



# LE INFEZIONI DA NON DIMENTICARE NEL PAZIENTE TRAPIANTATO

## TOXOPLASMA GONDII

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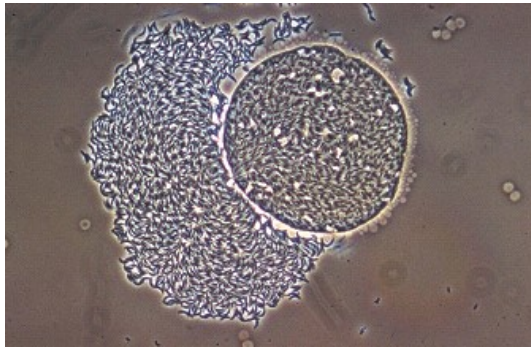
XLVI Congresso Nazionale AMCLI  
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Palacongressi di Rimini

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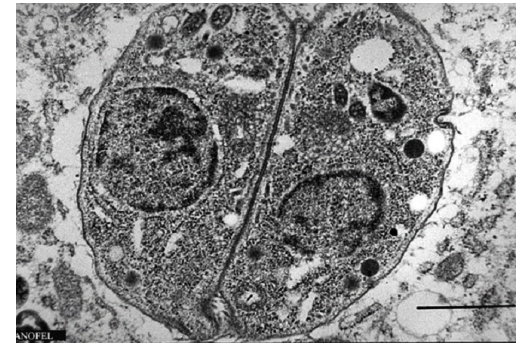
# TOXOPLASMOSIS IN IMMUNOCOMPROMISED PATIENT

Immunological impairment

- HIV infection
- Immunosuppressive therapies (transplant, biotherapy anti TNF)
- Haematological malignancies



Interconversion



# SYMPTOMS

- Neurotoxoplasmosis 60-80% (hemiparesis, dementia, focal or major motor seizure, lethargy, incoordination associated with fever )
- Pneumonitis (HSCT, AIDS)
- Retinichoroiditis
- Myocarditis
- Multiorgan failure

# AT RISK PATIENTS

<b>Not immune</b>	<b>Infection risk</b>
	<ul style="list-style-type: none"><li>•SOT R-/D+</li><li>•HIV (CD4&lt;100/mcl)</li><li>•BMT</li></ul>
<b>Immune</b>	<b>Reactivation risk</b>
	<ul style="list-style-type: none"><li>•HIV (CD4 &lt;50/mcl)</li><li>•BMT</li><li>•SOT</li></ul>

Transplant	Parasite
Heart	<i>Strongiloides stercolaris</i> ; <i>T. gondii</i> , <i>T. cruzi</i>
Lung	<i>T. gondii</i>
Liver	<i>Schistosoma</i> ; <i>T. cruzi</i> , <i>T. gondii</i>
Kidney	<i>Schistosoma</i> , <i>S. stercolaris</i> , <i>Tenia</i> , <i>t. cruzi</i> , <i>T. gondii</i>
Bone marrow	<i>Schistosoma</i> , <i>S. stercolaris</i> , <i>T. gondii</i>

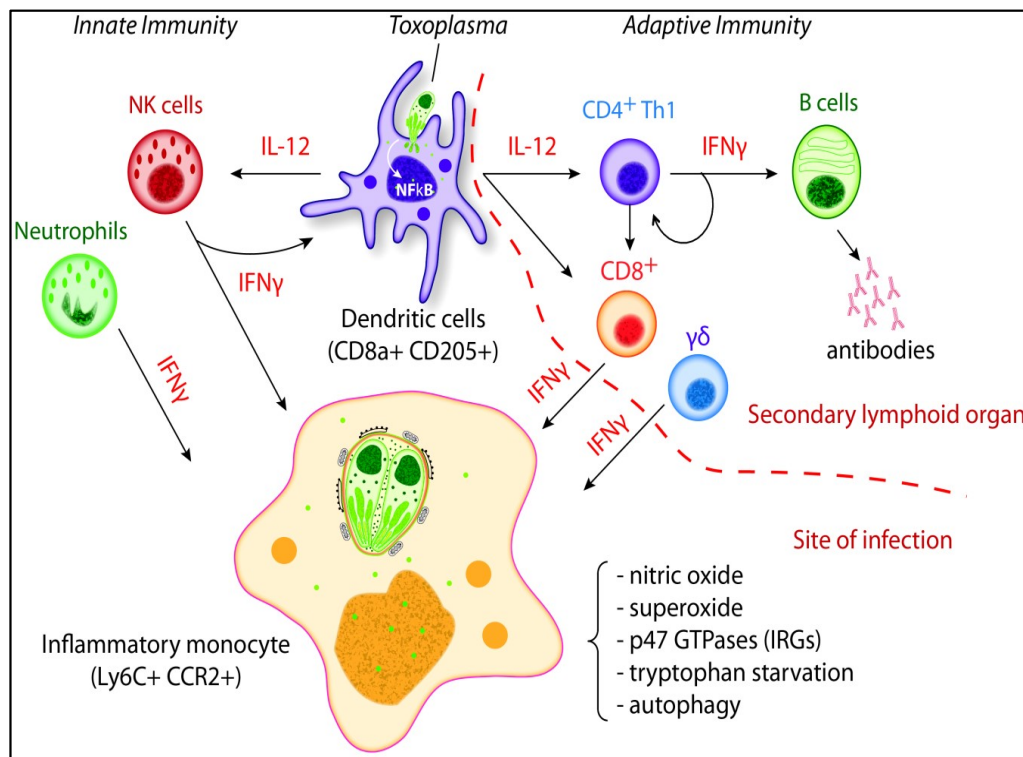
Walker e Zunt, CID; 2005

# RISK FACTORS

*Toxoplasma* infection (PCR+, fever+/-):

- inadequate or no prophylaxis with TMP-SMZ
- allogeneic transplant
- delayed immune reconstitution

# IMMUNE RESPONSE TO *T. GONDII*



**IFN- $\gamma$  è is the major lymphokine involved in the resistance to *T. gondii***

L'infezione da *T. gondii* stimola una risposta umorale mediante la produzione di anticorpi



# DIAGNOSIS

- Onset during the first 6-8 months after transplant
- Aspecific clinical sign
- Imaging techniques not diagnostic
- Serology useful to identify at risk patients
- PCR on peripheral blood and CSF
- IGRA

***Anti *Toxoplasma gondii* antibodies in  
1584 solid organ donors and recipients in  
Pavia (1997-2007)***

540 Donors 285 (53%) seropositive

8 (1,5%) IgM positive

1084 Recipients 611 (56%) seropositive

# SOLID ORGAN TRANSPLANT

D  
IgG + / -  
↓  
R  
IgG +

No prophylaxis

D  
IgG +  
↓  
R  
IgG -

prophylaxis TMP-SMX  
post transplant

Munoz P. 2003  
Montoya J.G. 2001

**Without prophylaxis**  
**D+/R-**

Transplant	Toxoplasmosis
heart	>50 %
liver	20 %
kidney	< 1 %

*J. Infectious Diseases 2004*

**Prophylaxis TMP-SMX**  
**D+/R-**

Transplant	Toxoplasmosis
heart	5 %

*Baden Transplantation 2003*

# SERONEGATIVE RECIPIENTS

Mean age 43.7 ANNI

FOLLOW-UP 2 months -17 years

## NEGATIVE DONOR 79

Follow up 2 – 175 months

59 males – 20 females

53 Tx heart, 25 Tx lung, 1 Tx heart-lung

**Hygienic alimentary prophylaxis**

**6 SEROCONVERSIONS**

5 heart

1 lung

## POSITIVE DONOR 82

Follow up 2 – 198 months

62 males – 20 females

66 heart, 15 lung, 1 heart-lung

**PIRIMETAMINE–**

**SULFAMETOPIRAZINE  
(METAKELFIN®) 30 DAYS**

**Hygienic alimentary prophylaxis**

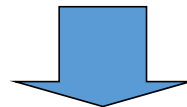
**12 SEROCONVERSION**

heart

Negative recipients			
	R- / D+	R- / D-	Tot.
Seroconversion	12	6	18
NoSeroconversion	70	73	143
Tot	82	79	161

Yates corrected chi-square  $P = 0,16$

No statistically significant difference in incidence of toxoplasmosis  
between R- / D- and R-/ D+



**Efficacy of chemioprophylaxis**

Sarchi E. et al New Microbiol 2007

## Reactivation

DATA	IgG	IgM	IgG AVIDITY
08/04/2003	118	NEG	
13/05/2003	139	NEG	0.725
Transplant 27/05/2003			
27/01/2004	965	NEG	0.727

**IgG WB**

**IgM WB**



***Anti-Toxoplasma gondii* antibodies in 479  
hematopoietic stem cells transplanted patients  
Pavia (2011-2015)**

292 adult recipients 111 (38%) seropositive

187 paediatric recipients 54 (28,8%) seropositive

## Diapositiva 15

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- P1**      nei pediaTRICI LA PREVALENZA è SUPERIORE ALL'ATTESO PER LA'ALTO NUMERO DI PAZIENTI PROVENIENTI DALL'EST EUROPA.  
Policlinico; 07/11/2017



“BMT recipients are at high risk of developing toxoplasmosis with up to 70% of recipients developing infection after mismatched allogeneic BMT”

Gonzales et al, Transpl. Infect. Dis.; 2000

“Of 3,803 bone marrow allograft recipients evaluated in Seattle 15% were seropositives for *T. gondii* and 2% of these seropositive patients later developed toxoplasmosis”

Slavin et al, Bone Marrow Transplants; 1994

## *TOXOPLASMA GONDII* INFECTION IN ALLOGENEIC BMT

	IgG	IgM	PCR
T0	14	neg	pos
1 month	7	neg	pos
2 months	4	neg	neg
9 months	5	neg	neg
12 months	7	neg	neg

## *TOXOPLASMA GONDII* INFECTION IN ALLOGENEIC BMT

	IgG	IgM	WB IgG/IgM	IFN- gamma	PCR
Transplant	neg	neg	nd		nd
1 month	neg	neg	nd		nd
2 months	14	neg	neg	neg	neg
12months	neg	neg	neg		nd

## **Anti-*Toxoplasma gondii* antibodies in 187 hematopoietic stem cells transplanted patients Pavia (2011-2015)**

	D-	D+	D? (MUD)
R+	33 (21.7%)	12 (7.9%)	35 (18.7%)
R-	84 (55.2%)	23 (15.1%)	
TOT	152 (81.3%)		
4 REINFECTION	3 D-/R+	1 D?/R+	(2.1%)

## Diapositiva 19

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- P2**      nei pediaTRICI LA PREVALENZA è SUPERIORE ALL'ATTESO PER LA'ALTO NUMERO DI PAZIENTI PROVENIENTI DALL'EST EUROPA.  
Policlinico; 07/11/2017

D  
IgG -



R  
IgG +

## *TOXOPLASMA GONDII* INFECTION IN ALLOGENEIC BMT (D<sup>+</sup>/R<sup>+</sup>)

II	IgG	IgM	PCR	
Transplant Peripheral blood	29	Neg	nd	
2 months Peripheral blood	38	neg	Pos Pheripheral blood CSF	
2 months biopsy			POS	DIED

## TOXOPLASMA GONDII INFECTION IN ALLOGENEIC BMT (D-/R+)

BA	IgG	IgM	PCR	
Transplant Periferal blood	134	neg	nd	
6 months Peripheral blood	29	neg	nd	
9 months Peripheral blood	25	neg	Pos peripheral blood CSF	
10 months Pheriferal blood	30	neg	Neg	DIED



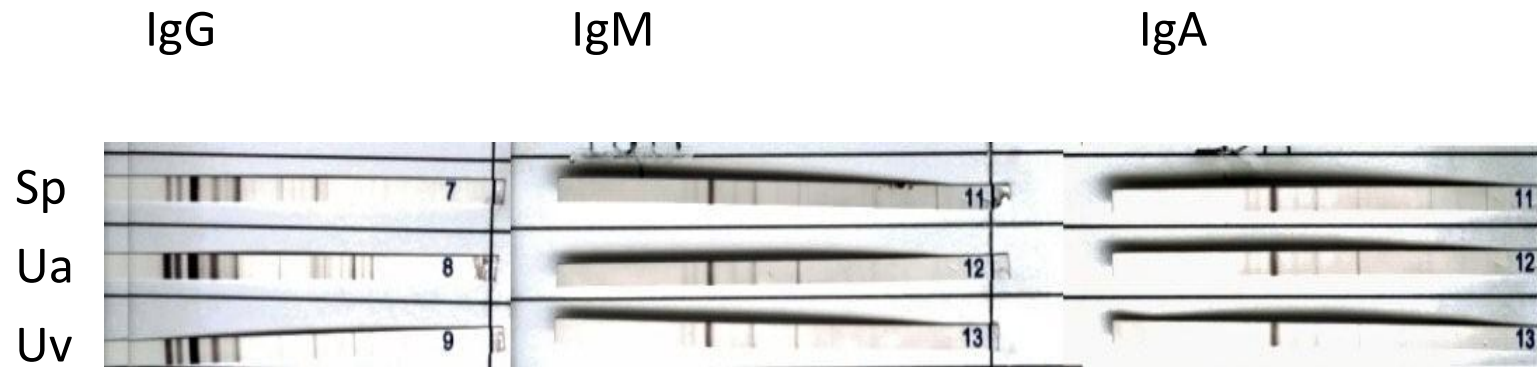
## *TOXOPLASMA GONDII* INFECTION IN ALLOGENEIC BMT (D-/R+)

RF	IgG	IgM	PCR	
Transplant Peripheral blood	15	neg	Nd	
1 month Peripheral blood	5	neg	Pos peripheral blood CSF	IFN-gamma neg
2 months Peripheral blood	38	neg	Pos Peripheral blood CSF	IFN-gamma neg
5 months CSF			Neg	
7 months Peripheral blood	112	neg	Neg Peripheral blood CSF	IFN-gamma pos Alive

## *TOXOPLASMA GONDII* INFECTION IN ALLOGENEIC BMT (D-/R+)

CP	IgG	IgM		
Transplant Periferal blood	2957	pos	High avidity	ALIVE

# CHOROIDORETINITIS REACTIVATION



Serological test	SP	UA/UV	2M SP	2m UA
IgG	218		266	
IgM	Neg		Neg	
IgG Avidity	0.575		0.591	
IgG/IgM WB	Neg	Pos/Pos	Neg	
RT PCR	Neg	Pos		Neg

## Risk factors for developing disseminated toxoplasmosis in HSCT

- Previous immunity (seropositive)
- Not immune donor (seronegative)
- Lack of chemioprophylaxis with cotrimoxazole
- Loss of antitoxoplasma specific IgG antibodies
- Severe immunocompromise (low CD4+ cell count, GVHD...)
- Other opportunistic infection (CMV, EBV...)

Despite effective treatment the outcome is still poor.

This subset of HSCT should undergo prophylactic treatment and be closely followed-up by clinical observation and PCR on peripheral blood and IGRA.

## **TOXOPLASMOSIS IN IMMUNODEPRIMED PATIENTS : DO NOT FORGET IT STILL EXISTS**

Toxoplasmosis disease in paediatric hematopoietic stem cell transplantation: do not forget it still exists

Decembrino N. et al. *Bone Marrow Transplantation* (2017) 52,1326–1329 (2017)