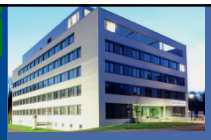

Therapie besonderer Mykosen:

Pneumocystis jirovecii

Prof. Dr. med. Peter-Michael Rath
Institut für Med. Mikrobiologie
UK Essen

pm.rath@uni-due.de

Interessenkonflikte: keine

Universitätsklinikum Essen

Pneumocystis jirovecii

Biologisch ein Pilz	**ohne Ergosterol**
Bei Säugetieren verbreitet	
Maximal an Wirt adaptiert (lange Co-Evolution)	**(nicht) anzüchtbar, kein Tiermodell für *P. jirovecii***
Habitat	**Alveolen**
Übertragungsweg	**Luft (?)**
Prävalenz in der Bevölkerung	**hoch (mindestens 80 %)**
Klinik	**Interstitielle Pneumonie bei Immunsupprimierten** (AIDS, TX-Patienten, hämatoonkologische Patienten u.a.)

Proinflamatorischer Effekt der Kolonisation bei pulmonalen Erkrankungen ?

Diagnose	**Anamnese, Klinik, Labor (Mikroskopie, PCR, (1-3)-ß-D-Glucan)**

Increasing *Pneumocystis* Pneumonia, England, UK, 2000–2010

Rishma Maini, Katherine L. Henderson, Elizabeth A. Sheridan, Theresa Lamagni, Gordon Nichols,

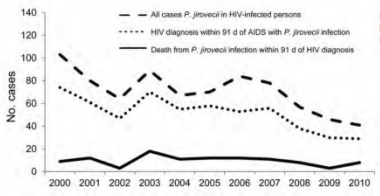

Figure 3. *Pneumocystis jirovecii* infections and deaths among persons with diagnosed HIV infection, England, UK, 2000–2010.

HIV

Risk category*	No. admissions (% all cases) 2000–2005	2006–2010	Rate ratio between periods (95% CI)
Any transplant†	59 (6.3)	193 (14.7)	3.80 (2.84–5.09)
Other lung disease‡	120 (12.8)	276 (21.0)	1.97 (1.47–2.64)
Hematologic disorders	217 (23.1)	354 (26.9)	2.55 (2.00–3.25)
Hematologic malignancy	349 (37.1)	568 (43.1)	1.89 (1.66–2.16)
Connective tissue/inflammatory disease§	71 (7.6)	120 (9.1)	2.02 (1.56–2.61)
Renal failure and dialysis	95 (10.1)	208 (15.8)	2.23 (1.56–3.17)
Immunosuppressive/ chemotherapeutic drugs	47 (5.0)	90 (6.8)	1.90 (1.60–2.25)
Malignancy other than hematologic	92 (9.8)	160 (12.2)	2.67 (2.16–3.31)
Not in the above risk categories	255 (27.1)	177 (13.4)	0.81 (0.67–0.98)
Total no. cases¶	941	1,317	1.62 (1.50–1.77)

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 19, No. 3, March 2013

Update on the diagnosis and treatment of *Pneumocystis* pneumonia

Eva M. Carmona and Andrew H. Limper

Table 1. Immunosuppressive agents associated with the development of *Pneumocystis* pneumonia.

Corticosteroids
Alkylating agents
Cyclophosphamide
Temozolomide
Antibiotics/Immunosuppressants
Bleomycin
Sirolimus
Tacrolimus
Antimetabolites
Cytarabine
Fluorouracil
Methotrexate
Polypeptides
Cyclosporine
Purine analogs
Azathioprine
Cladribine
Fludarabine
TNFα inhibitors
Adalimumab[a]
Etanercept
Infliximab[a]
Monoclonal antibodies
Alemtuzumab[a]
Rituximab[a]

[a]Monoclonal antibodies
TNF, tumor necrosis factor.

Ther Adv Respir Dis
(2011) 5(1) 41–59

Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France

Antoine Roux, Emmanuel Canet, Sandrine Valade, Florence Gangneux-Robert,

Table 2. Clinical management of 544 AIDS and non-AIDS patients after diagnosis with PCP, France, January 1, 2007–December 31, 2010*

Characteristic	AIDS patients, n = 223	Non-AIDS patients, n = 321	p value
Days from admission to treatment initiation, median (IQR)	1 (0–2)	2 (0–6)	<0.0001
Immediate oxygen needed	87 (49)	160 (69)	<0.0001
Mechanical ventilation			
Invasive needed	25 (11.0)	98 (30.5)	<0.0001
Hospital deaths	8 (4)	75 (27)	<0.0001

Table 3. Multivariate analysis of independent predictors of hospital death for AIDS and non-AIDS patients with PCP, France, January 1, 2007–December 31, 2010*

Variable	Odds ratio (95% CI)
HIV infection	0.33 (0.12–0.92)
Solid organ transplant	0.08 (0.02–0.31)
Age, per additional year	1.04 (1.02–1.06)
Allogeneic HSCT	8.6 (1.40–53.02)
Need for immediate oxygen therapy	4.06 (1.44–11.5)
Need for intubation and mechanical ventilation	16.70 (7.25–38.47)
Time to PCP treatment, per additional day	1.11 (1.04–1.18)

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 9, September 2014

Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France

Antoine Roux, Emmanuel Canet, Sandrine Valade, Florence Gangneux-Robert,

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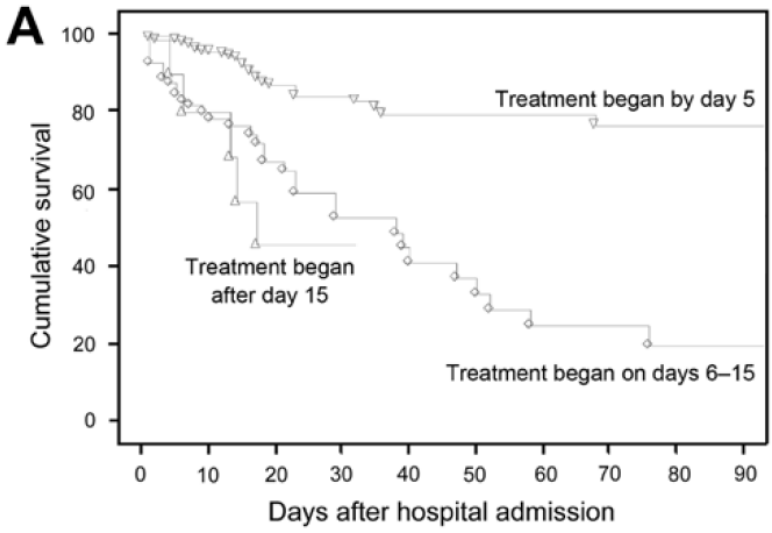
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 9, September 2014



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 9, September 2014

Medikamente und Angriffspunkte

Trimethoprim-Sulfamethoxazol	**DHPS/DHFR**	**DHPS-Mutationen***
Clindamycin/Primaquin	**Protein-Synthese?**	**Keine**
Atovaquon	**Zytochrom-B-Komplex**	**Mutationen der Q-Enzym-Bindungsstelle**
Pentamidin	**DNA-Synthese**	**?**
Dapsone/Trimethoprim	**DHPS/DHFR**	**DHPS-Mutationen**
Trimetrexat/Leucovorin	**DHFR**	**keine**
Echinocandine	**(1-3)-ß-D-Glucan**	**keine**

DHPS: Dihydropteroat-Synthetase

DHFR: Dihydrofolat-Reduktase

*** Klinische Bedeutung fraglich**

AWMF 055/006,

S2k, 2011

Therapie und Prophylaxe opportunistischer Infektionen bei HIV-infizierten Patienten

Deutsch-Österreichische Leitlinie

Therapie/Prophylaxe der PcP (soweit nicht anders angegeben, Tagesdosierungen), Therapiedauer 21 Tage anzustreben

Akuttherapie		Dauer: Immer mindestens drei Wochen
Erste Wahl bei mittelschwerer/ schwerer PcP	TMP/SMX	TMP 15-20 mg pro kg/ Tag (+SMX 75-100 mg pro kg/ Tag) verteilt auf 3-4 Einzeldosen (meist 4 x 4 oder 3 x 5 Ampullen à 480 mg i.v.) Prednison 50-100 mg (ca. 1mg/kgKG) (i.d.R. 5-10 Tage in absteigender Dosis.
Leichte PcP	TMP/SMX	3 x 3 Tbl. à 960 mg p.o.
Alternativen	Pentamidin	4 mg/kg i.v. 5 Tage, dann ggf. Reduktion auf 2mg/kg (bei first-line Einsatz ggf. Begleitantibiotikum); BZ-Kontrollen!
	Atovaquon	2 x 750 mg [5ml] Suspension p.o. mit einer Mahlzeit
	Clindamycin + Primaquin	(3-)4 x 600 mg i.v. oder p.o. plus Primaquin 30 mg p.o.
	Dapson + Trimethoprim	Dapson 1 x 100 mg pro Tag, Trimethoprim 5 mg/kd KG 3 x pro Tag

Alle Alternativtherapien sind weniger wirksam.

Clindamycin–primaquine for pneumocystis jiroveci pneumonia in renal transplant patients

P. Nickel · M. Schürmann · H. Albrecht · R. Schindler · K. Budde · T. Westhoff · J. Millward · N. Suttorp · P. Reinke · D. Schürmann

Charité-University Medicine Berlin, Berlin, Germany

Table 3 Outcome of renal transplant patients with primary PCP episodes according to treatment regimen and severity of PCP (on-treatment-analysis)

Severity of PCP	Number of patients (% per patient group)		*p* value
	C–P	TMP/SMX	
Mild-to-moderate PCP	18	18	
Treatment success	14 (77.8)	15 (83.3)	1.000
Reasons of treatment failure			
Lack of efficacy (treatment switch)	4 (22.2)	1 (5.6)	0.338
Adverse reactions leading to switch	0	2 (11.1)	0.486
Severe PCP	5	16	
Treatment success	2 (40)	6 (37.5)	1.000
Reasons of treatment failure			
Lack of efficacy	3 (60)	6 (37.5)	0.611
Treatment switch	3 (60)	2 (12.5)	
Death on primary treatment	0	4 (25)	
Adverse reactions leading to switch	0	4 (25)	0.532

Clindamycin-Primaquin (etwas) weniger wirksam als TMP/SMX

Infection (2014) 42:981–989

COMPARISON OF ATOVAQUONE (566C80) WITH TRIMETHOPRIM–SULFAMETHOXAZOLE TO TREAT *PNEUMOCYSTIS CARINII* PNEUMONIA IN PATIENTS WITH AIDS

WALTER HUGHES, M.D., GIFFORD LEOUNG, M.D., FRANÇOISE KRAMER, M.D., SAMUEL A. BOZZETTE, M.D., SHARON SAFRIN, M.D., PETER FRAME, M.D., NATHAN CLUMECK, M.D., HENRY MASUR, M.D.,

Table 2. Intention-to-Treat Analysis of End Points on Day 49, Four Weeks after the End of Therapy.

END POINT	TREATMENT		DIFFERENCE IN PROPORTIONS	95% CONFIDENCE INTERVAL	P VALUE
	ATOVAQUONE (N = 160)	TRIMETHOPRIM–SULFAMETHOXAZOLE (N = 162)			
	no. (%)				
Lack of therapeutic efficacy*	28 (20)	10 (7)	0.15	0.05 to 0.25	0.002
Treatment-limiting adverse effects†	11 (7)	33 (20)	−0.14	−0.21 to −0.06	0.001
Alternate therapy required	55 (34)	55 (34)	0.01	−0.11 to 0.11	1.00
Successful therapy	99 (62)	103 (64)	−0.02	−0.13 to 0.09	0.82
Survival (no. of deaths)‡	11 (7)	1 (0.6)	0.06	−0.02 to 0.11	0.003

Atovaquon weniger wirksam als TMP/SMX, weniger Nebenwirkungen

THE NEW ENGLAND JOURNAL OF MEDICINE May 27, 1993

Trimethoprim-sulfamethoxazole versus pentamidine for Pneumocystis carinii pneumonia in AIDS patients: results of a large prospective randomized treatment trial.

Klein, Natalie C.; Duncanson, Frederick P.; Lenox, Theodore H.; Forszpaniak, Christine; Sherer, Clark B.; Quentzel, Howard; Nunez, Miguel; Suarez, Militza; Kawwaff, Omar; Pitta-Alvarez, Africa; Freeman, Katherine; Wormser, Gary P.

163 Patienten

Versagen	**TMP/SMX**	**42 %**	
	Pentamidin	**40 %**	**p=0.733**
Toxizität	**TMP/SMX**	**34 %**	
	Pentamidin	**17 %**	**p=0.235**
Überleben	**TMP/SMX**	**67 %**	
	Pentamidin	**74 %**	**p=0.402**

Pentamidin gleich wirksam wie TMP/SMX

AIDS 62 (1992): 301-305

Oral Atovaquone Compared with Intravenous Pentamidine for *Pneumocystis carinii* Pneumonia in Patients with AIDS

Michael N. Dohn, MD; Winkler G. Weinberg, MD; Ramon A. Torres, MD; Stephen E. Follansbee, MD;

Table 4. Therapy Outcome in Patients with Histologically Confirmed *Pneumocystis carinii* Pneumonia

Outcome	Study Group		*P* Value
	Atovaquone (n = 56)	Pentamidine (n = 53)	
	n (%)		
Successful therapy	32 (57)*	21 (40)	0.085
Failure of therapy			
Absence of response	16 (29)	9 (17)	0.18
Treatment-limiting adverse events	2 (4)	19 (36)	<0.001
Patients unevaluable	6 (11)	4 (8)	0.74
Deaths			
After 4 weeks of therapy	7 (13)	4 (8)	0.53
After 8 weeks of therapy	9 (16)	9 (17)	1.00

* Values derived from intent-to-treat analysis.

Pentamidin weniger wirksam als Atovaquon, mehr Nebenwirkungen

1 August 1994 • *Annals of Internal Medicine* • Volume 121 • Number 3 175

Comparison of Three Regimens for Treatment of Mild to Moderate *Pneumocystis carinii* Pneumonia in Patients with AIDS

A Double-Blind, Randomized Trial of Oral Trimethoprim–Sulfamethoxazole, Dapsone–Trimethoprim, and Clindamycin–Primaquine

Sharon Safrin, MD; Dianne M. Finkelstein, PhD; Judith Feinberg, MD; Peter Frame, MD;

Table 2. Outcome of Therapy According to Treatment Assignment

Variable	All Patients	Trimethoprim–Sulfamethoxazole Group	Dapsone–Trimethoprim Group	Clindamycin–Primaquine Group	*P* Value
	← *n* (%) →				
Completion of therapy	97 (53.6)	32 (50.0)	35 (59.3)	30 (51.7)	>0.2
Therapeutic failure					
On or before day 7	11 (6.1)	5 (7.8)	3 (5.1)	3 (5.2)	>0.2
On or before day 21	17 (9.4)	6 (9.4)	7 (11.9)	4 (6.9)	>0.2
Death on or before day 81	8 (4.4)	4 (6.2)	2 (3.4)	2 (3.4)	>0.2
Dose-limiting toxicity	56 (30.9)	23 (35.9)	14 (23.7)	19 (32.8)	>0.2

Dapson/Trimethoprim bzw. Clinda/Prima gleich wirksam

wie TMP/SMX mit ähnlicher NW-Rate

Ann Intern Med. 1996;124:792-802.

A Meta-analysis of Salvage Therapy for *Pneumocystis carinii* Pneumonia

Raymond A. Smego, Jr, MD, MPH, DTM&H; Shashi Nagar, BSc; Bonnie Maloba,

497 Patienten (456 HIV+), 28 Studien

	Therapierfolg
Clinda/Prima	88-92 %
Atovaquon	80 %
Pentamidin	39 %

Conclusion: The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for patients with *P carinii* pneumonia who are unresponsive to conventional antipneumocystis agents.

Arch Intern Med. 2001;161:1529-1533

Echinocandine

4 HIV-negative Patienten Scand J Infect Dis 45 (6): 484-8, 2013	**Salvage**	**kein Erfolg**
1 HIV-negativer Patient Chin Med Science J 26 (4): 246-248, 2011	**Kombi mit Clindamycin**	**kein Erfolg**
1 HIV-Patient AIDS 25 (17): 2192-2193, 2011	**Kombi mit Clindamycin**	**Erfolg**
1 HIV-negativer Patient Chin Med J 122 (8): 996-998, 2009	**Salvage**	**Erfolg**
1 HIV-negativer Patient Mycoses 51 (Suppl 1): 67-677, 2008	**primäre Therapie**	**Erfolg**
4 HIV-negative Patienten Transplantation 84 (6): 685-686, 2007	**Kombi mit TMP-SMX**	**Erfolg**
2 HIV-negative Patienten Clin Infect Dis 43 (9): e92-94, 2006	**Kombi mit TMX-SMX**	**kein Erfolg**
1 HIV-negativer Patient Kin Pädiatrie 218 (3): 177-179, 2006	**Kombi mit TMX-SMX**	**Erfolg**
3 HIV-negative Patienten Nephrology 18: 736-742, 2013	**Kombi mit TMP-SMX** (low dose)	**Erfolg**
1 HIV-negativer Patient Eur J Clin Microbiol Infect Dis 25 (1): 52-54, 2006	**Salvage**	**Erfolg**

Therapeutic Potential of Caspofungin Combined with Trimethoprim-Sulfamethoxazole for *Pneumocystis* Pneumonia: A Pilot Study in Mice

Maria Luísa Lobo[1], Francisco Esteves[1], Bruno de Sousa[2], Fernando Cardoso[1], Melanie T. Cushion[3], Francisco Antunes[4], Olga Matos[1]*

Table 1. Results of qPCR quantification of *P. murina* mtLSU RNA gene in the lungs of the nine distinct mice groups enrolled in the study.

Groups/Subgroups of mice				qPCR (average concentration)		
				Day 0	Day 14	Day 21
Group 1	*Pm* uninfected control [a]			MB	MB	MB
Group 2	*Pm* infected, untreated control[b,c]			7.17×10^8	7.40×10^8	7.94×10^8
Group 3	*Pm* infected, Caspofungin[b,c]	3.1	(0.1 mg/kg/day)	7.17×10^8	3.55×10^8	2.59×10^8
		3.2	(0.05 mg/kg/day)	7.17×10^8	1.93×10^8	3.93×10^8
		3.3	(0.001 mg/kg/day)	7.17×10^8	2.02×10^9	6.46×10^8
Group 4	*Pm* infected, TMP-SMX[b,c]	4	(12.25 mg–62.5 mg/day)	7.17×10^8	1.13×10^7	MB
Group 5	*Pm* infected, Caspofungin/TMP-SMX[b,c]	5.1	(0.1 mg/kg/day+12.5 mg–62.5 mg/day)	7.17×10^8	5.67×10^6	MB
		5.2	(0.05 mg/kg/day+12.5 mg–62.5 mg/day)	7.17×10^8	MB	MB
		5.3	(0.001 mg/kg/day+12.5 mg–62.5 mg/day)	7.17×10^8	7.98×10^6	MB

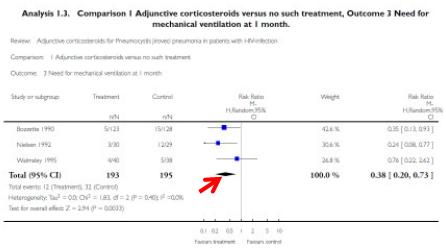
Keimload

Im Mausmodell **Echinocandin mono wenig wirksam**
Kombination besser

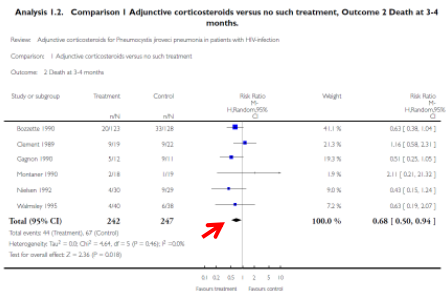
Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection (Review)

Briel M, Bucher H, Boscacci R, Furrer H

Beatmungspflichtigkeit



Letalität



Steroide sinnvoll (weniger Beatumungspflichtigkeit, geringere Letalität)

Zusammenfassung

First line: **TMP/SMX**

Second line:

	Wirksamkeit	Nebenwirkungen
Clindamycin/Primaquin	gleich (?) TMP/SMX	gleich TMP/SMX
Trimethoprim/Dapsone	gleich TMP/SMX	gleich TMP/SMX
Atovaquon	weniger als TMP/SMX	weniger TMP/SMX
Pentamidin iv	weniger als Atovaquon (CE: effective as TMP/SMX)	mehr als Atovaquon
Pentamidin lokal	weniger als alle	

ClinicalEvidence
HIV: treating *Pneumocystis* pneumonia (PCP)
Search date May 2008
Richard Bellamy
modifiziert