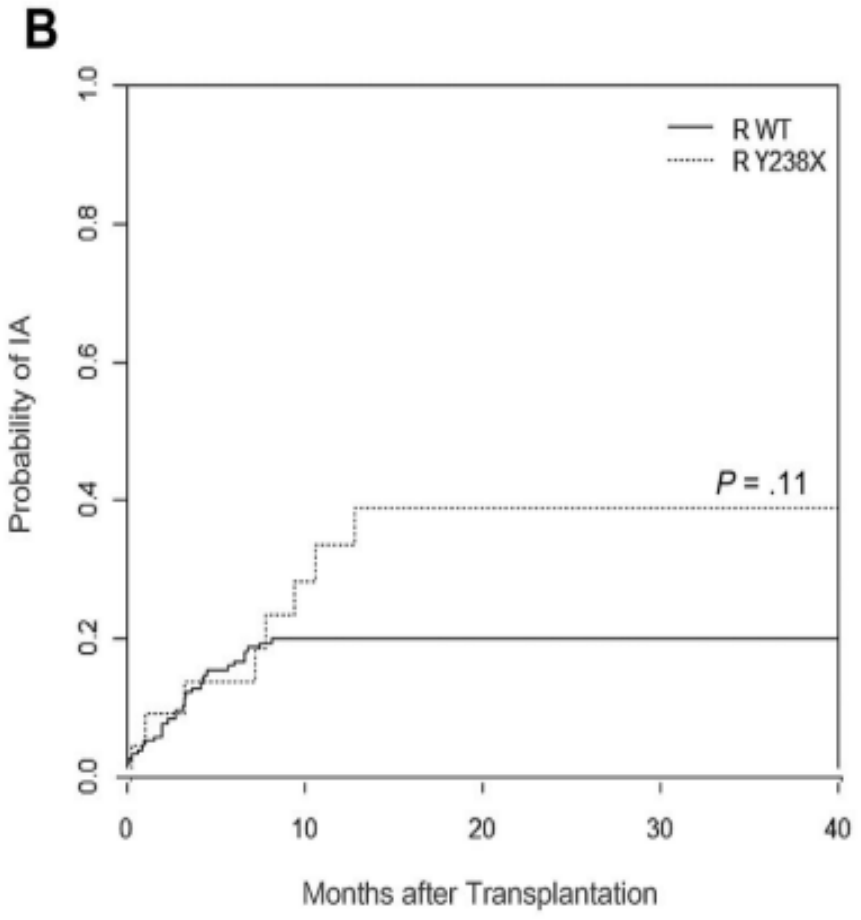


Cunha C et al. Dectin 1 Y238X polymorphism associates with susceptibility to invasuve aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity

Blood 2010; 116: 5394-5402



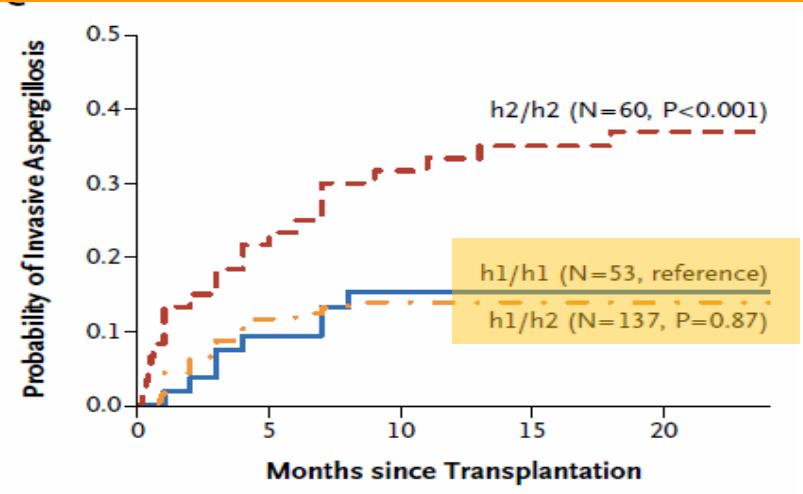
Donor genotype



Recipient genotype

Cunha C et al. Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell transplantation

New england J Med 2014; 370: 421-32



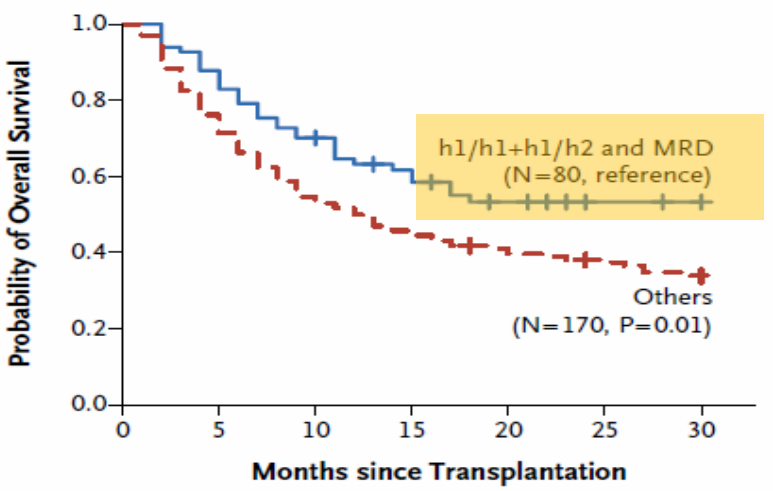


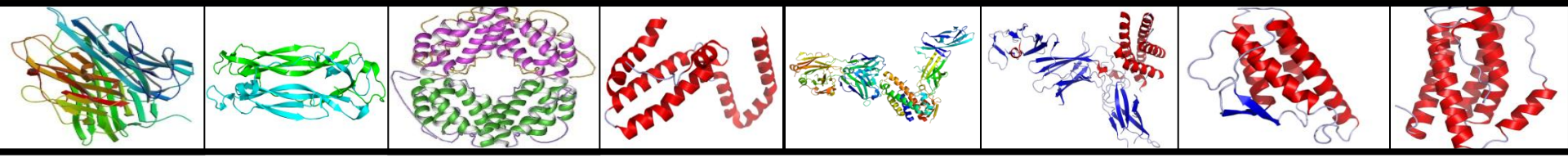
Table 2. Multivariate Analysis of the Association of Donor *PTX3* Variants with the Risk of Invasive Aspergillosis among Transplant Recipients in the Discovery and Confirmation Studies.*

Donor *PTX3* Variant	Discovery Study (N=268)		Confirmation Study (N=330)	
	Adjusted Hazard Ratio (95% CI)†	P Value	Adjusted Odds Ratio (95% CI)‡	P Value
+281A/G SNP, GG genotype	2.92 (1.69–5.05)	<0.001	2.14 (1.20–3.80)	0.01
+734A/C SNP, AA genotype	2.62 (1.52–4.54)	<0.001	1.92 (0.91–3.04)	0.07
Haplotype h2/h2	3.08 (1.47–6.44)	0.003	2.78 (1.22–8.93)	0.03

*HLA-maching, total body irradiation, GVHD, antifungal prophilaxis

Garcia-Vidal C et al. Host response to invasive aspergillosis in HSTC recipients and AL patients

Unpublised data



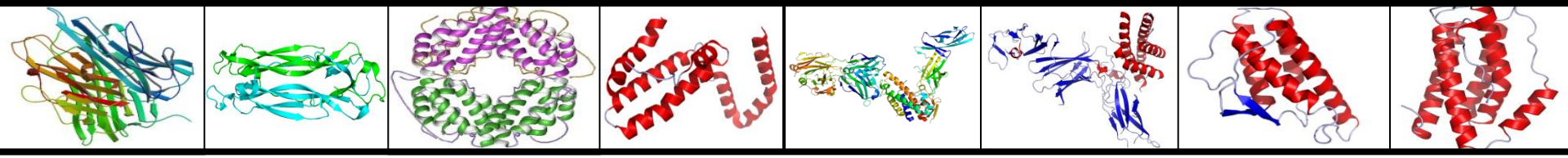
TNF-alpha | IL-17 | INF gamma | IL-10 | IL-23 | IL-12 | IL-4 | IL-6

- **Estudio prospectivo comparativo de 36 pacientes con LA y/o TPH diagnósticados de AI y 36 controles de igual edad, EF de base, tratamiento y día del tto**

Características	
Edad	55.54 (12)
LA/TPH	63% / 37%
Neutropenia	55 (70.5%)
AI probadas/probables	15.5%/84.5%

Garcia-Vidal C et al. Host response to invasive aspergillosis in HSTC recipients and AL patients

Unpublised data



TNF-alpha | IL-17 | INF gamma | IL-10 | IL-23 | IL-12 | IL-4 | IL-6

- **Resultados complicados de interpretar**

IL-17

- **Relación con el diagnóstico y el pronóstico de la enfermedad**

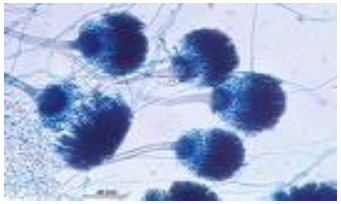
IL-10

- **Relación con el diagnóstico y el pronóstico de la enfermedad**

IL-6

Fisiopatología molecular de la infección fúngica invasora

Citoquinas proinflamatorias



Citoquinas antiinflamatorias

TNF-alpha, INF-gamma
IL-12, IL-15

Th 1/Th17

PROTECCIÓN FRENTE A LA INFECCIÓN FÚNGICA

Sistema Inmune innato

IL-10, IL-4

Th 2/Treg

PROGRESIÓN DE LA INFECCIÓN FÚNGICA

Garcia-Vidal C, et al
Curr Opin Infect Dis 2014

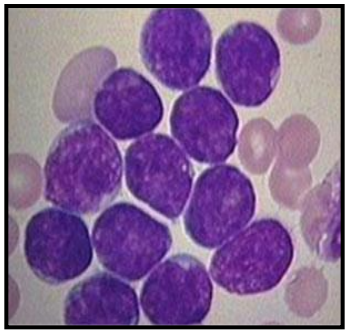
- Fisiopatogenia de la aspergilosis invasora

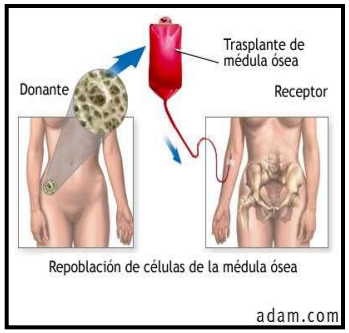
- **Factores de riesgo de la aspergilosis invasora**

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

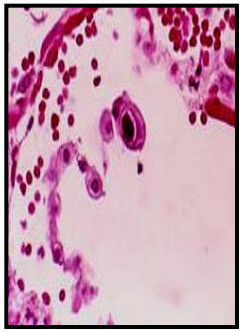
Clin Infect Dis 2008; 47 1041-50

INFECCIÓN PRECOZ





INFECCIÓN TARDÍA



- > 40 años
- Enfermedades de base
- Características del transplante
- Citopenias
- Virus respiratorios
- Enfermedad por CMV
- Enfermedad Injerto-húesped
- Corticoesteroides
- Nº de transfusiones sanguíneas

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

Clin Infect Dis 2008; 47 1041-50

> 40 años

Enfermedades de base

Características del transplante

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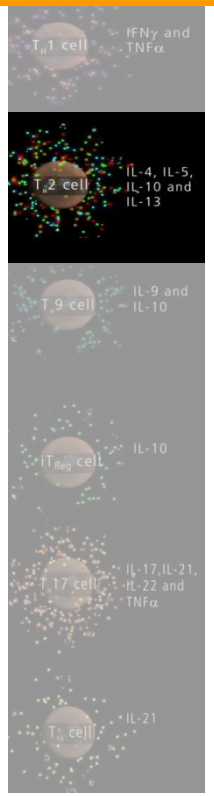
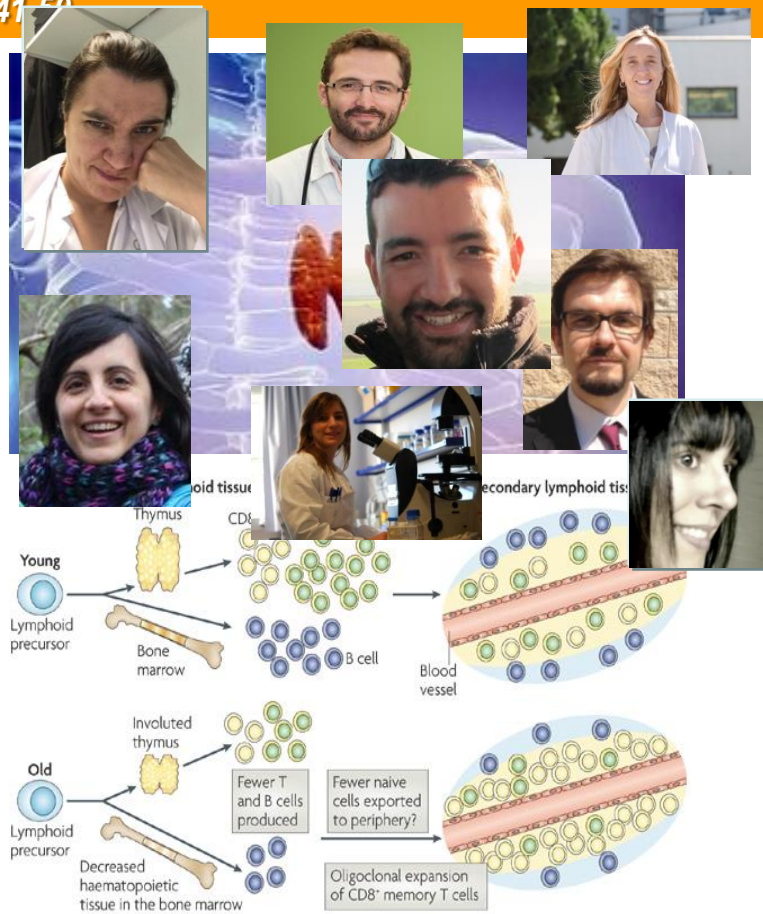
Enfermedad por CMV

Enfermedad Injerto-húesped

Corticoesteroides

Nº de transfusiones sanguíneas





Nature Reviews | Immunology

declines [10]. These changes start early in life and are almost complete by the age of 40–50 years [11]. As a con-

Dorshkind K et al, Nature reviews immunology 2009

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

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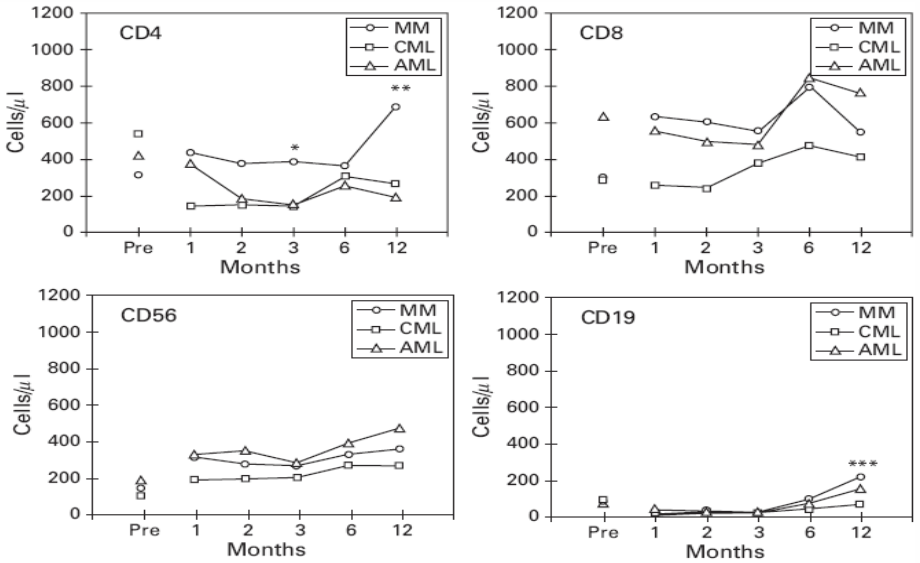

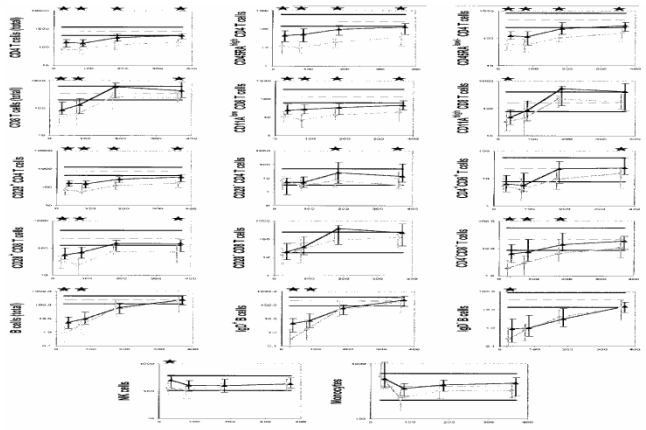

Rondelli R, Bone Marrow Transplantation 2000

Storek J, Blood 2001

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

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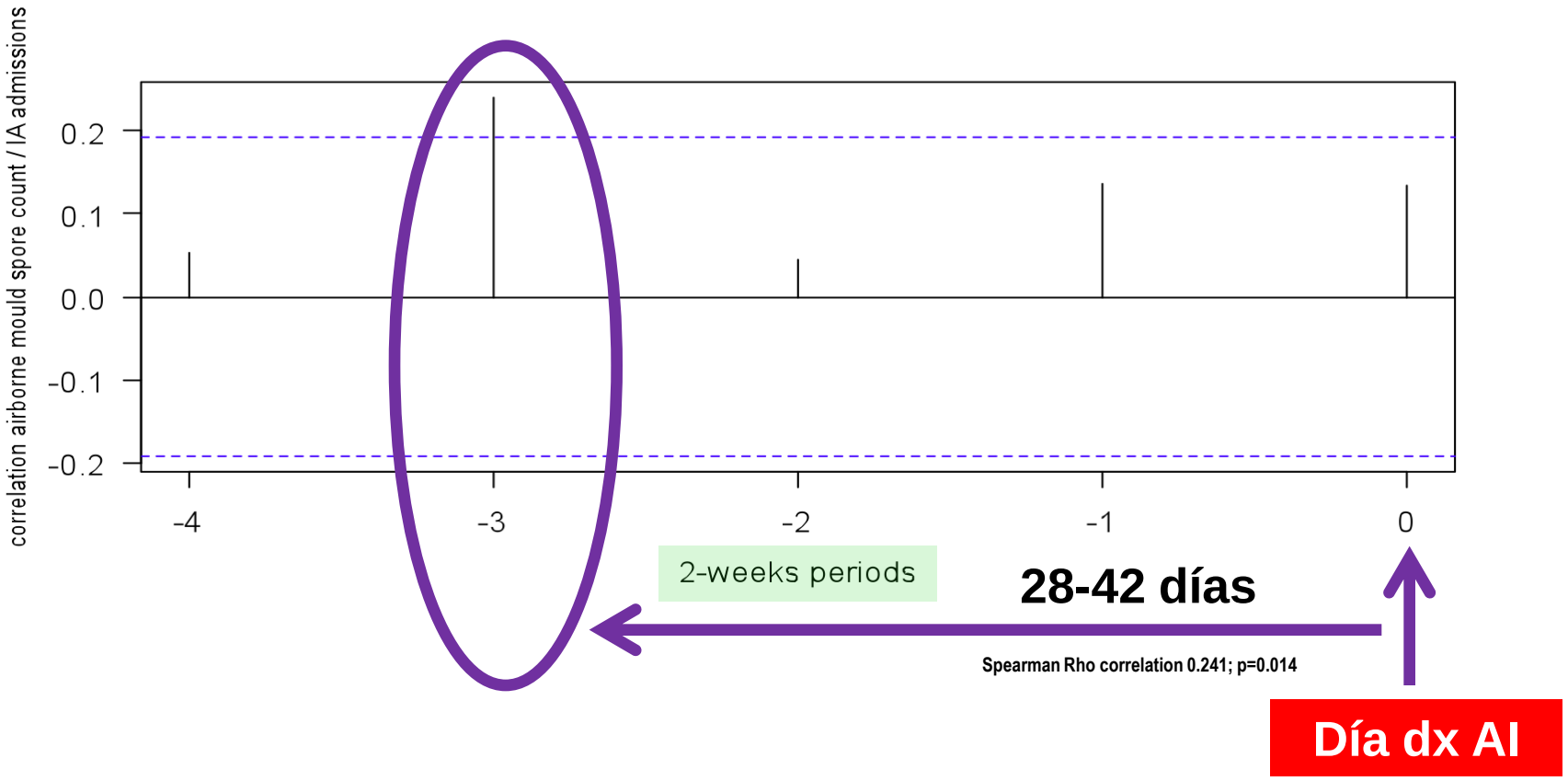
Corticoesteroides

Nº de transfusiones sanguíneas

Garcia-Vidal C, et al. Environmental variables associated with an increased risk of invasive aspergillosis

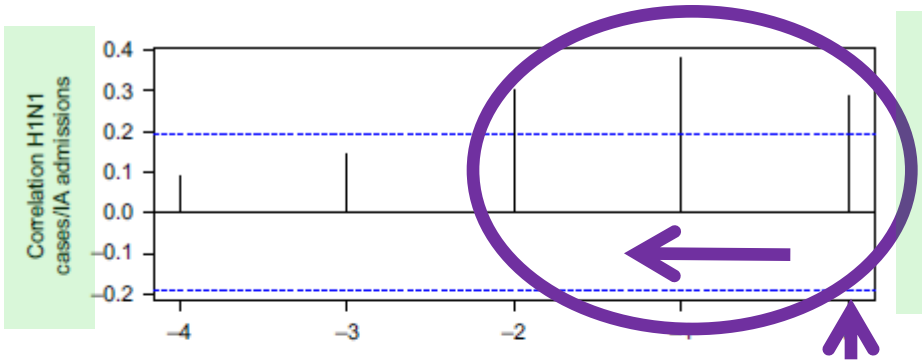
Clin Microbiol Infect 2014; 20:939-945



- **En picos de esporas ambientales el diagnóstico de AI aumentaba 6 veces tras este período de tiempo**

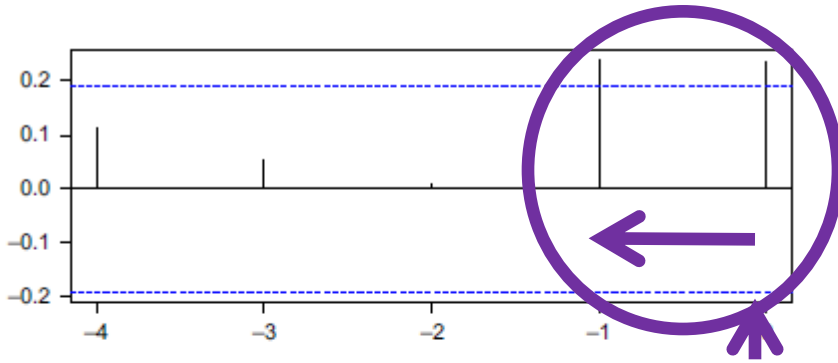
Garcia-Vidal C, et al. Environmental variables associated with an increased risk of invasive aspergillosis

Clin Microbiol Infect 2014; 20:939-945



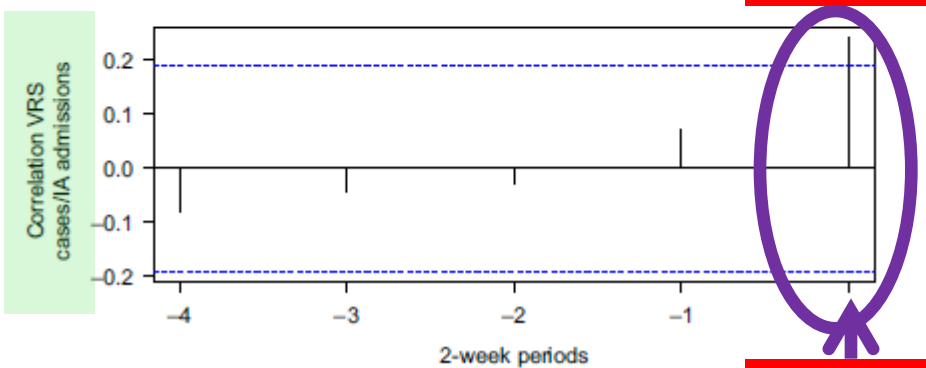
7-28 días

Día dx AI



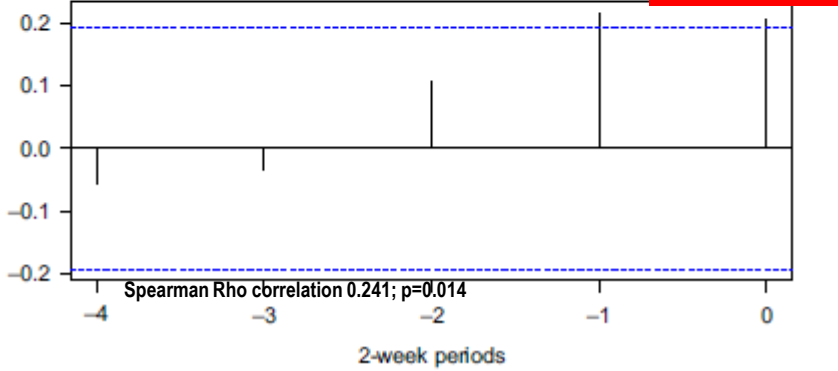
7-14 días

Día dx AI



7 días

Día dx AI



- **En picos de esporas ambientales el diagnóstico de AI aumentaba hasta 55 veces más tras este período de tiempo**

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

Clin Infect Dis 2008; 47 1041-50

> 40 años

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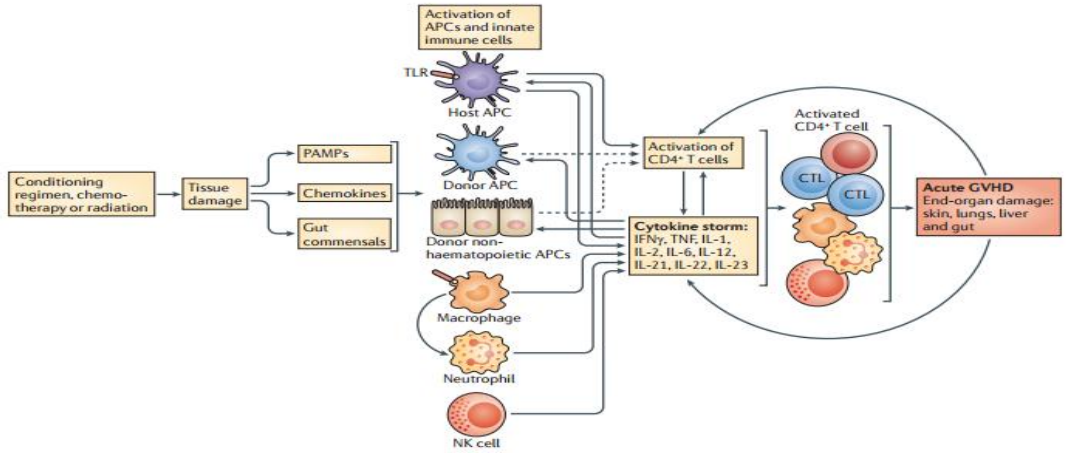
Enfermedad por CMV

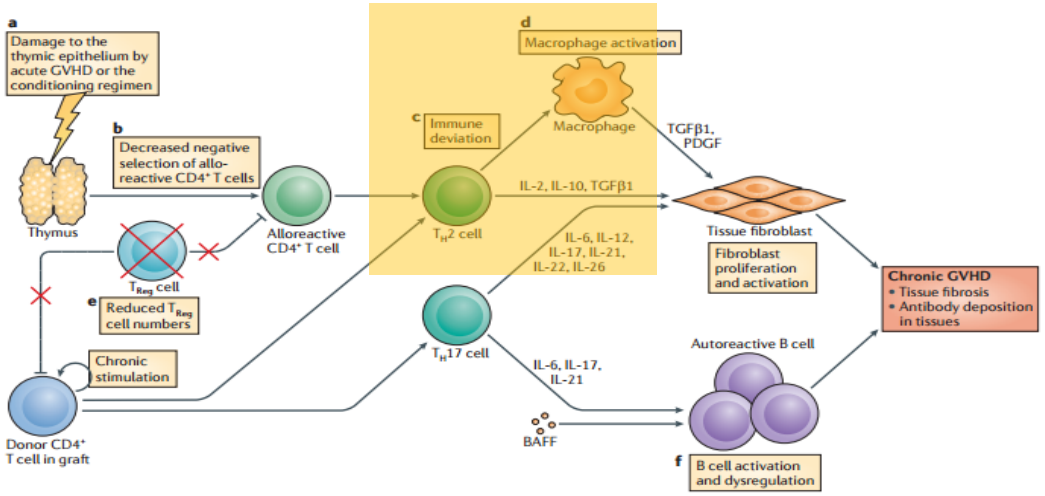
Enfermedad Injerto-húesped

Corticoesteroides

Nº de transfusiones sanguíneas



The overal acute GVHD cascade



Crucial factors in the development of chronic GVHD

Blazar B, Nature rev immunol 2012

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

Clin Infect Dis 2008; 47 1041-50

> 40 años

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Virus respiratorios

Enfermedad por CMV

Enfermedad Injerto-húesped

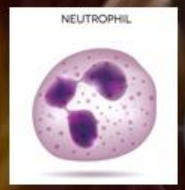
Corticoesteroides

Nº de transfusiones sanguíneas

Lionakis M, et al. Glucocorticoids and invasive fungal infections

The Lancet 2003 362: 1828–1838

Impaired phagocytosis, degranulation and oxidative burst
Impaired formation of nitric oxide
Inhibition of apoptosis



Impaired phagocitosis and oxidative killing
Impaired maduration of macrophages
Inhibition of pro-inflammatory citokine productin

Lymphopenia
Decreased proliferation and migration of lymphocytes
Decreased citokine production
Decreased Th1 and increased Th2 cytokine production

Decreased counts of alveolar dendritic cells
Impaired antigen-presenting capacity of dendritic cells
Decreased cell-killing capacity

Ng TT, et al. Hydrocortisone-enhanced growth of Aspergillus spp: implications for pathogenesis

Microbiology 1994 140: 2475–2479

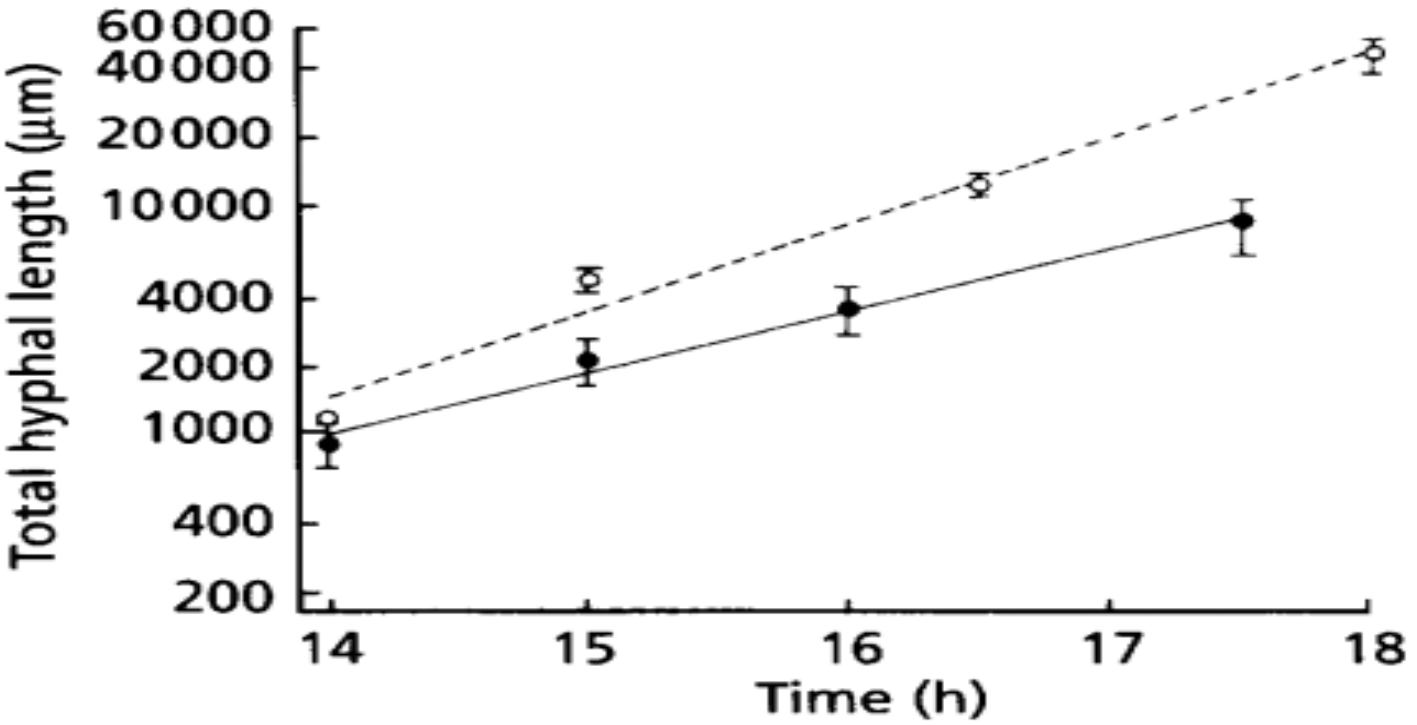


Fig. 1. Increase in total hyphal length (µm) with time (h) in germlings of isolate AF-6 grown at 37 °C with (○) or without (●) 10^{-6} M hydrocortisone. At each time point the mean ± SEM of five replicate germlings was plotted.

Garcia-Vidal C et al. Epidemiology of invasive mold infections in allogenic SCT recipients:biological risk factors for infection according to time after transplantation

Clin Infect Dis 2008; 47 1041-50

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Corticoesteroides

Nº de transfusiones sanguíneas

- Decreased Th1 and increased Th2 cytokine production in vitro
- Reduced responses in mixed lymphocyte culture
- Decreased proliferative response to mitogens or soluble antigens in vitro, thus causing impaired delayed-type hypersensitivity skin responses
- Increased CD8 T cells or suppressor function in vitro
- Decreased natural killer cells and activity in vitro
- Decreased CD4 helper T cells
- Decreased monocyte/macrophage function in vitro and in vivo
- Enhanced production of anti-idiotypic antibodies suppressive of mixed lymphocyte response in vitro
- Decreased cell-mediated cytotoxicity against target cells in vitro
- Humoral alloimmunization to cell-associated and soluble antigens
- Increased T-regulatory cells and function

Iron Overload

In addition to patients with hemoglobinopathies (eg, thalassemia, sickle cell disease), those with

Dasararaju R, Cancer control 2015

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