Infecciones por *P. jirovecii* en la era de los nuevos inmunosupresores

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XVII CONGRESO SADI
JUNIO 2017 | MAR DEL PLATA | ARGENTINA

- Comisión de Infecciones en el Paciente Inmunocomprometido- SADI
- Comisión de Infecciones en Trasplante de Órgano Sólido- SADI - SAT

- Sanatorio de la Trinidad Mitre
- Sanatorio Anchorena
- Iptei

- Sin conflicto de interés

Epidemiología

- 2/3 de inmuncompetentes tienen Ac.específicos a los 4 años de vida.
- Inicialmente en neonatos y desnutridos.
- Incremento casos en pacientes HIV negativos.

- UK incidencia 3.15 casos / millón hab. 2000-2005 vs 5.13 en 2005-2010.
- Tasa de mortalidad permanece muy alta en pts OH (30-59%) en particular TCHP (48-70%) comparado con 17-30% en HIV.

Cordonniere C et al. JACH. 2016

Presentación Clínica

Table 2. Main differences in clinical presentation of *Pneumocystis* pneumonia between HIV-positive and HIV-negative patients

Difference	HIV-positive	HIV-negative	References
PCP may reveal the underlying disease	yes	exceptional (three cases of adult T cell leukaemia due to HTLV infection revealed by PCP)	90,91
Corticosteroids received before the diagnosis of PCP	no	yes (90%), mostly during tapering or after withdrawal	12,27,28,31,32
Onset	progressive	acute	71,86,92
Duration of symptoms before diagnosis	long (3–5 weeks)	short (4–8 days)	
Hypoxaemia	mild	often severe	25,27,35
LDH elevation			
specificity and sensitivity	good	low	12,79
levels	high	moderate	
Characteristics of BAL fluid	high number of cysts; few neutrophils	low number of cysts; many neutrophils	25,35,71
Mortality rate	17%–30%	28%–53%; especially high after HSCT	13,26,28,31,70,80

Cordonniere C et al- JACH. 2016

Diagnóstico microbiológico.

- IFI directa o indirecta (AII)
- BAL: mejor método con buen valor predictivo negativo (AII)
- PCR: E 83-100% ; S 82-100% (AII). Considerar falsos positivos y negativos

	ESPUTO INDUCIDO	BAL
Examen Directo(%)	35-78	60-92
IFI (%)	43-78	89-98
PCR (%)	86-100	86-100

Dudovic T. Rev Med Sus - 2010

Factores de riesgo

- **Enfermedad de base Oncohematológica**

LLA.

Síndromes linfoproliferativos, inclusive LNH, LLC, MM.

Aprox. 83%

Reportes: S. mieloproliferativos crónicos en Tto.

LMA.

Mielodisplasias.

- **Linfopenia,** bajo nivel CD4, pero también hay con nivel normal.
- **Terapias específicas:** Corticoides.

Quimioterápicos.

Ac monoclonales.

Cordonniere C et al- JACH. 2016

Factores de riesgo

- Tumores sólidos.
- Trasplante de células hematopoyéticas (TCHP)
- Trasplante de órgano sólido (TOS)
- Patología reumatológica

Factores de riesgo: Oncohematológicos no Tx

Terapias específicas: Corticoides.

Table 1.—Predisposing Factors and Underlying Disease in Cases of Patients With *Pneumocystis carinii* Pneumonia

	Predisposing Factors				
	Corticosteroids	Other Risk	No Known Risk	Unknown	Totals (%)
Hematologic neoplasm	56	5	3	3	67 (47)
Lymphoma	34	3	...	2	39 (27)
Hodgkin's	11	...	...	...	11
Non-Hodgkin's	23	3	...	2	28
Leukemia	19	2	3	1	25 (18)
Acute lymphoblastic	5	1	...	...	6
Acute nonlymphoblastic	2	...	2	...	4
Chronic lymphocytic	6	...	...	...	6
Chronic myelogenous	6	...	1	1	8
Hairy cell	...	1	...	...	1
Other*	3	...	...	...	3
Solid tumors	37	...	4	3	44 (31)
Brain	15	...	...	...	15
Breast	8	...	...	1	9
Lung	8	...	...	...	8
Genitourinary	3	...	2	...	5
Other†	3	...	2	2	7
Bone marrow transplantation‡	18	5	...	2	25 (18)
Other§	5	1	...	...	6 (4)
Totals	**116**	**11**	**7**	**8**	**142**

Fueron el Factor de riesgo en 87% (116/132 evaluables)

70% en fase de descenso

Mediana: 3 meses

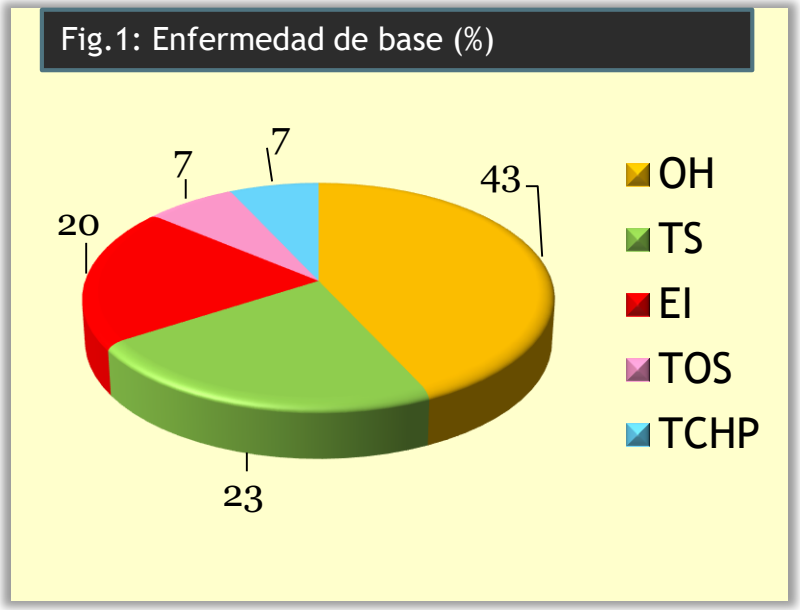
Sepkowitz y Limper recomiendan profilaxis cuando ≥ 20 mg prednisona/ día o equivalente por ≥ 1 mes.

Sepkowitz K et al- CID. 1993
Limper A et al- Am Rev Resp D. 1989

Pneumocystis jirovecii pneumonia in HIV-negative patients: A prospective study with focus on immunosuppressive drugs and markers of immune impairment

FRANCE ROBLOT[1], GWENAEL LE MOAL[1], CATHERINE KAUFFMANN-LACROIX[2], FREDERIC BASTIDES[3], DAVID BOUTOILLE[4], RENAUD VERDON[5], CENDRINE GODET[1], PIERRE TATTEVIN[6] & ON BEHALF OF THE GROUPE D'ETUDES ET DE RECHERCHE EN INFECTIOLOGIE CLINIQUE DU CENTRE OUEST (GERICCO)

- Multicéntrico, observacional, 56 casos.



80% recibieron esteroides dentro del año, 2/3 por más de 1 mes.

60% se hallaban recibiendo esteroides al momento del diagnóstico PCP.

Roblot F et al-Scand J Inf Dis. 2014

Quantification of the effect of chemotherapy and steroids on risk of *Pneumocystis jiroveci* among hospitalized patients with adult T-cell leukaemia

Table II. PCP events, risks, and crude odds ratios among ATL patients without prophylaxis.

	PCP		Crude		
	n	%	OR	95% CI	*P*-value
Treatment group					
No agent	30	3·2		Reference	
Chemotherapy	10	9·7	3·21	1·52–6·77	0·002
Chemotherapy plus steroid	80	10·0	3·32	2·15–5·10	<0·001
Steroid	94	16·6	5·94	3·88–9·10	<0·001

Table III. Logistic regression analyses results estimating adjusted odds ratio of each treatment group on risk of PCP, with no agent group as the reference category.

	Model 1			Model 2		
	AOR	95% CI	*P*-value	AOR	95% CI	*P*-value
Treatment group						
No agent		Reference			Reference	
Chemotherapy	3·32	1·57–7·02	0·002	3·30	1·55–7·02	0·002
Chemotherapy plus steroid	3·34	2·17–5·14	<0·001	3·35	2·18–5·17	<0·001
Steroid	5·99	3·91–9·18	<0·001	6·12	3·99–9·38	<0·001

Maeda T et al. BJH. 2015

Factores de riesgo: Oncohematológicos no Tx

Terapias específicas: Quimioterapia.

Análogos de las Purinas:

- **Fludarabina:** linfopenia profunda y prolongada.
- Riesgo aumentado aún sin Rituximab

Vincristina, ciclofosfamida, metotrexate, y citarabina (en S. linfoproliferativos): sólo reportes aislados

Cordonniere C et al- JACH. 2016

Terapias específicas: Quimioterapia

Atypical *Pneumocystis jirovecii* pneumonia in previously untreated patients with CLL on single-agent **Ibrutinib**. Ahn IE et al. Blood 2016

- 5 casos PCP /96 pts. Mediana: 6 meses.
- CD4 >500 / IgG >500 mg/dL
- No profilaxis universal sin otros factores de riesgo. Crear conciencia.

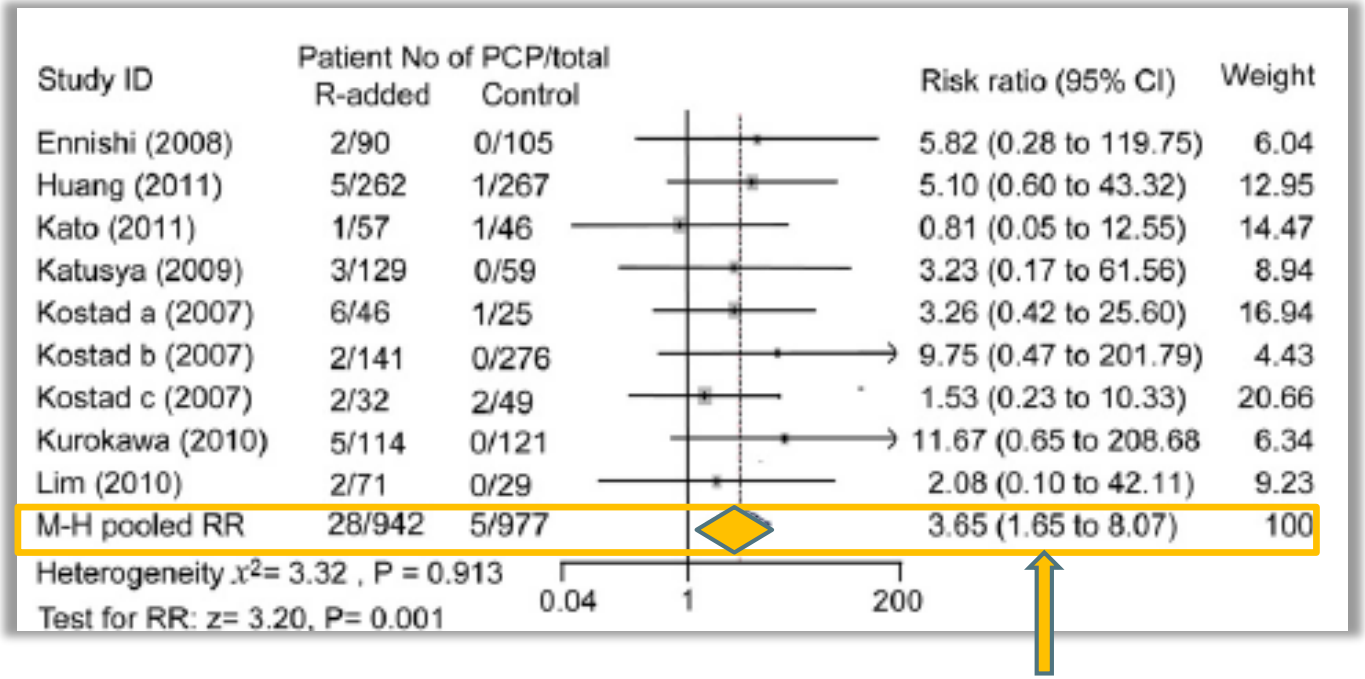
Pneumocystis jirovecii pneumonia in **Everolimus**-treated renal cell carcinoma. Di Fiore et al. JCO 2014

- Dosis más altas que en TOS.
- DD: neumonitis inducida por Everolimus vs infecciosa. Sospechar si no mejora con la suspensión y reducción de dosis de Everolimus.

Factores de riesgo: Oncohematológicos no Tx

Terapias específicas: Ac. Monoclonales.

Prophylaxis and Treatment of *Pneumocystis jirovecii* pneumonia in lymphoma patients subjected to Rituximab-contained therapy: a systemic review and meta-analysis. Jiang W et al. Plos One 2015



CHOP-14: la adición de Rtx incrementa el riesgo de 4 a 13% sin profilaxis.

Cordonniere C et al. JACH. 2016

Factores de riesgo: TCHP

- Sin profilaxis: riesgo 16% los primeros 6 meses.

- ´90: incidencia 0-2,5% en T. alogénico y 1,4 % en T. autólogo.
- Raro actualmente si cumple con la profilaxis.

Características de los casos:

- Tardíos, 6 meses.
- EICH crónico o agudo x lo cual reciben esteroides / IS.
- CD4 ??

Cordonniere C et al- JACH. 2016

The incidence, mortality and timing of *Pneumocystis jiroveci* pneumonia after hematopoietic cell transplantation: a CIBMTR® analysis

1995-2005: 0,63% TCHP alogénico y 0,28% en autólogo.

2006-2012: 0,53% TCHP alogénico y 0,32% en autólogo.

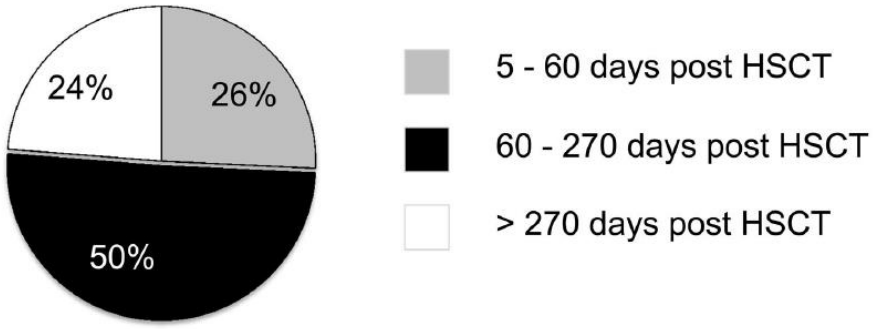


Figure 2. Timing of PJP after allogeneic HSCT
This chart shows the relationship between time after allogeneic HSCT and development of PJP disease.

Williams KM et al. BMT-2016

The incidence, mortality and timing of *Pneumocystis jiroveci* pneumonia after hematopoietic cell transplantation: a CIBMTR® analysis

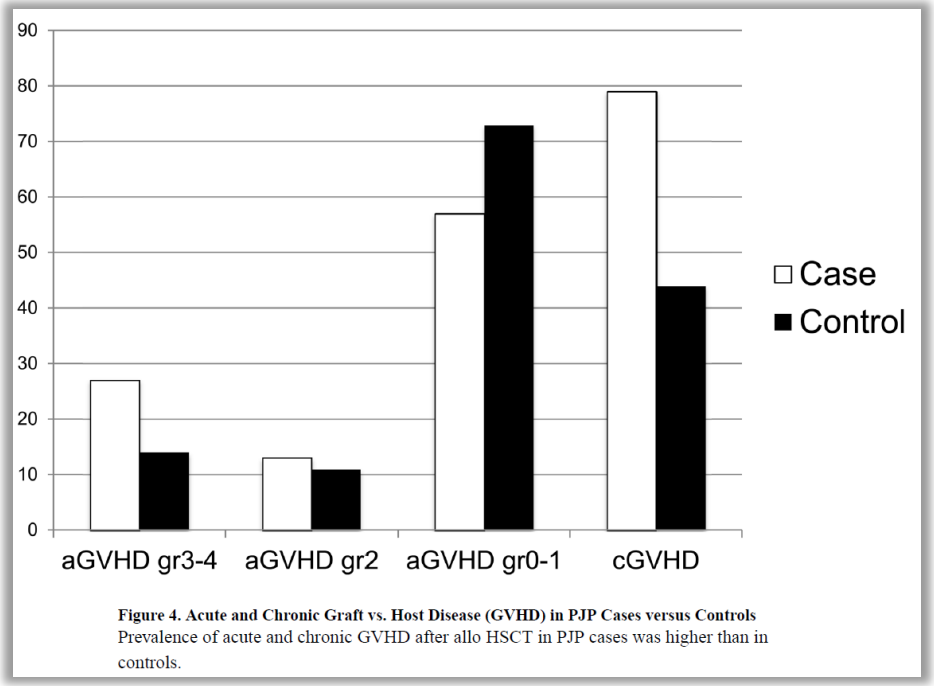


Figure 4. Acute and Chronic Graft vs. Host Disease (GVHD) in PJP Cases versus Controls
Prevalence of acute and chronic GVHD after allo HSCT in PJP cases was higher than in controls.

TCHP alogénico:
deterioro de reconstitución inmune (uso de esteroides, linfopenia, neutropenia y/o EICH .

Mortalidad: 7 veces más riesgo comparado con los controles

Williams KM et al. BMT-2016

Profilaxis: TCHP

Table 1. ECIL guidelines in haematology patients at risk of *Pneumocystis* pneumonia: indication and duration of prophylaxis

	Adults		Children	
Indication for prophylaxis	disease/condition	duration of prophylaxis	disease/condition	duration of prophylaxis
Main (A)	ALL	from induction to end of maintenance	ALL	from induction to end of maintenance
	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing
	alemtuzumab	>6 months after completion of treatment	alemtuzumab	
	fludarabine/cyclophosphamide/ rituximab	≥6 months after completion of treatment	SCID, WAS, X-linked agammaglobulinaemia, HLA II combined immunodeficiency	life-long or until restoration of underlying defect
	steroids (>20 mg/day prednisone for 4 weeks)		steroids (>0.4 mg/kg or 16 mg/day for ≥1 month)	
Optional (B)	Lymphoma treated with R-CHOP14 or escalated BEACOPP		AML	duration of chemotherapy
	nucleoside analogues (fludarabine, cladribine, mycophenolate mofetil)		solid tumours	duration of chemotherapy
	radiotherapy for brain tumours/ metastasis + high-dose steroids			

Maertens. J et al. Ecil2016

Profilaxis: TCHP

Table 3. Summary of the ECIL guidelines about choice of drugs and doses for PCP prophylaxis in haematology patients

	Adults	
	drug grading	dose
First-line choice		
trimethoprim/sulfamethoxazole; all other alternatives are inferior (**A-II**)	**A-II**	one single-strength (80/400 mg) tablet/day or one double-strength tablet (160/800 mg)/day or thrice a week: **B-II**
Second-line choice[a]		
dapsone	**A-II**	50 mg×2/day: **B-II**
atovaquone	**B-II**	1500 mg/day: **B-II**
pentamidine aerosols	**A-II**	300 mg once/month: **B-II**
pentamidine intravenously	no data	—

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Factores de riesgo: Tumores sólidos

- No hay evidencia clínica que sustente el uso rutinario de profilaxis.

- La inclusión de esteroides en el esquema constituye factor de riesgo: 16-25 mg prednisolona o ≥ 4 mg dexametasona /día por ≥ 4 semanas.
- Durante el tto esteroideo o descenso.

T. Cerebrales con esteroides: 1,7% PCP,+ irradiación craneana: 6,7% al año.

Cooley L et al.Int Med J 2014

Pneumocystis jirovecii pneumonia prophylaxis during Temozolamide treatment for high-grade gliomas. De Vos FY et al. Vrit Re Oncol/Hemat 2013

- Temozolomida + radioterapia o el uso crónico de esteroides: iniciar prof. desde el inicio de temozolomida, con Rto linfocitos < 500 células/L o de CD4 < 200 células/L y continuar hasta normalización de linfocitos o CD4.

Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014

L. Cooley,[1] C. Dendle,[2,3] J. Wolf,[4,5] B. W. Teh,[6] S. C. Chen,[7,8,9] C. Boutlis[10,11] and K. A. Thursky[6,12]

Solid tumours (grade of recommendation)

Regimens where 16–25 mg prednisolone or ≥4 mg dexamethasone for ≥4 weeks is planned (C)

Brain tumours, particularly if temozolomide or craniospinal irradiation is planned (B)

Other solid tumours undergoing myelosuppressive chemotherapy (children only) (C)

La profilaxis debe continuarse por al menos 6 semanas después de finalizado el tto con esteroides

Int Med J- 2014

Factores de riesgo: TOS

Antes de implementación rutinaria de profilaxis: 5-15%.

- Estado neto de inmunosupresión: principal factor de riesgo.

Table 1. Attack rate of *Pneumocystis* pneumonia (PCP) in transplant recipients. Adapted from Rodriguez *et al.* [31].

Organ Transplanted	Patients not Receiving Prophylaxis		Patients Receiving Prophylaxis *	
	Attack Rate (%)	Reference	Attack Rate (%)	Reference
Kidney	0.6–14	[30,32–34]	0.4–2.2 [a]	[16,24,25,27]
Liver	3–11	[35–37]	1.1–3.7	[16,25,27,38]
Heart	2–41	[30,39–41]	2–5.1	[16,27]
Heart–lung/lung	6.5–43	[39,42]	5–5.8	[16,25]

Martin SI et al. AJT 2013iart X
Iriart X et al. J of Fungi- 2015

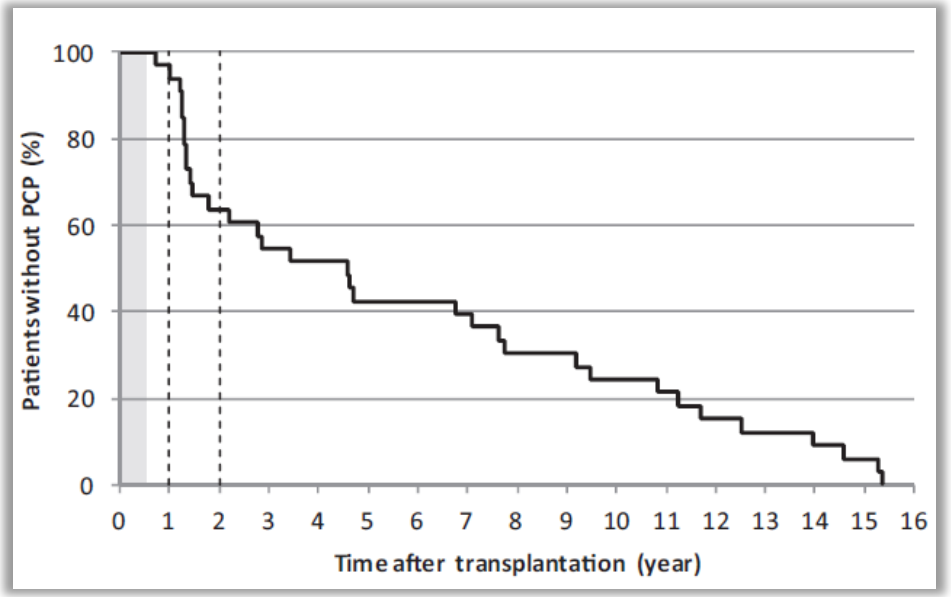
Factores de riesgo: TOS

Table 1: Risk factors for the development of *Pneumocystis* pneumonia expected or observed in solid organ transplant recipients

Risk factors	Comments
Immunosuppressive therapies	
Corticosteroids	• Retrospective case series in non-HIV patients identified corticosteroids in up to 90% • Median dose and duration of therapy in one series of non-HIV patients with PCP was 30 mg/day of prednisone for 12 weeks (13)
Antilymphocyte therapy	• Antilymphocyte antibodies are linked to the highest risk for PCP in the 1–6 month posttransplant period (14) • Alemtuzumab, a monoclonal antibody with activity against B-, T-, and NK cells may confer the highest risk (15)
Mycophenolate mofetil	• The anti-*Pneumocystis* effects of mycophenolate mofetil *in vitro* and in animal models have not been confirmed in prospective clinical trials (16)
Calcineurin inhibitors	• At a single institution where cyclosporine A replaced azathioprine in renal transplantation, the incidence of PCP increased from 3% to 9% (17) • One retrospective study suggested a higher incidence of PCP among renal transplant recipients on tacrolimus-based regimens compared to cyclosporine A (18)
Other clinical factors	
CMV disease	• CMV may be an independent risk factor for PCP (19) • Coinfection with CMV and PCP may be observed in solid organ transplantation (20–22)
Allograft rejection	• PCP has been related to the intensity of immunosuppression in transplant recipients (18) • PCP has been linked to treatment and number of episodes of acute rejection (21)
Low CD4+ T cell counts	• In HIV infection, the risk for PCP is linked to CD4+T cell counts <200 cells/mL, or $<20\%$ of the total circulating lymphocytes (23) • PCP has been linked to decreased CD4+T cell counts in HSCT recipients (24), solid tumor patients receiving chemotherapy (25), autoimmune disease and hematological malignancy patients (26) • Transplant patients with CD4+T cell lymphopenia are expected to be at risk for PCP, though clinical data to support this are lacking (19)
Neutropenia	• Prolonged neutropenia is a potential risk factor for PCP in transplant recipients (19)
Exposure	• In solid organ transplant recipients not taking effective prophylaxis, being in close proximity to other transplant recipients with PCP may increase the risk for developing infection (6–11)

Martin SI et al. AJT- 2013

Profilaxis en TOS



- ✓ Edad
- ✓ Rto Linfocitos
- ✓ Viremia CMV

Table 6: Appraisal of criteria of establishment of PCP prophylaxis in transplant recipients

	SOT recipients who would have benefited from a PCP prophylaxis in the period of 180 days before D0		
Criteria of establishment of prophylaxis	With PCP, n = 33	Without PCP, n = 66	p-Value
Patient ≥65 years old in the second year after transplantation, n (%)	8 (24.2%)	9 (13.6%)	0.187[1]
Patient with lymphocytes <750/mm^3 for more than 1 month, n (%)	10 (30.3%)	11 (16.7%)	0.118[1]
Patient with detectable CMV viremia, n (%)	16 (48.5%)	8 (12.1%)	<**0.001**[1]
All these criteria, n (%)	23 (70.0%)	20 (30.3%)	<**0.001**[1]

Iriart X et al. AJT-2015

Profilaxis en TOS

- Recomendada por 6 – 12 meses post Tx, pero su duración puede prolongarse (III).

Ocurrencia más tardía: algunos consideran 12-18 meses en receptores con alto riesgo o quiénes requieren > 10 mg/día de prednisona.

- Historia previa de PCP o Tx intestino delgado o Tx pulmonar: de por vida (AIII)

Droga de elección: TMS

Martin SI, AJT 2013

Factores de riesgo: Patología Reumatológica

Table 1 Risk factors for the development of PCP in patients with CTD

Established	Suspected[a]	Possible
Low CD4+ count	Glucocorticoids	Younger age[b]
Lymphopenia	Cyclophosphamide	Male[b]
	Rituximab	Hispanic decent[b]
	Methotrexate	Asian decent[b]
	Anti-TNF inhibitors	Private medical insurance[b]
	Azathioprine	Interstitial pulmonary fibrosis[c]
		Caucasian decent[d]
		Australian autumnal season[d]

Mortalidad :

- Elevada, varía por enfermedad y paciente, 9-85%
- Factor de riesgo: difícil de evaluar x lo heterogéneo de la población.
- Comorbilidades + co- infección, la cual sugiere enf. de base más severa y uso de IS más agresivos.

Wolfe R, et al. Curr Reumatol Rep- 2017

Profilaxis en Patología Reumatológica

El desafío de elaborar guías:

- Baja frecuencia de PCP
- Diversidad de enfermedades bajo la categoría ETC

Disease	Prophylaxis?	To whom?	Conditional factors[b]	NNT [5••]
GPA	Yes	All patients undergoing induction therapy		32
SLE	Conditional[a]	High dose GC	Lymphopenia Low CD4+ count Immunosuppressive regimen	110
PM/DM	Conditional[a]	High-dose GC	Lymphopenia Low CD4+ count More severe disease	73
PAN, AAV	Conditional[a]	During induction therapy and/or high dose GC	Lymphopenia Low CD4+ count	110
RA	No	–	–	1099
GCA	No	–	–	–
Scleroderma	No	–	–	110

Table 3 Authors' recommendations for PCP prophylaxis in CTD

Wolfe R, et al. Curr Reumatol Rep- 2017

Tratamiento de PCP en no-HIV

Criterios (A-III)

Tabla 1. Indicaciones para el inicio de Tto para *Pneumocystis*

- Pacientes en riesgo

con

- Signos clínicos y síntomas

Disnea o tos
Fiebre (ausente a veces)
Hipoxemia
Dolor torácico (raro; neumotórax)

con

- Rx / TAC sugestiva encontrar compatibles con PCP

con o sin

- Elevación de LDH sérica inexplicable.

Dos series muestran:

Fiebre 86%
Disnea 78%
Hipoxemia 70%

43% requirieron UTI
20% ARM
Co-infección: 28-70%

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Tratamiento de PCP en no-HIV

Factores de mal pronóstico al inicio:

- Enfermedad de base no controlada
- Corticoides prolongado
- Retraso en el inicio de tratamiento para PCP
  Hipoalbuminemia
- Co infección con HSV o CMV
- Alto recuento de neutrófilos en el BAL
- APACHE-II o SAPS II elevados

Factores de mal pronóstico durante el tratamiento

- Mala evolución clínica al día 8
- **Uso de vasopresores / Shock**
- Altas dosis de esteroides
- ARM

El retraso en el inicio del Tto incrementa la necesidad de ARM y mortalidad

Maertens. J et al. Ecil2016

Tratamiento de PCP en no-HIV

Table 4. Recommended first-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune/ inflammatory diseases	to cure	TMP/SMX 15–20 mg/kg (TMP) 75–100 mg/kg (SMX) per day for ≥14 days	**A**	**IIr**
		pentamidine iv 4 mg/kg/day	**C**	**IIt**
		primaquine + clindamycin 30 mg/day oral + 600 mg×3/day iv or oral	**C**	**IIt**
		atovaquone 750 mg×2(or 3)/day oral	**C**	**IIt**

Evitar la co-administración con metotrexate y TMS por potenciales EA

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Tratamiento de PCP en no-HIV

Re-evaluar no antes de los 8 días de Tto completo (AIII)

Vogel y col.: mejoría de TC 57% a los 13 días de Tto.

8° día sin mejoría clínica y/o deterioro respiratorio con TM

↓

Sospechar fallo clínico

↓

Repetir BAL para descartar co-infección (AIII)

Evitar la rotación innecesaria a una segunda línea en quién recibe altas dosis de TMS (AII).

Considerar el cambio habiendo descartado co-infección u otras causas

Maertens. J et al - Ecil2016

Vogel MN et al. Euro J Radiol -2012

Tratamiento de PCP en no-HIV

Table 5. Options for second-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune diseases	cure	primaquine (30 mg) + clindamycin (600 mg×3) per day	**B**	**IIt**
		pentamidine iv 4 mg/kg/day	**B**	**III**
		TMP/SMX (15–20 mg/kg/day) + caspofungin (70–50 mg/day)	**C**	**IIu**
		echinocandin alone	**D**	**IIu**

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Tratamiento de PCP en no-HIV

- Duración del tratamiento es de 3 semanas (B-II).
- En los casos leves, debe ser por lo menos 2 semanas (A-II).
- En el caso de lenta mejoría clínica, el tratamiento debe continuarse durante al menos 3 semanas (A-II).

Maertens. J et al. Ecil2016

Conclusión:

Reconocer tempranamente el paciente de riesgo y la enfermedad es crítico para su optimo manejo.

Profilaxis con TMP-SMX redujo significativamente las infecciones por *Pneumocystis jirovecii* y la mortalidad relacionada pacientes inmunodeprimidos no infectados por HIV con riesgo de PCP.

La profilaxis con PCP se justifica para pacientes adultos con un riesgo esperado de PCP de 3,5% o más durante el período de inmunodeficiencia Green Mayo clinic 2007

FIN.

Muchas gracias.