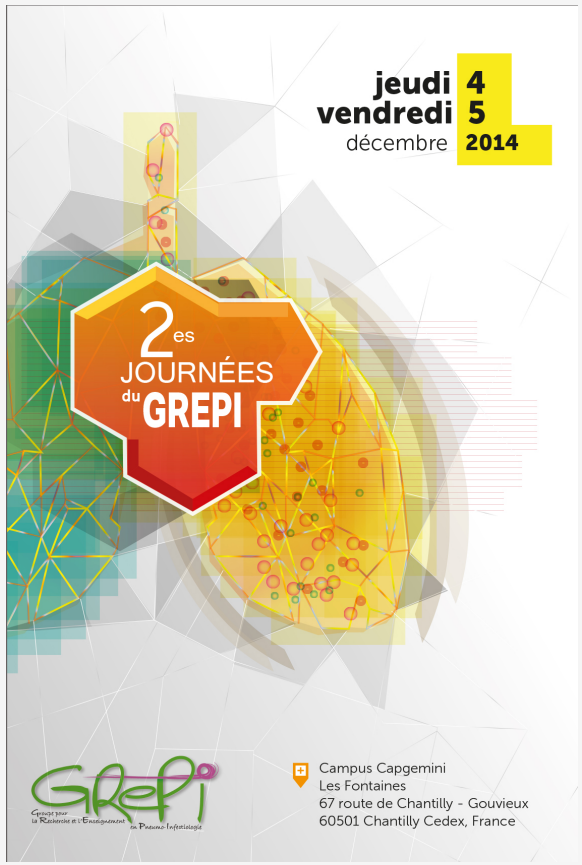


Nouveaux visages de la pneumocystose et impact sur la pratique quotidienne

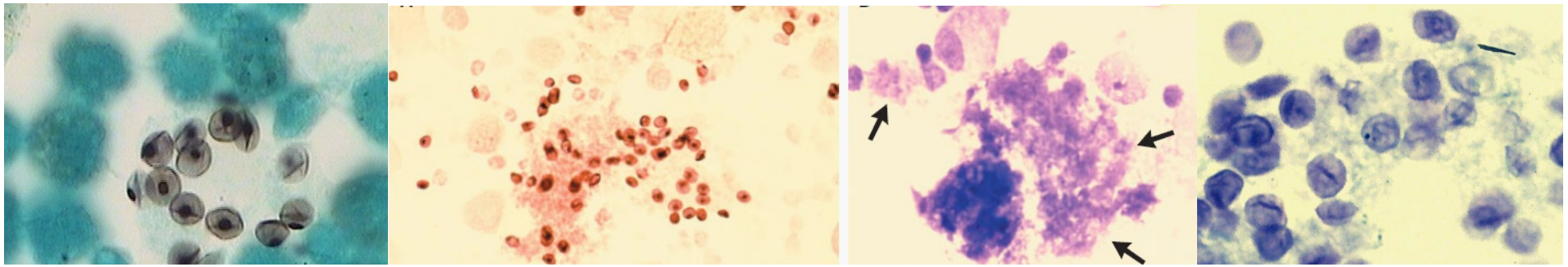
Annabelle Stoclin
Réanimation USCM
Gustave Roussy
114, rue Edouard Vaillant
94805 Villejuif Cedex – France
Tel : 01 42 11 42 11

Conflits d'intérêts

- Aucun

INTRODUCTION

- 1910 A. Carini: poumon de rat
- 1912 Tropisme pulmonaire «kyste » → Pneumocystis carinii
- 1940 Prématurés… grands immunodéprimés.
- 1981 SIDA
- 1988 Champignon ubiquitaire atypique
  - Ne pousse pas sur les milieux de culture fongique
  - Spécificité hôte /espèce
  - Pas sensible aux antifongiques
- 2005 Pneumocystis jirovecii



CYCLE ?

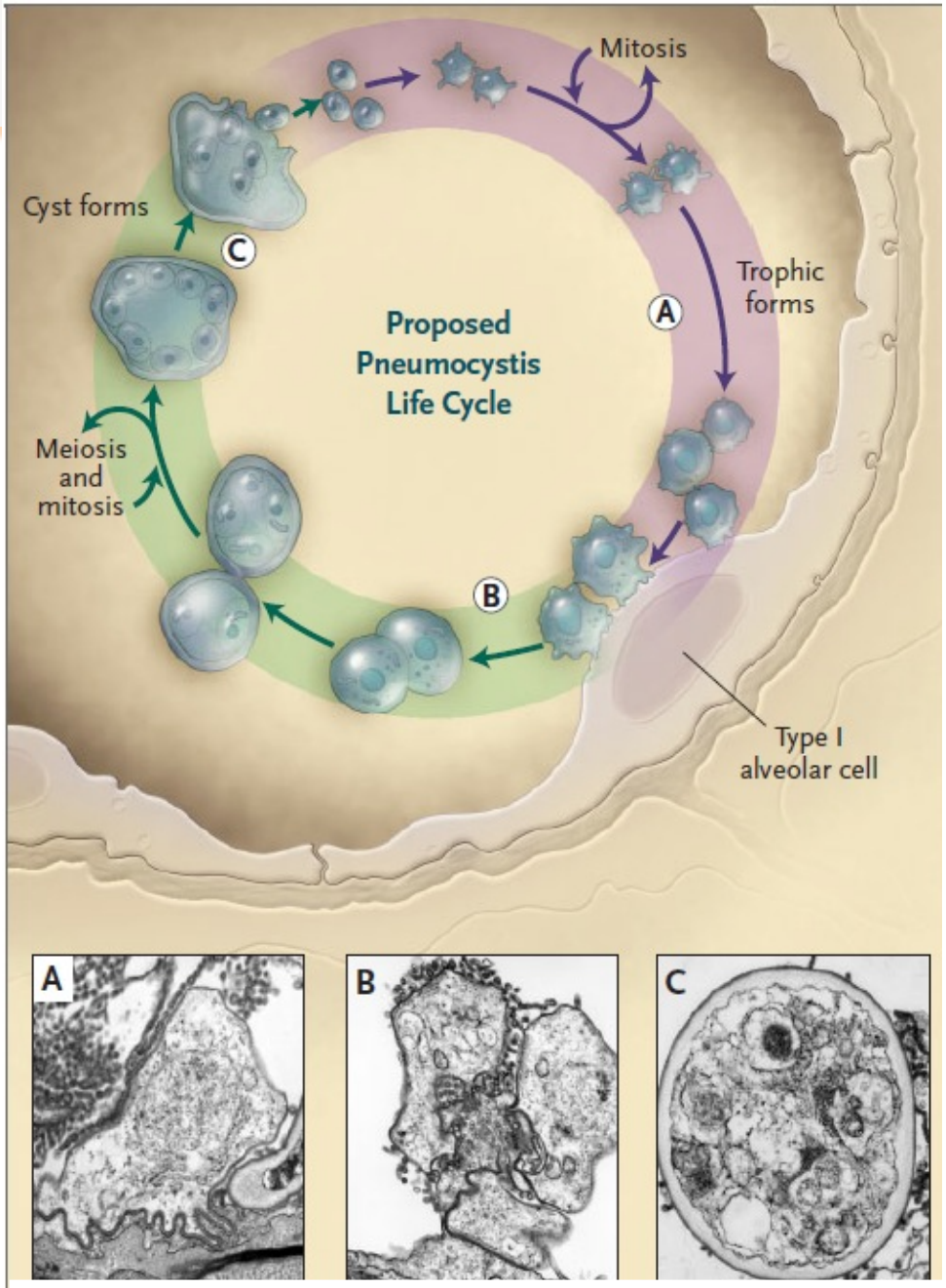
Kystes

éléments probablement infectants (6 à 8 µm), libèrent *in situ* 8 corps intra-kystiques qui se transforment rapidement en :

Trophozoïtes

variables en forme et en taille (2 à 12 µm) mononucléés, amiboïdes, élongations permettant de s'arrimer aux cellules épithéliales de type I où ils se multiplient

grands trophozoites → **prékystes**, ovoïdes (3 à 8 µm) d'abord mono puis multinucléés avec 3 stades (précoces, intermédiaires, tardifs) en fonction du nombre de noyaux (1 à 8) et de la structure de la paroi

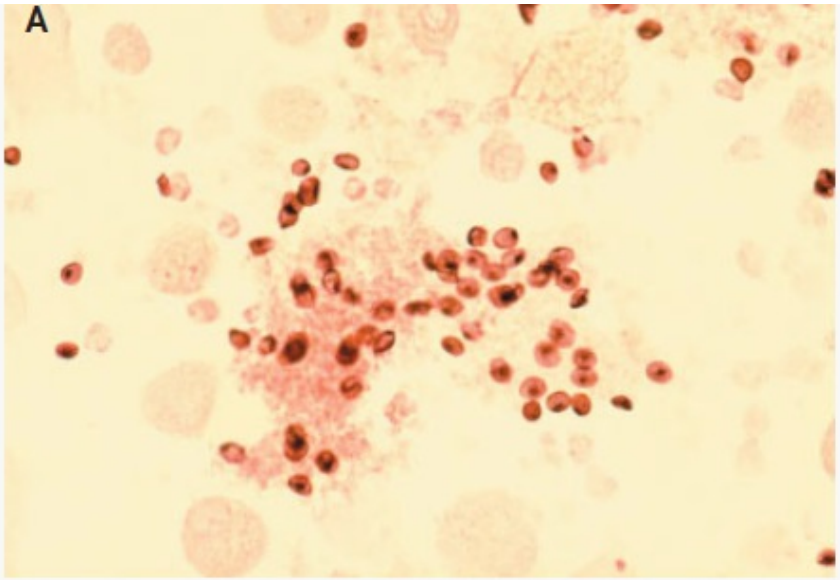


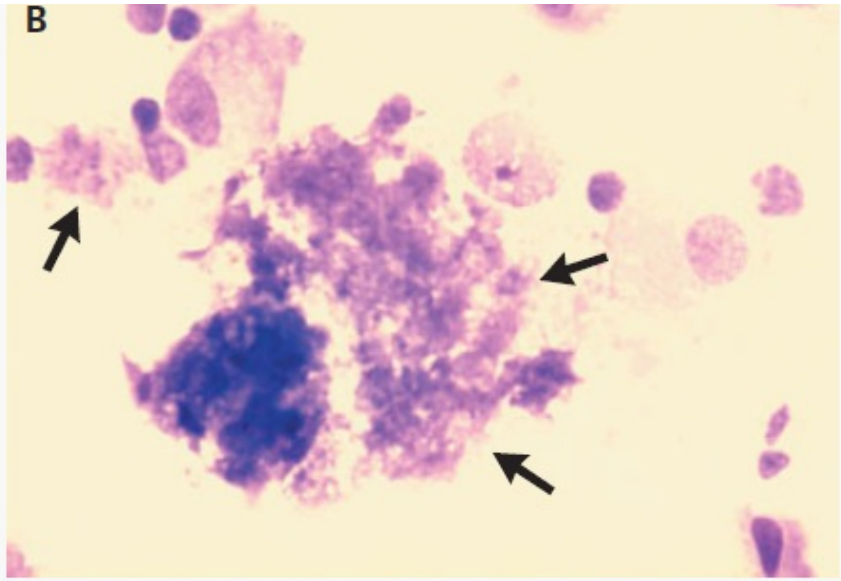
Thomas et Limper NEJM 2004

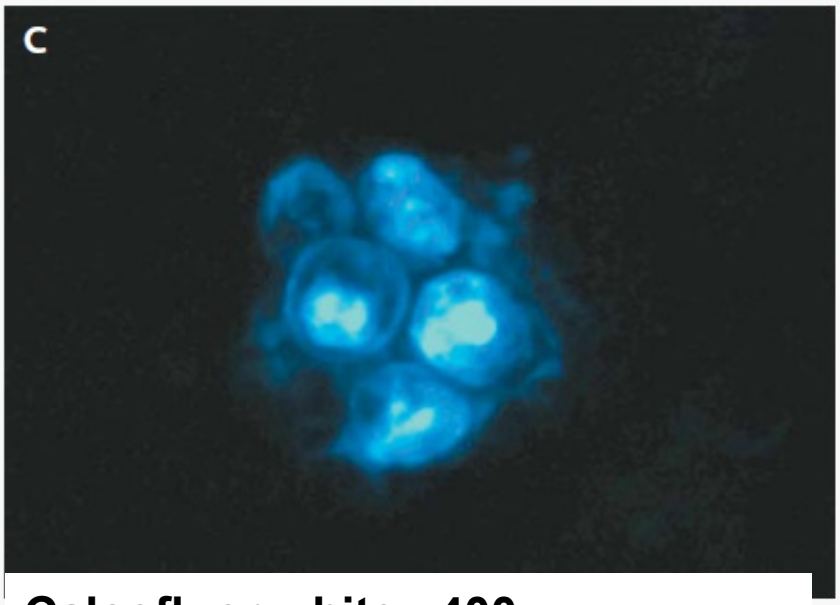
Figure 3. Proposed Pneumocystis Life Cycle.

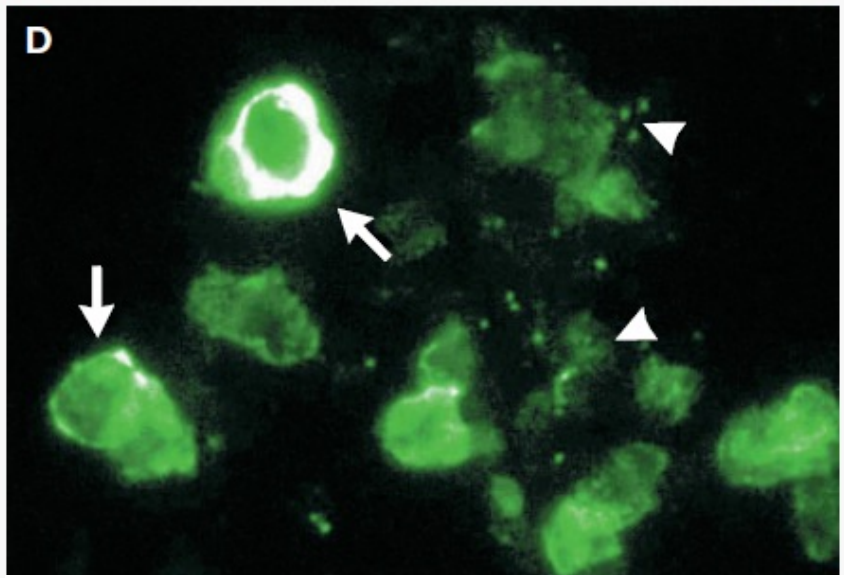
Gomori méthénamine x100
Kystes typiques

Wright–Giemsa staining x100
Formes trophiques









Calcofluor white x400
kystes

IF staining x400 les 2
formes trophiques (têtes flèches) et Kystes (flèches)

INTRODUCTION

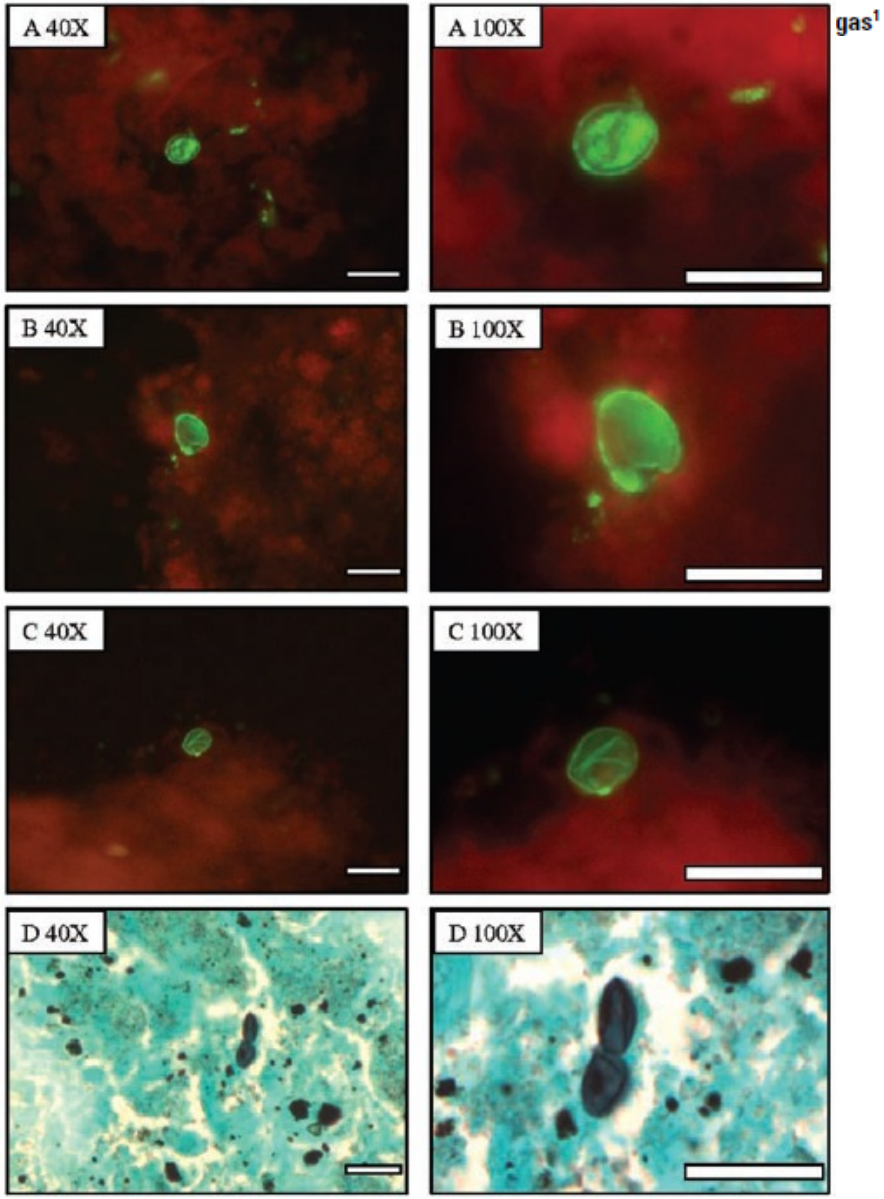
- Primo-infection 90% avant 2-4ans
- Colonisation et transmission inter-humaine

Nevez et al. Pneumocystosis vs pulmonary colonization in HIV-negative and HIV positives patients AIDS.1999;13:535-6

Ponce et al. Pneumocystis colonization is highly prevalent in the autopsied lungs of the general population. CID 2010;50:347-53

Reid et col. Pneumocystosis jirovecii pneumonia in non-VIH-infected patients: new risks and diagnostic tools. Curr. Opin. Infec. Dis. 2011

Pneumocystis Colonization Is Highly Prevalent in the Autopsied Lungs of the General Population



Chili 2005-2008

77 autopsies/adultes immunocompétents

64.9% PCR + → IF +

PCR - → IF-

Ponce et al. CID 2010

Eur J Clin Microbiol Infect Dis (2011) 30:673–675
DOI 10.1007/s10096-010-1139-0

ARTICLE

Pneumocystosis: a network survey in the Paris area 2003–2008

D. Magne · A. Ang
C. Bouges-Michel ·
C. Chochillon · M.
G. Galeazzi · H. Ye

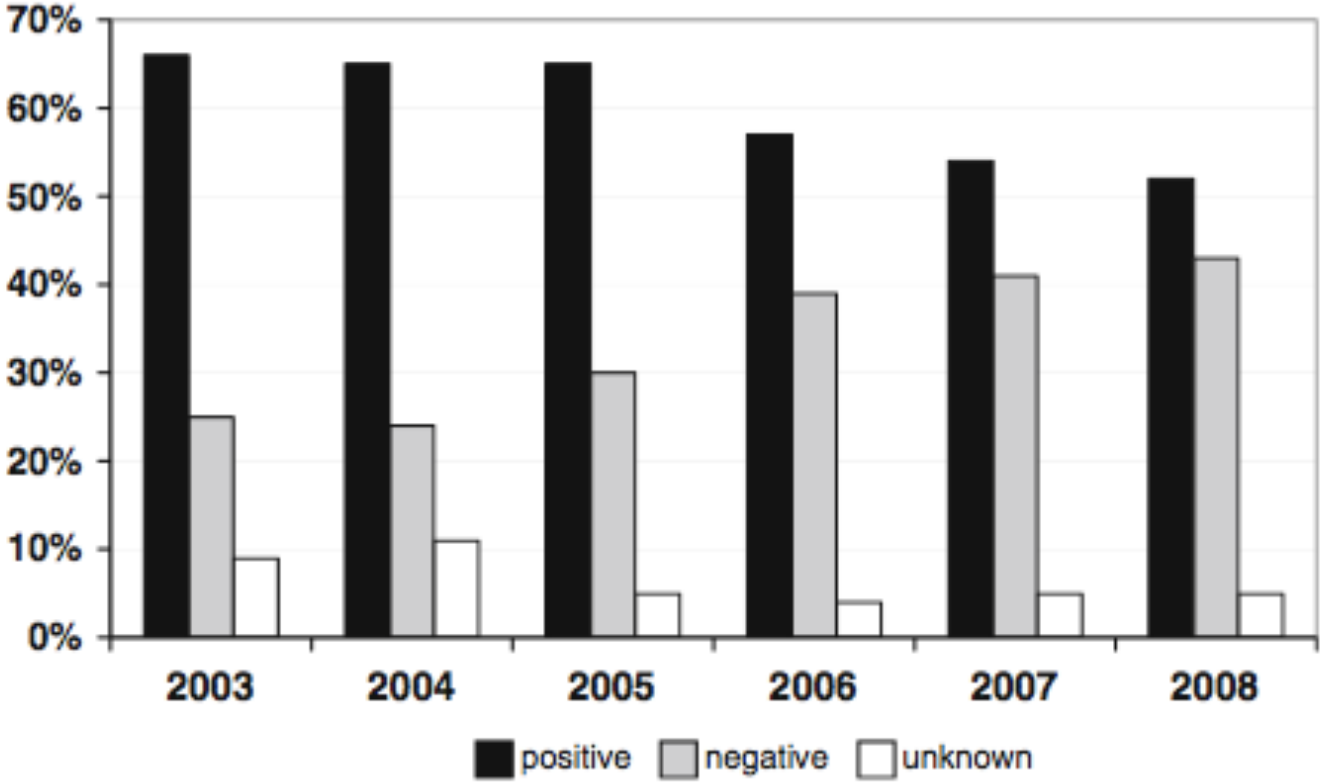


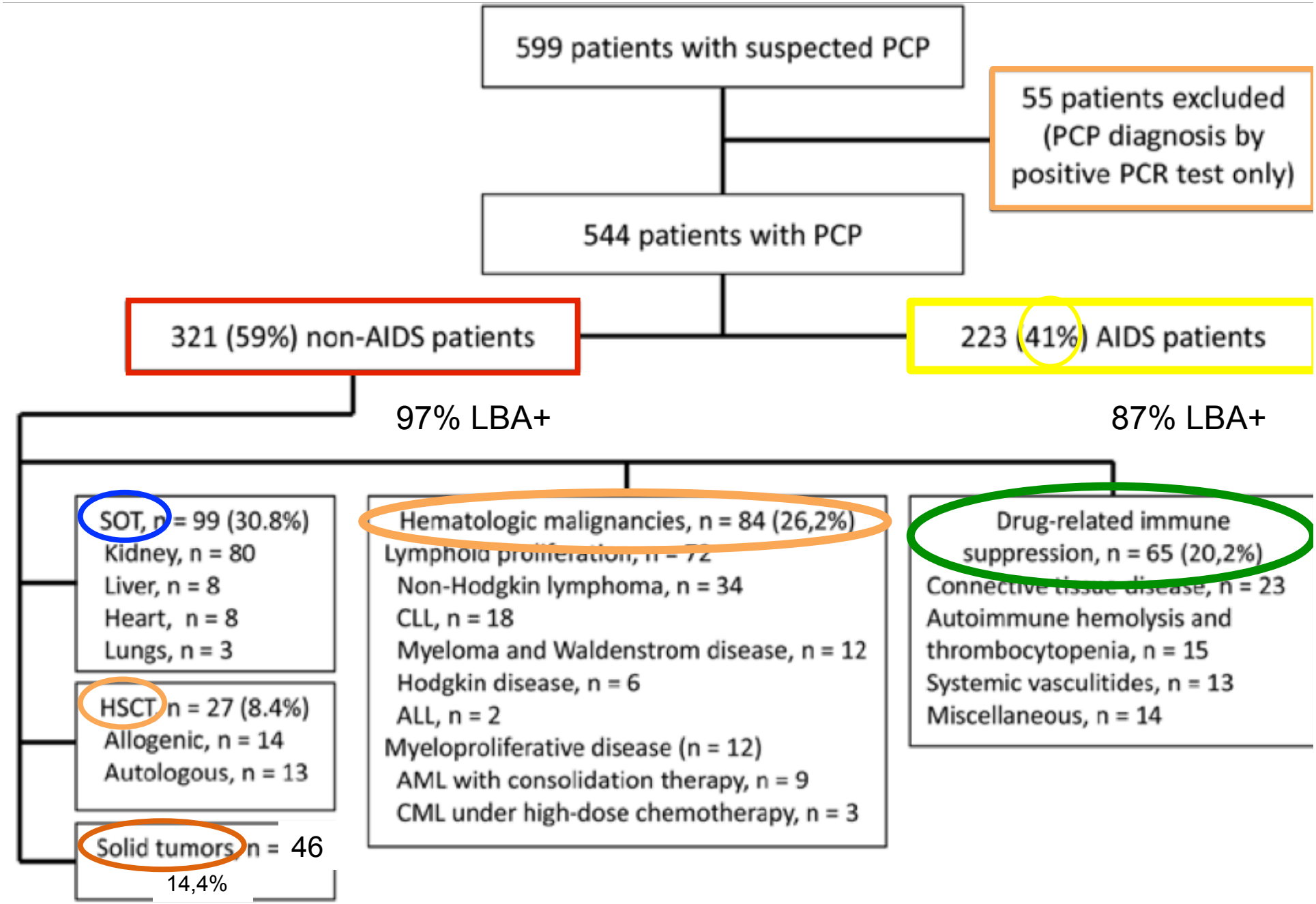
Fig. 1 HIV serological status

Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France

Antoine Roux, Emmanuel Canet, Sandrine Valade, Florence Gangneux-Robert, Samia Hamane, Ariane Lafabrie, Daniéle Maubon, Anne Debourgogne, Soléne Le Gal, Fréderic Dalle, Marion Leterrier, Dominique Toubas, Christelle Pomares, Anne Pauline Bellanger, Julie Bonhomme, Antoine Berry, Isabelle Durand-Joly, Denis Magne, Denis Pons, Christophe Hennequin, Eric Maury, Patricia Roux,[1] and Élie Azoulay

Emerging Infectious Diseases Vol. 20, No. 9, Sept 2014

- 17 Hôpitaux universitaires
- Prospectif janvier 2007 à décembre 2010



Roux et al. Emerging Infectious Diseases 2014

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

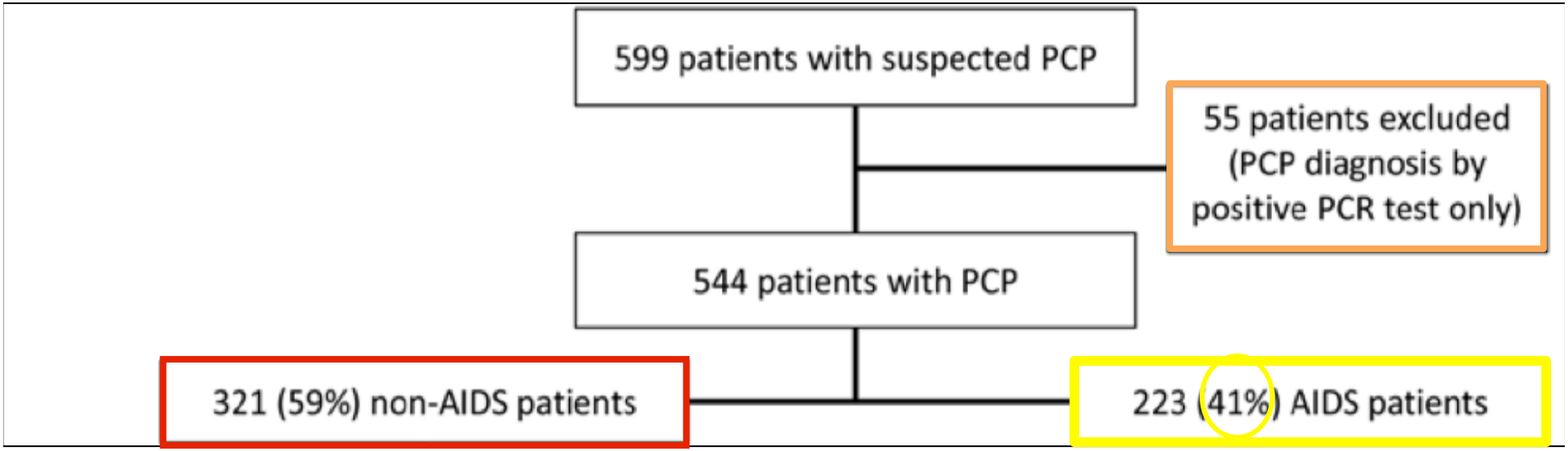
Corticosteroids	Purine analogs
Alkylating agents	Azathioprine
Cyclophosphamide	Cladribine
Temozolomide	Fludarabine
Antibiotics/immunosuppressants	Mycophenolate mofetil
Bleomycin	TNF-α inhibitors
Antimetabolites	Adalimumab
Cytarabine	Etanercept
Fluorouracil	Infliximab
Methotrexate	Monoclonal antibodies
Calcineurin inhibitors	Alemtuzumab
Cyclosporine	Rituximab
Tacrolimus	Tocilizumab
mTOR inhibitors	CTLA4-Ig[a]
Everolimus	Belatacept
Sirolimus	

Tasaka et Tokuda J Infect Chemother (2012) 18:793-806

Mortalité VIH+ 10-20% VIH- 20-60%

Etudes	N	ventilation	Mortalité
Ewig ERJ 1995	16	31%	50%
Pareja Chest 1998	31	67%	40% à l'hôpital
Roblot J Infect. 2003	60	30%	33% à 30 jours
Festic Chest 2005	30	97%	67% à l'hôpital
Bollée Chest 2007	56	20%	19,6%
Zahar CID 2009	39	41%	33% à 30 jours
Matsumura BMC inf dis 2011	82	27%	24% à 30 jours
Moon AAC 2012	88	61%	32% à 30 jours
Lemiale Resp Res 2013	59	100%	56% en réanimation
Ainoda J Inf Chemother 2012	24	50%	45,8% à 90 jours

Mortalité



75 décès 27%

8 décès 4% p<0.0001

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

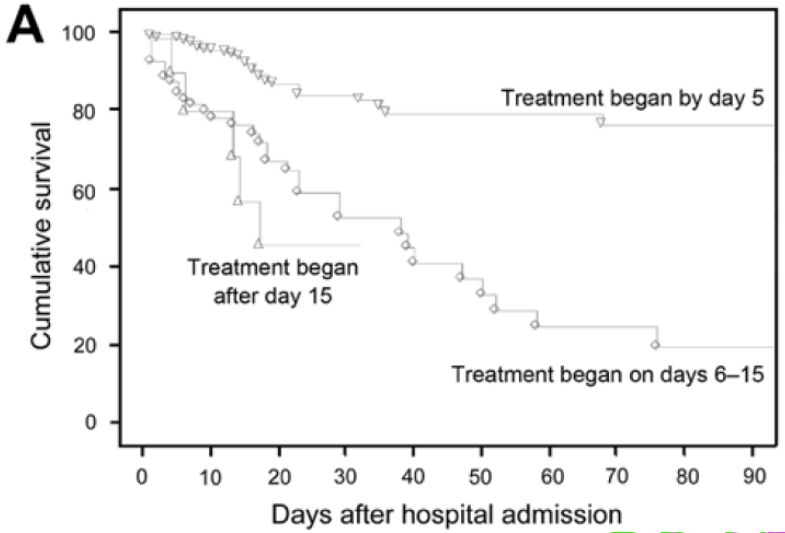
Characteristic	AIDS patients, n = 223	Non-AIDS patients, n = 321	p value
Days from admission to treatment initiation, median (IQR)	1 (0–2)	2 (0–6)	<0.0001
Intensive care admission	65 (35)	134 (50)	0.0015
Immediate oxygen needed	87 (49)	160 (69)	<0.0001
Oxygen flow rate, L/min, mean (95% CI)	2 (1.3–2.8)	3.8 (2.8–4.8)	0.015
Mechanical ventilation			
Noninvasive needed	17 (8)	50 (16)	0.0053
Noninvasive failed	16 (8)	46 (15)	0.013
Invasive needed	25 (11.0)	98 (30.5)	<0.0001

Roux et al. Emerging Infectious Diseases 2014

Mortalité

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)



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CLINIQUE

Table 1. Clinical characteristics of 544 patients with and without AIDS at diagnosis with PCP, France, January 1, 2007–December 31, 2010*

Characteristic	AIDS patients, n = 223	Non-AIDS patients, n = 321	p value
Clinical features			
Prophylaxis prescribed†	3 (1)	12 (4)	0.06
Temperature >38°C	165 (74)	263 (82)	0.05
Days from constitutional symptom onset to diagnosis, median (IQR)	30 (14–60)	7 (2–15)	<0.0001
Shock	5 (2.2)	23 (7)	0.01
Respiratory symptoms			
Cough	170 (76.2)	173 (54)	<0.0001
Dyspnea	176 (79)	234 (73)	0.10
Days from respiratory symptom onset to diagnosis, median (IQR)	21 (7–30)	5 (1–15)	<0.0001
Laboratory test results			
SpO_2, median (IQR)	95 (90–97)	91 (86–96)	0.003
Lymphocyte count, cells/mm^3, median (IQR)	802 (499–1,200)	500 (278–880)	0.0004
CD4+ T-cell count, cells/mm^3, median (IQR)	167 (89–342)	32 (12–75)	<0.0001
C-reactive protein	48 (17–128)	120 (59–210)	<0.0001
Radiologic findings			
Chest radiograph results typical for PCP	183 (82)	247 (77)	0.23
Chest radiograph results atypical for PCP‡	31 (14)	48 (15)	0.66
Pneumothorax	7 (3.1)	7 (2.2)	0.50
Chest radiograph results unremarkable	9 (4)	26 (8)	0.34
Atypical computed tomography scan pattern§	15 (14)	22 (14)	0.47

30% Co infections: bactériennes surtout, virales et fongiques

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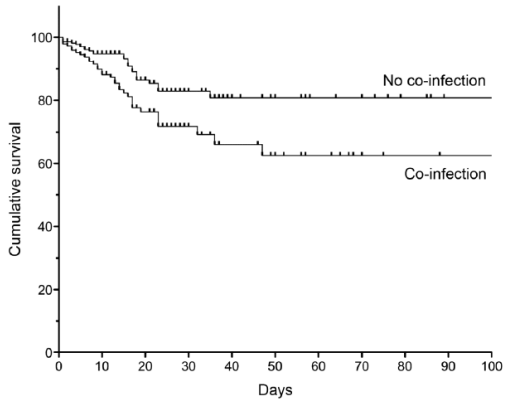
Co-infections

Co-infection	All, n = 544	AIDS, n = 223	Non-AIDS, n = 331	p value
≥1 microbial co-infection	169 (31)	68 (30.5)	101 (30.5)	0.99
≥2 microbial co-infections	32 (5.8)	12 (5.3)	20 (6)	0.83
Pathogen				
Virus	65 (11.9)	30 (13.4)	35 (10.5)	0.34
CMV	44	21	23	
HSV	18	7	11	
Influenza	2	1	1	
RSV	1	1	0	
Bacteria	92 (16.9)	41 (18.3)	37 (11.1)	0.018
Pneumococcus	12	6	6	
Enterococcus sp.	4	3	1	
Streptococccus sp.	4	2	2	
Haemophilus or *moraxella catharallis*	8	6	2	
Staphylococcus aureus	13	11	2	
Other Staphylococcus spp.	5	1	4	
Pseudomonas	17	6	11	
Enterobacteria	13	4	9	
Mycobacterium tuberculosis	2	2	0	
Others	14			
Fungus	38 (6.9)	10 (4)	28 (8)	0.08
Aspergillus sp.	18	0	18	
Candida sp.	20	10	10	
Cryptococcus neoformans	2	2	0	
Parasite	6 (1.1)	6 (2.6)	0 (0)	0.0041
Cryptosporidum sp.	1	1	0	
Toxoplasma gondii	1	1	0	
Schistosoma sp.	1	1	0	
Isospora belli	1	1	0	

*Values are no. (%) patients. p values by χ^2 test. CMV, cytomegalovirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus.



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CLINIQUE

Table 2. Clinical and Laboratory Features at Presentation in Patients with Pneumocystis Pneumonia

	Patients with the Acquired Immunodeficiency Syndrome		Patients with Other Immunosuppressive Diseases	
	Evaluable Patients	Number of Patients and Values	Evaluable Patients	Number of Patients and Values
Symptoms, *n (%)*				
Fever	48	38 (81)	38	33 (87)
Chills	48	12 (26)	38	10 (26)
Shortness of breath	48	32 (68)	38	25 (66)
Cough	48	38 (81)	38	27 (71)
Sputum	48	11 (23)	38	8 (21)
Chest pain	48	11 (23)	38	9 (24)
Median duration of symptoms (range)*, *d*	40	28 (1-270)	37	5 (1-42)
Temperature ≥ 38.0 °C, *n (%)*	45	34 (76)	38	35 (92)
Median respiratory rate per minute (range)†	42	24 (14-40)	38	26 (16-60)
Rales, *n (%)*	46	14 (30)	38	13 (34)
Chest radiograph, *n (%)*				
Bilateral infiltrate	49	46 (94)	39	34 (87)
Unilateral infiltrate	49	1 (2)	39	2 (5)
No infiltrate	49	2 (4)	39	3 (8)
Median blood gas values (range), *mm Hg*				
Room air arterial oxygen tension*	45	69 (35-116)	33	52 (29-91)
Alveolar-arterial oxygen gradient†	45	41 (1-99)	33	59 (23-91)

VIH+ VIH-

Kovacs et al. Annals of Internal medecine 1984; 100:663-671. PcP : A Comparison Between Patients with the AIDS and Patients with Other Immunodeficiencies

IMAGERIE

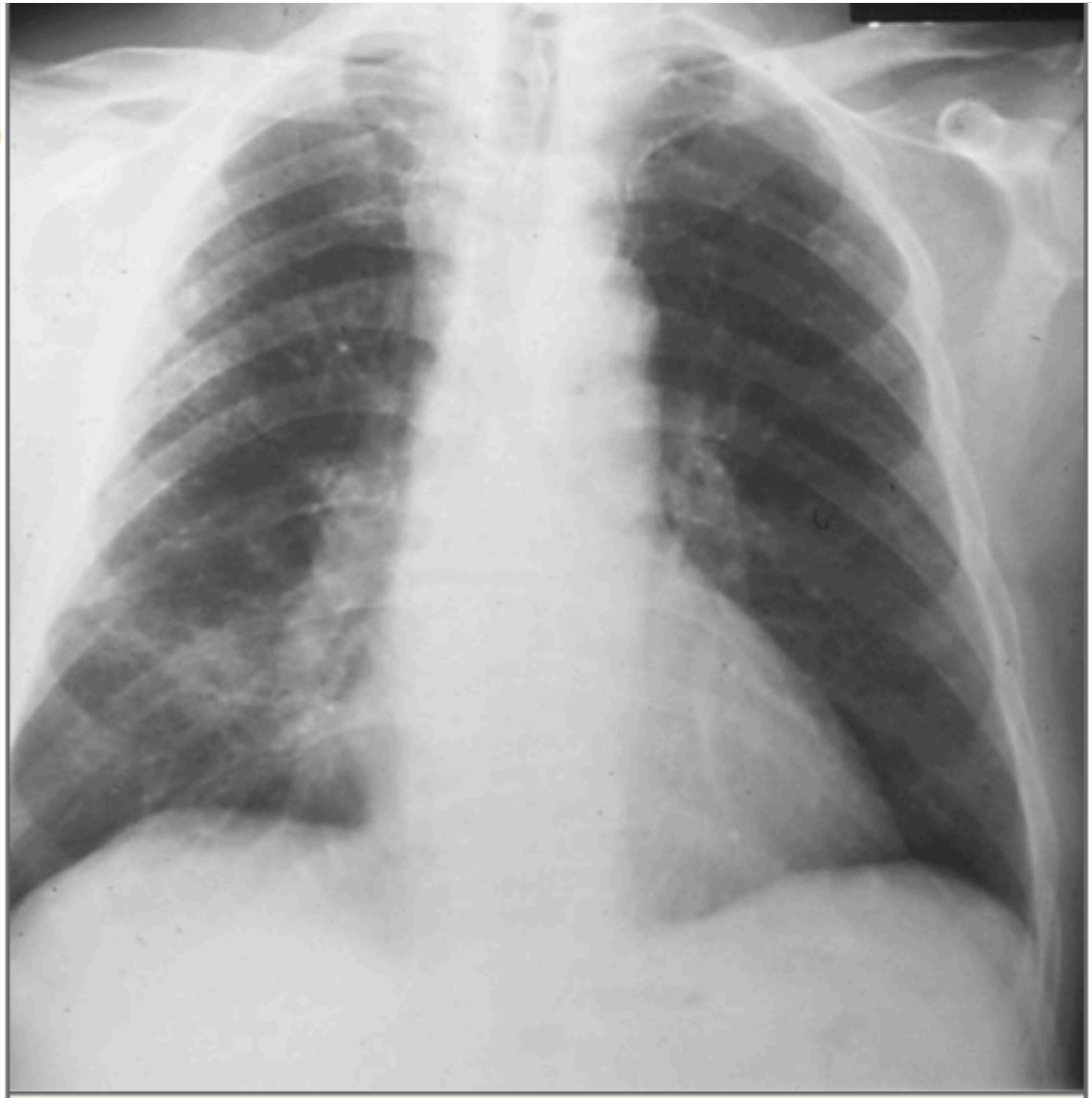
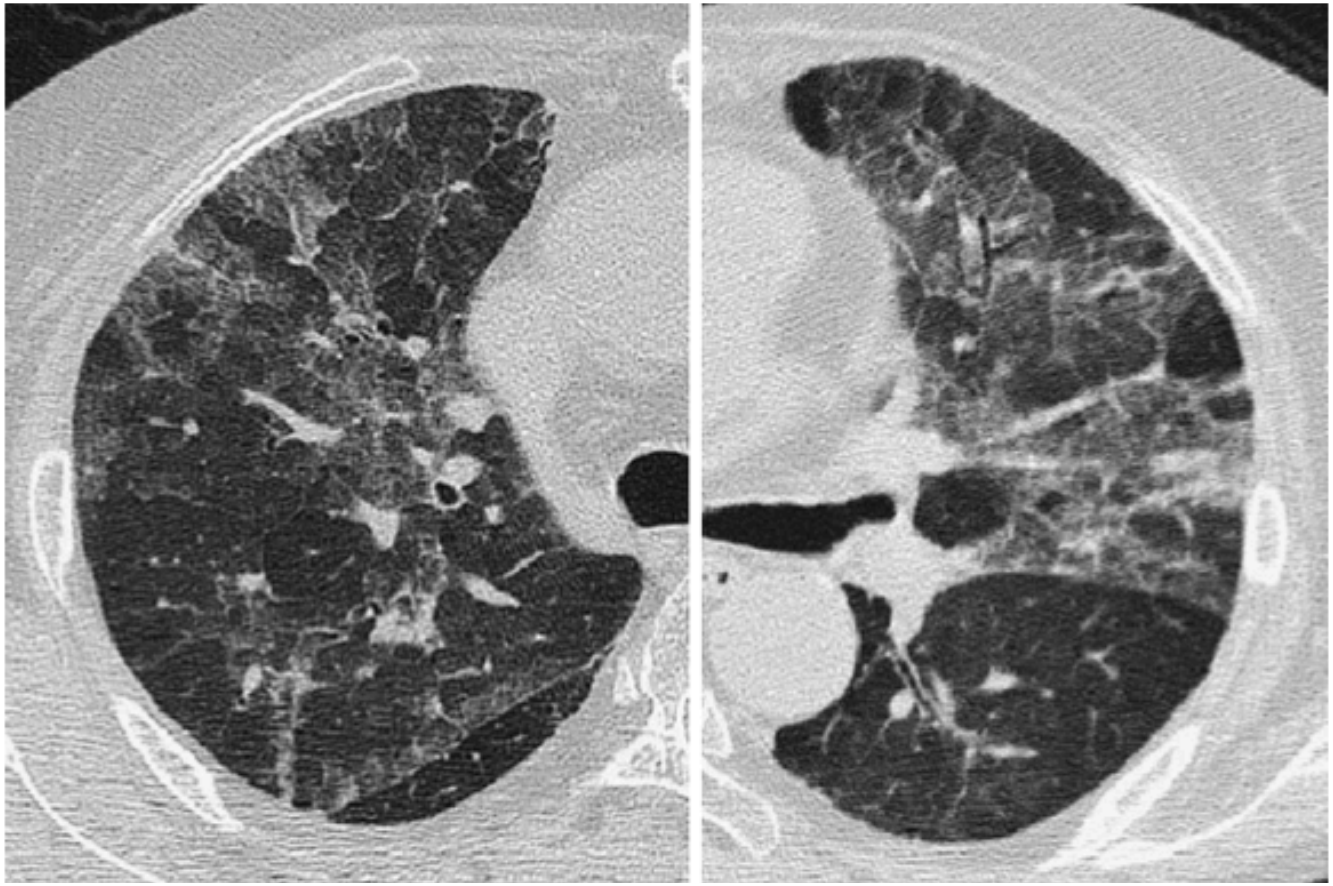


Figure 1. Posteroanterior Chest Radiograph of a 68-Year-Old Patient with Pneumocystis Pneumonia That Developed as a Consequence of Long-Term Corticosteroid Therapy for an Inflammatory Neuropathy.

Mixed alveolar and interstitial infiltrates are more prominent on the right side than on the left.

Thomas et Limper N Engl J Med 2004;350:2487-98.

IMAGERIE



Type A

58 ans LNH et RA MTX depuis 4 ans

Verre dépoli nette délimitation par les septa interlobulaires du poumon normal

Tasaka et al. Internal Medecine 2010

IMAGERIE

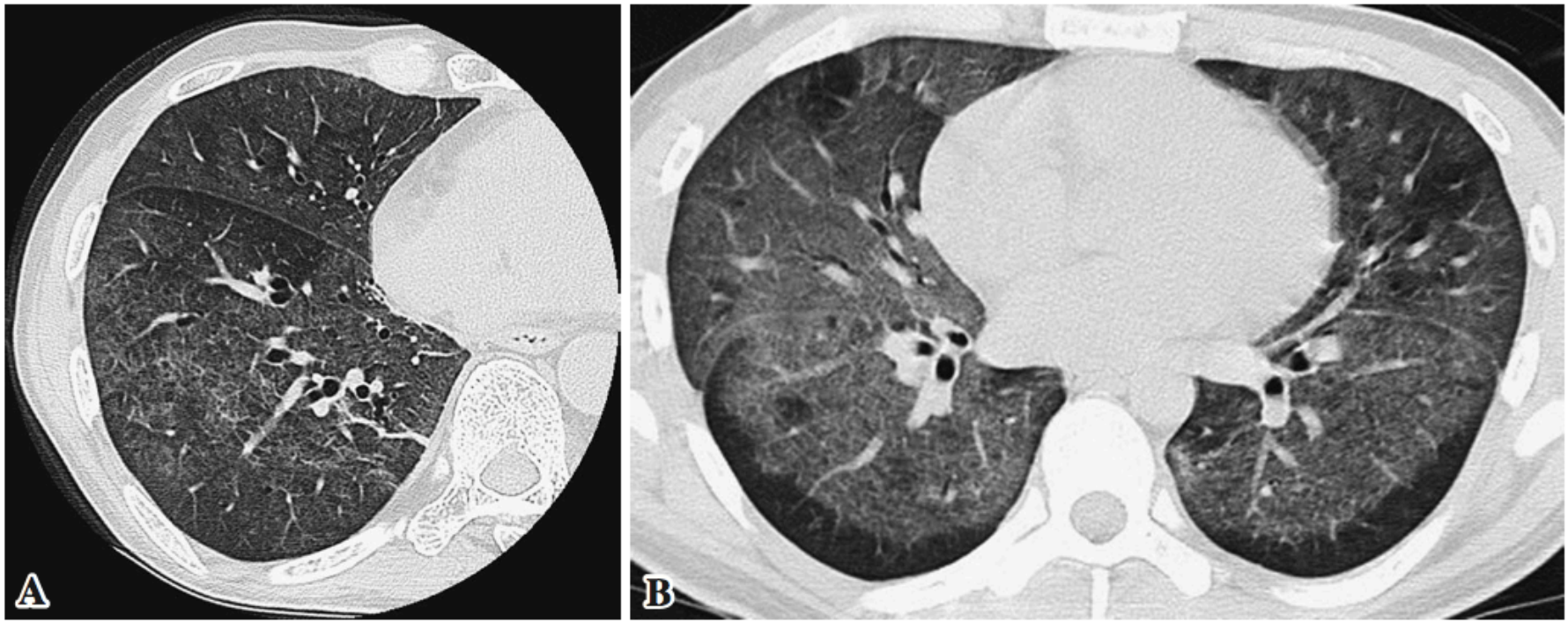
TYPE B

76 ans K œsophage

VD diffus de distribution inhomogène sans lien avec les lobules secondaires

30 ans SIDA

Idem respect de la zone sous pleurale



Tasaka et al. Internal Medecine 2010

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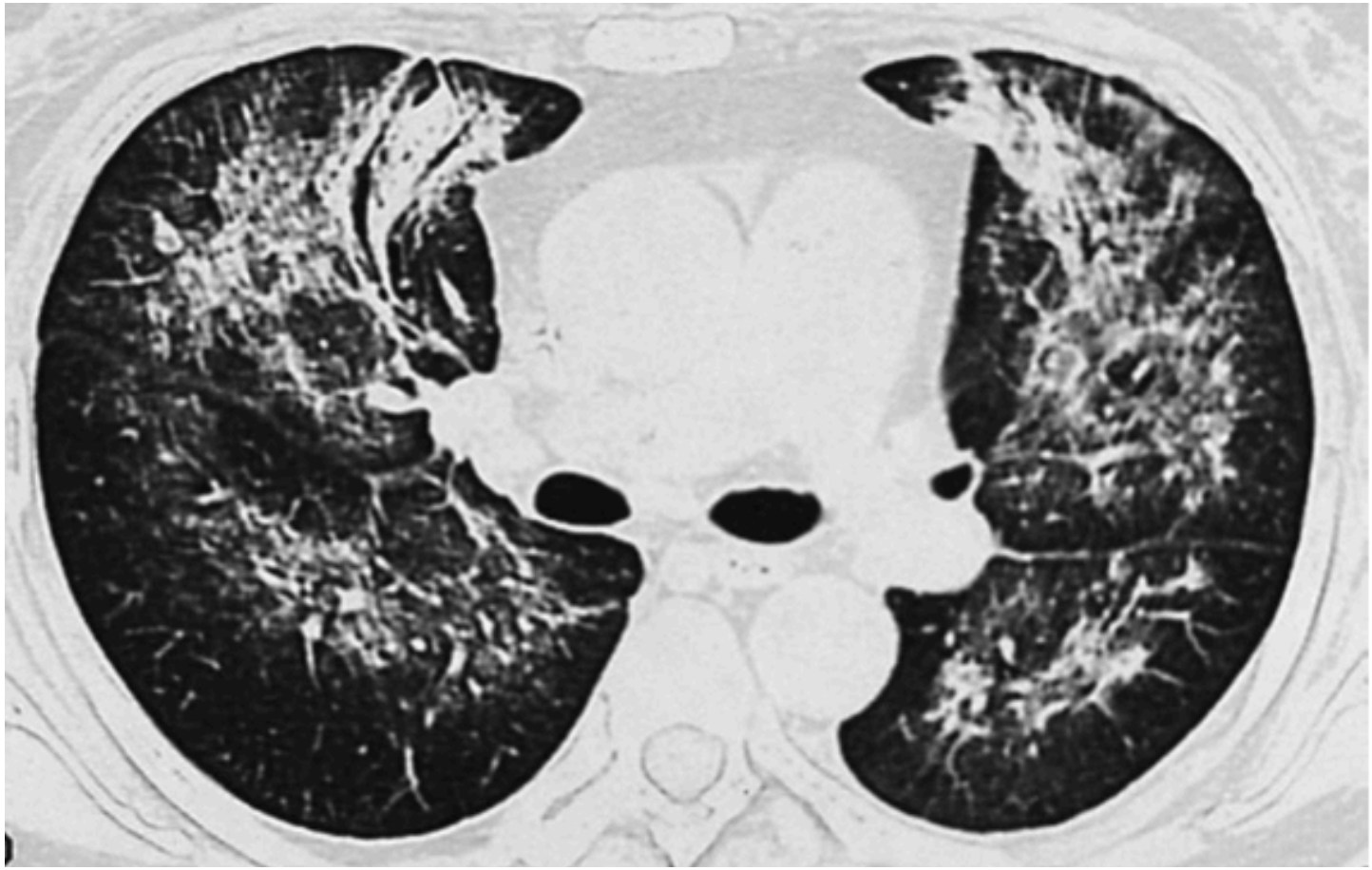


TYPE C

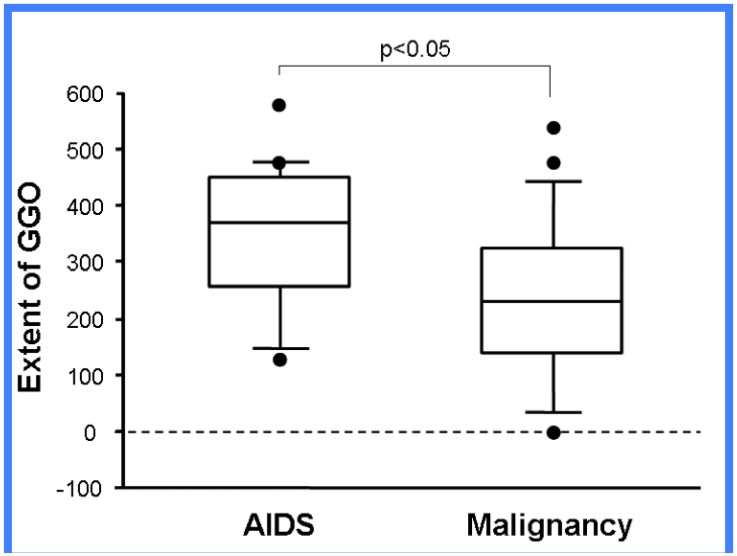
60 ans LNH, consolidation le long des axes broncho-vasculaires, distorsion, épaississements des septa inter-lobulaires

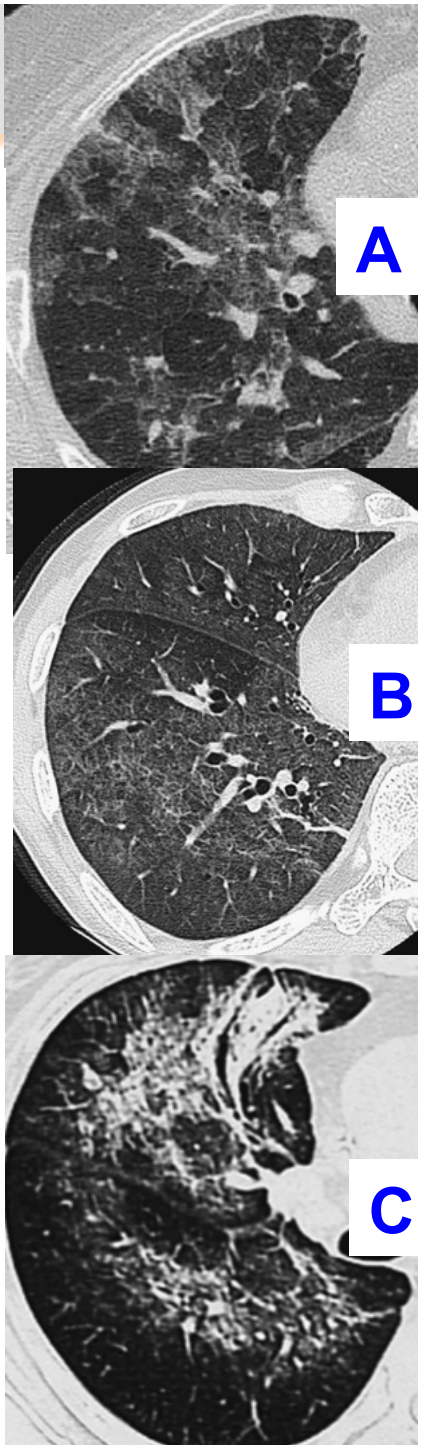
Tasaka et al. Internal Medecine 2010

IMAGERIE

Table 2. Occurrence of Image Patterns and Characteristic Findings on CT

	Malignancy (n=21)	AIDS (n=17)	p value†
Image patterns			
Type A	1* (5%)	0 (0%)	
Type B	10 (48%)	17 (100%)	<0.01
Type C	10 (48%)	0 (0%)	
Characteristic findings			
Consolidation along the bronchovascular bundle	9 (43%)	1 (5%)	<0.02





IMAGERIE

J1 J3 condensation

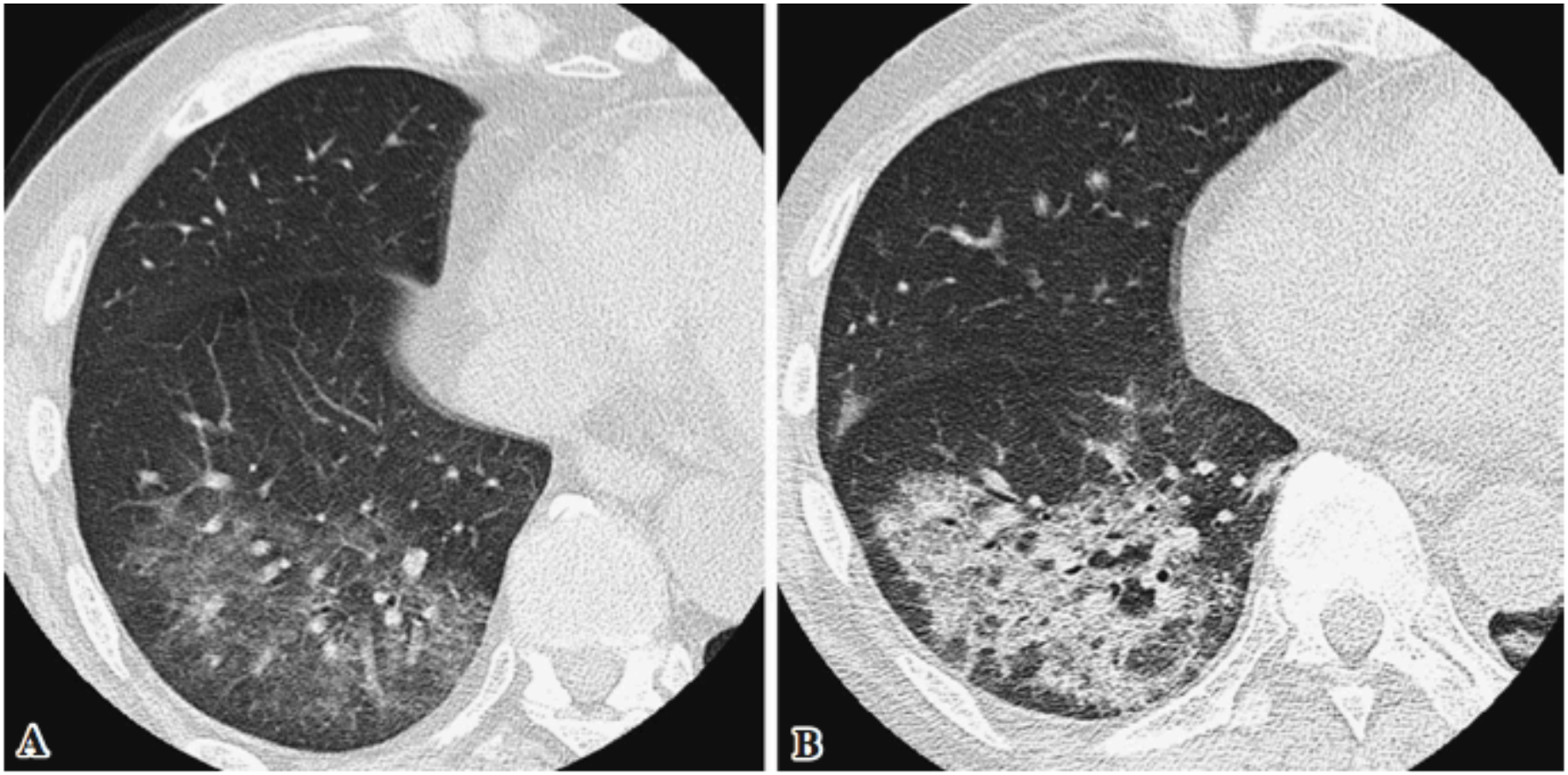


Figure 4. HRCT images of a 64-year-old man with non-Hodgkin lymphoma. (A) On the day of onset, HRCT shows diffuse GGO with inhomogeneous distribution. PCP was diagnosed through positive PCR in induced sputum and the serum β-D-glucan level elevated as high as 64.7 pg/mL. (B) Three days later, consolidation in addition to GGO was observed.

Tasaka et al. Internal Medecine 2010

IMAGERIE

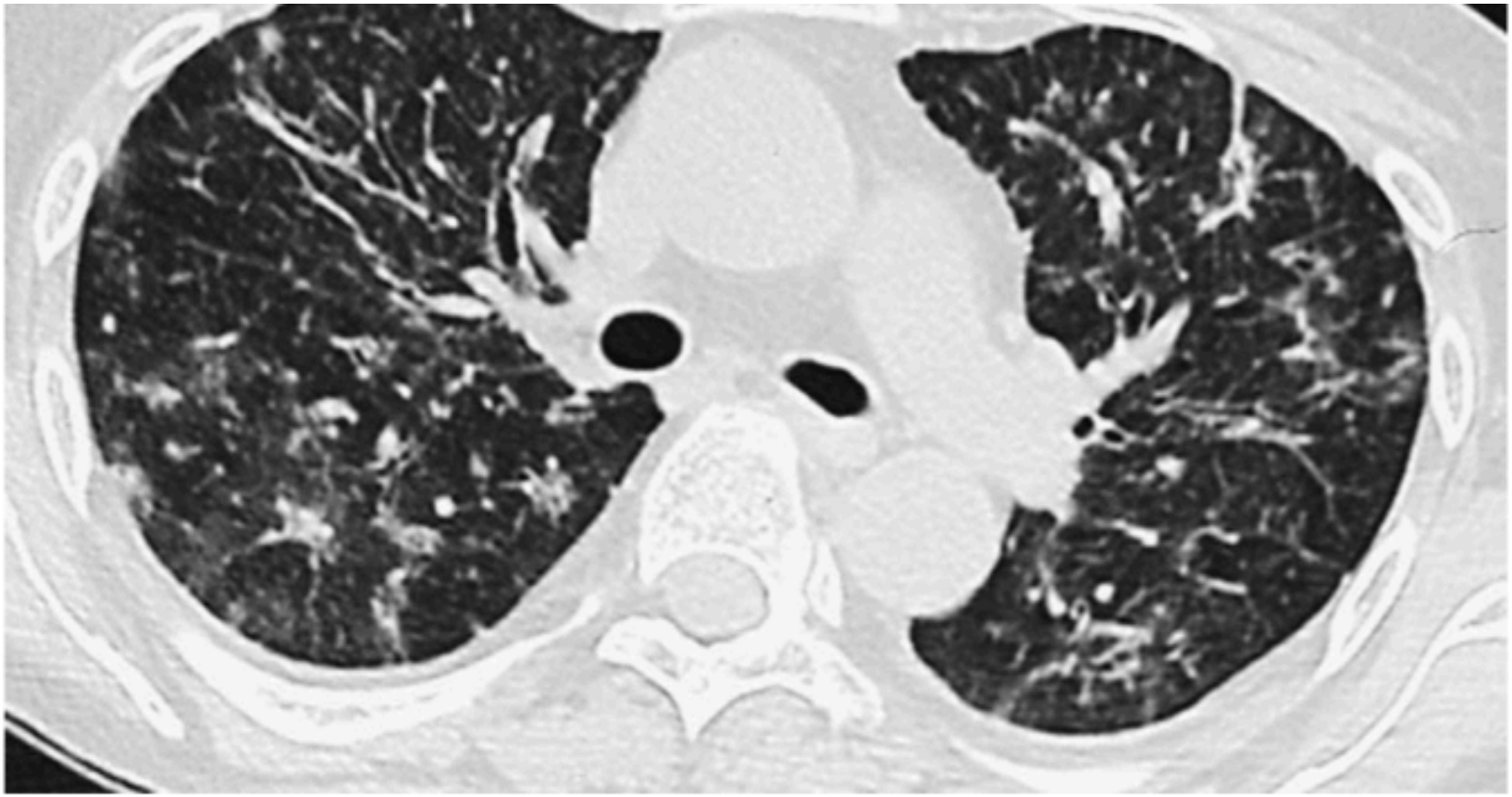


Figure 7. **HRCT appearance in a 42-year-old female patient with acute lymphoblastic leukemia, showing diffuse GGO with inhomogeneous distribution unrelated to secondary lobules and centrilobular nodules.**

LBA

Pneumocystis carinii Pneumonia

Differences in Lung Parasite Number and Inflammation in Patients with and without AIDS[1,2]

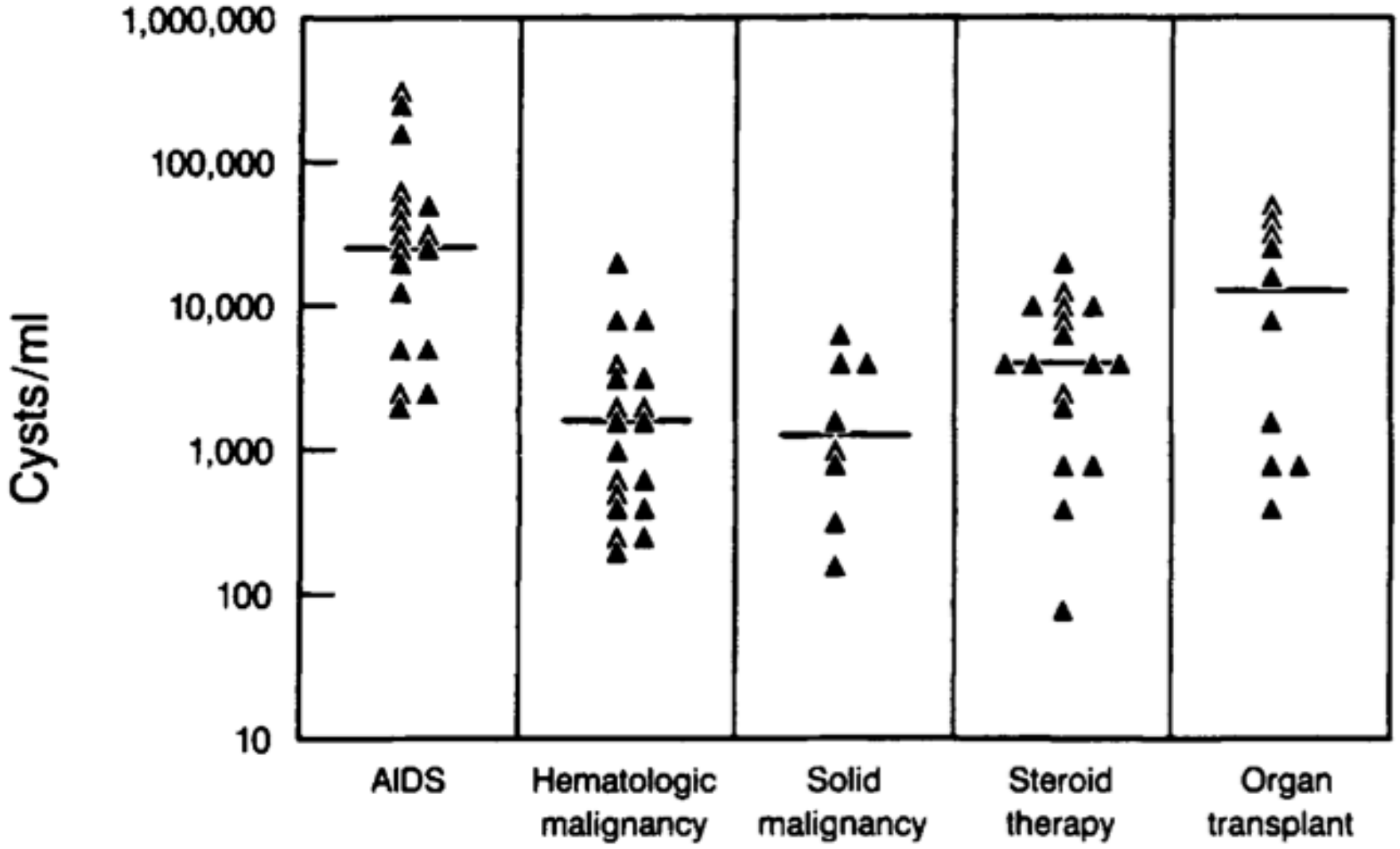
ANDREW H. LIMPER, KENNETH P. OFFORD, THOMAS F. SMITH, and WILLIAM J. MARTIN II

This investigation demonstrates substantial differences in lung inflammation and parasite number during *P. carinii* pneumonia in patients with and without AIDS. The data further suggest that lung inflammation contributes substantially to respiratory impairment in patients with *P. carinii* pneumonia.

AM REV RESPIR DIS 1989; 140:1204–1209

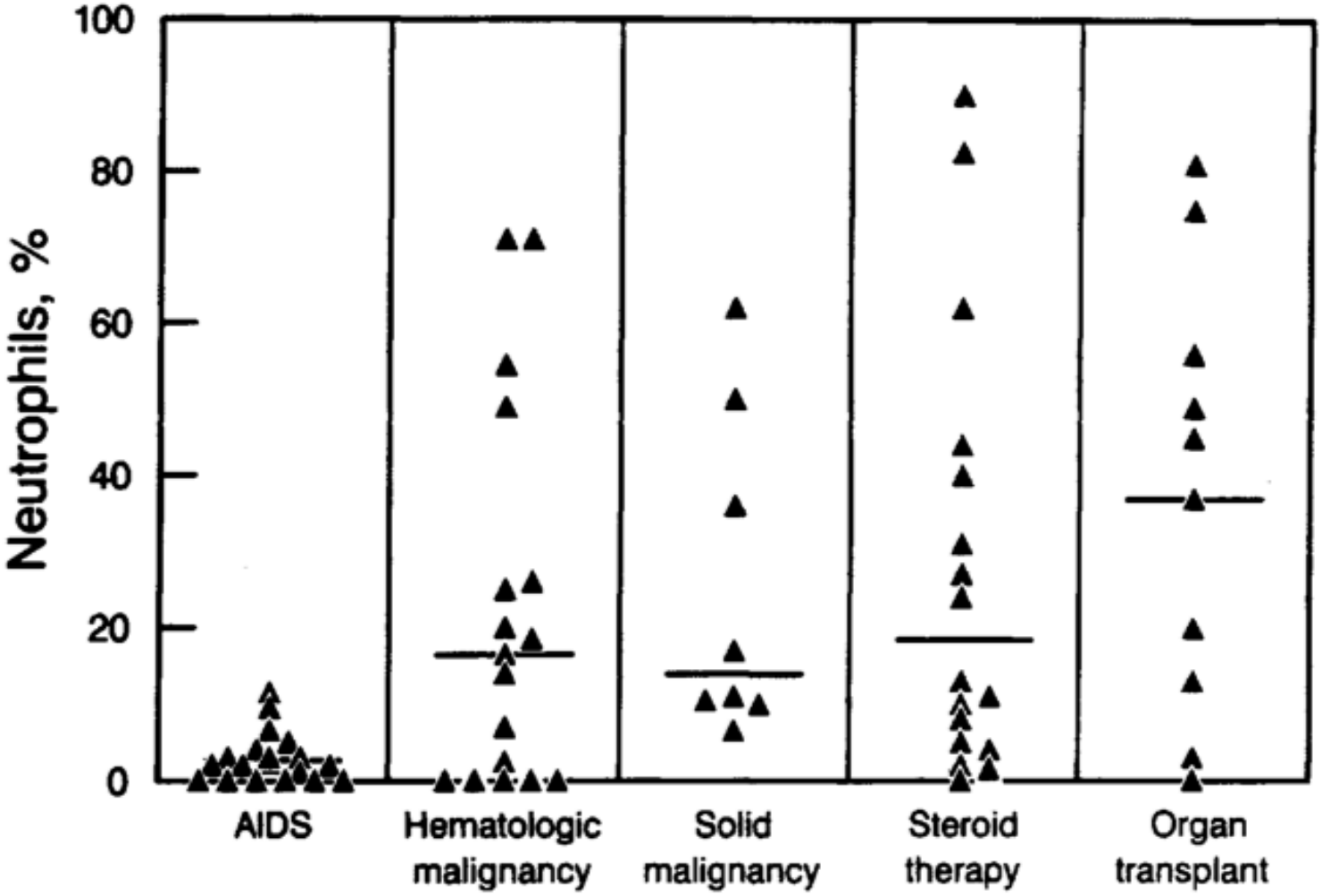
Limper et al. AM REV RESPIR DIS 1989; 140:1204-1209

LBA



Limper et al. AM REV RESPIR DIS 1989; 140:1204-1209

LBA



Limper et al. AM REV RESPIR DIS 1989; 140:1204-1209

DIAGNOSTIC

Repose sur la mise en évidence du microorganisme dans EI ou LBA → Colorations et IF

Colorations: Sp 100%, Se EI: 35 à 78% LBA: 60-92% voire moins chez le VIH- (38-58%)

IF Se 43-78% chez le non VIH

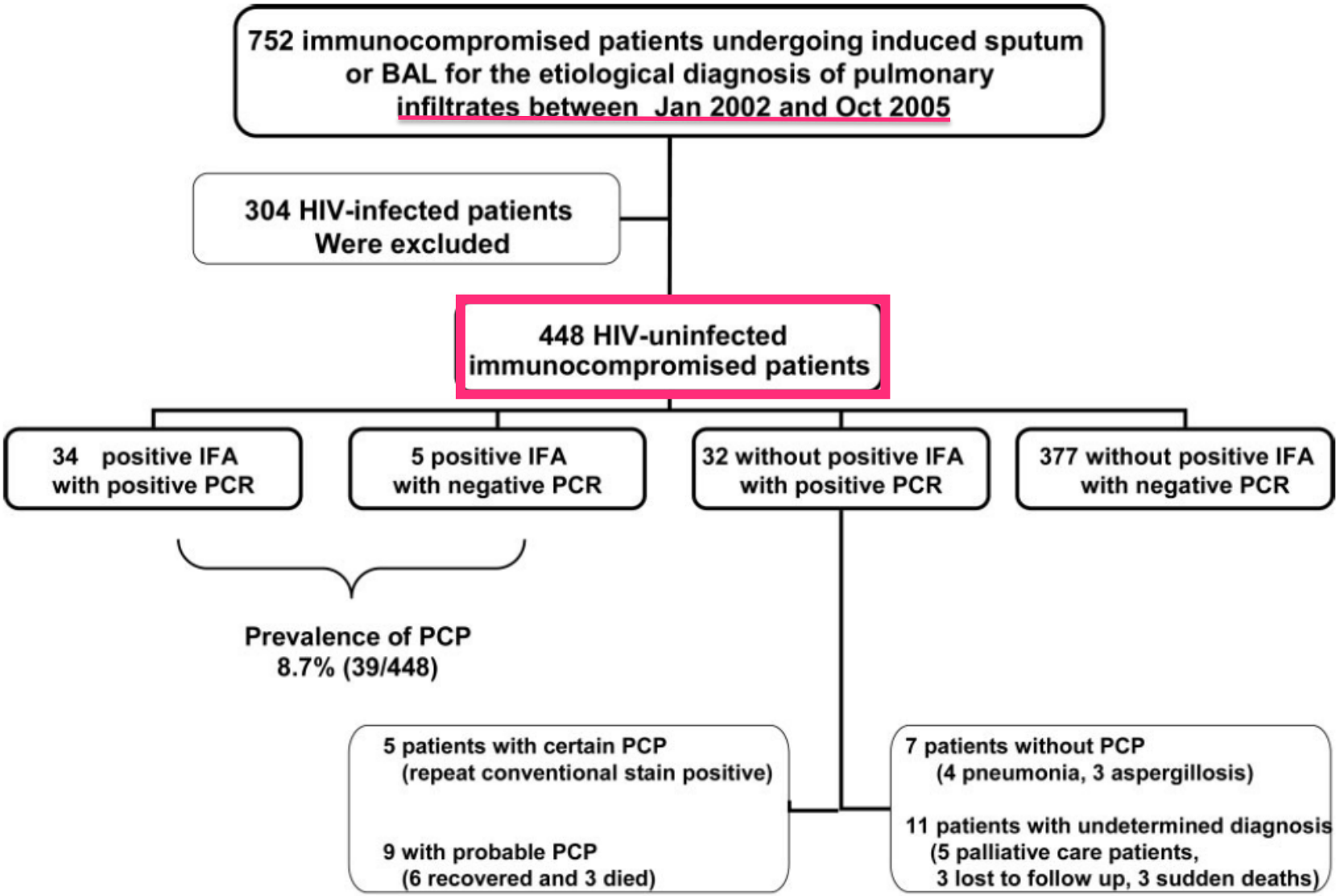
Insuffisant … développement de nouveaux outils: PCR et BDglucan

Polymerase Chain Reaction for Diagnosing Pneumocystis Pneumonia in Non-HIV Immunocompromised Patients With Pulmonary Infiltrates*

Élie Azoulay, MD, PhD; Anne Bergeron, MD, PhD; Sylvie Chevret, MD, PhD; Nicolas Bele, MD; Benoît Schlemmer, MD; and Jean Menotti, PhD

Resp Inf Chest Mars 2009

DIAGNOSTIC


752 immunocompromised patients undergoing induced sputum or BAL for the etiological diagnosis of pulmonary infiltrates between Jan 2002 and Oct 2005
304 HIV-infected patients Were excluded
448 HIV-uninfected immunocompromised patients
34 positive IFA with positive PCR
5 positive IFA with negative PCR
32 without positive IFA with positive PCR
377 without positive IFA with negative PCR
Prevalence of PCP 8.7% (39/448)
5 patients with certain PCP (repeat conventional stain positive)
9 with probable PCP (6 recovered and 3 died)
7 patients without PCP (4 pneumonia, 3 aspergillosis)
11 patients with undetermined diagnosis (5 palliative care patients, 3 lost to follow up, 3 sudden deaths)

DIAGNOSTIC

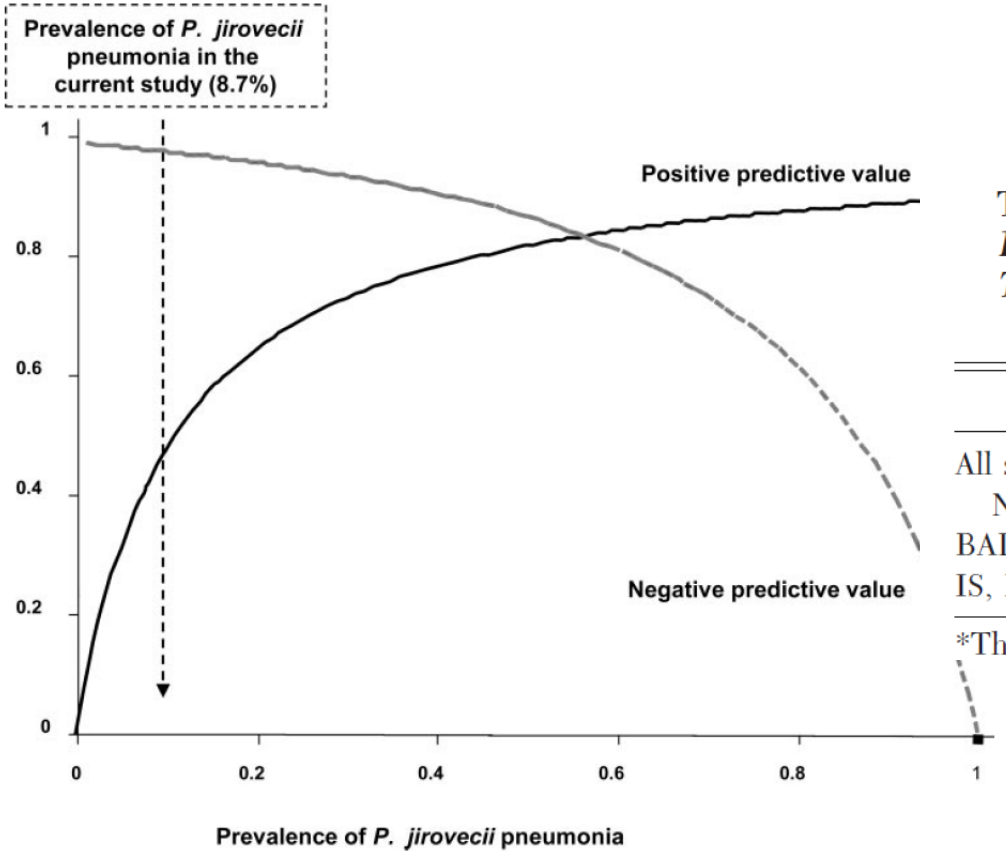


FIGURE 2. Negative and positive predictive values of PCR for *P jiroveci* according to prevalence of PCP. The arrow indicates the prevalence in our study population (8.7%).

Table 2—*Estimation of Diagnostic Performance of PCR for Detecting* P jiroveci *According to Sample Type, Compared to Indirect Fluorescent Antibody Staining*

	Sensitivity	Specificity	PPV*	NPV*
All samples, N = 448	87.2	92.2	51.5	98.7
BAL, N = 351	84	93	53.1	98.3
IS, N = 97	100	90	87	100

*These values refer to a population with a PCP prevalence of 8.7%.

Tableau 2. Performances de la PCR chez les patients non VIH[9]

	Expectorations induites (EI)	Lavage broncho-alvéolaire (LBA)
Sensibilité	100	84
Spécificité	90	93
VPP	87	53,1
VPN	100	98,3

DIAGNOSTIC

Tableau 3. Valeurs de sensibilités des différents tests pour le diagnostic de PPJ

	Expectorations induites (EI)	Lavage broncho-alvéolaire (LBA)
Examen direct (ED)[5]	35-78%	60-92%
Immunofluorescence (IF)[2]	43-78%	89-98%
PCR conventionnelle[2,4,5,7]	86-100%	86-100%
PCR quantitative[5]	–	100%

qPCR pourrait distinguer l'infection de la colonisation

Pb: méthodes maisons → harmoniser/définir des seuils

Tapparel et col. Revue médicale Suisse 2010

Real-time PCR chez le patient non VIH

Table 1 Major studies evaluating diagnosis of *Pneumocystis jirovecii* pneumonia by real-time PCR in non-HIV immunocompromised patients: comparative test performance

Study	Target gene	PCR format	Specimen (no.)	No. PJP episodes	Patient population (no.)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hauser *et al.* [104••]	*mtLSU* rRNA	Real-time (MycAssay Pneumocystis)	Respiratory tract (110) BAL (101)	14	HIV (9) and non-HIV (101)	93	90–91	59–65	98-99
Chumpitazi *et al.* [105•]	*MSG*	Real-time (TD-PCR)	BAL (66)	18	Immunocompromised HIV/AIDS (5) Non-HIV/AIDS (49)	100	97.7	95.5	100
de Boer *et al.* [109••]	*DHPS*	Real-time	BAL	21	Non-HIV immunocompromised (31)	100	100	NA	NA
Alanio *et al.* [95•]	*mtLSU* rRNA	Real-time	BAL (163) IS (115)	16	Immunocompromised HIV/AIDS (69) Non-HIV/AIDS (169)	Overall: 100	85.7	72.4[a]	100
Dini *et al.* [106]	*mtLSU* rRNA	Real-time	Respiratory tract (mainly sputum) (932)	150	General population in SA (712)	100	83[a]	78.1[a]	100[a]
Fillaux *et al.* [107]	*MSG*	Real-time	BAL (400)	66	General patient population (101)	100	90.5	47	100
Fujisawa *et al.* [97]	ITS2	Real-time	IS (86)	17	Non-HIV/AIDS (86)	82.4	98.6	93.3	95.8
	ITS2	Single-plex				88.2	81.2	53.6	NA
Rohner *et al.* [92]	β-tubulin	Real-time	BAL (186)	NA	Immunocompromised (including HIV/AIDS and chronic respiratory disease) (130)[a]	100	94.3[a]	67.7[a]	100[a]
	Kex-1	Real-time				100	92.4	63.6	100
Bandt and Monecke [91]	*DHFR*	Real-time	BAL (69)	26	Immunocompromised	82	97	92[a]	92.1[a]
	5.8S rRNA	Real-time				79	100	100	90.9[a]
Linssen *et al.* [108]	*DHPS*	Real-time	BAL (124)	At least 41	HIV and non-HIV immunocompromised, respiratory disease	97.6[a]	91.2[a]	85.1[a]	98.8[a]
	MSG	Real-time				100	90.2[a]	82[a]	100[a]
	MSG (T)	Real-time				97.6[a]	89.2[a]	80[a]	98.8[a]
Alvarez-Martinez *et al.* [103]	*DHPS*	Real-time	BAL, IS, alcohol-fixed slides (total = 213)	111 (microscopy-positive)	HIV and non-HIV	94	96	NA	NA
		Nested				94	81	NA	NA
Flori *et al.* [89]	*MSG*	Real-time	BAL (173)	11	HIV-positive and HIV-negative (150)	100	98.6	84.6[a]	100[a]
	mtLSU	Single-plex	BAL (173)			100	87	NA	NA

BAL, bronchoalveolar lavage; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthase; IS, induced sputum; ITS, internal transcribed spacer; MSG, major surface glycoprotein; *mtLSU*, mitochondrial large subunit; NA, not available; NPV, negative predictive value; PJP, *Pneumocystis jirovecii* pneumonia; PPV, positive predictive value; T, TAMRA dye used; TD-PCR, touchdown PCR.
[a]Calculated from data presented in respective publication and in Chumpitazi *et al.* [105•].

Reid et col. Pneumocystosis jirovecii pneumonia in non-VIH-infected patients: new risks and diagnostic tools. Curr. Opin. Infec. Dis. 2011

The MIQE Guidelines

CONSTAT: manque de consensus sur la meilleure façon d'effectuer et interpréter les **quantitative real-time PCR (qPCR)**.

The Minimum Information for Publication of **Quantitative Real-Time PCR Experiments (MIQE) guidelines** visent la fiabilité des résultats pour aider à assurer l'intégrité de la littérature scientifique, accroître la transparence expérimentale.

→ guidelines qui décrivent le minimum d'informations nécessaires pour évaluer les expériences de qPCR.

→ Suivre ces directives encouragera une meilleure pratique expérimentale, l'interprétation plus fiable et sans équivoque des résultats qPCR.

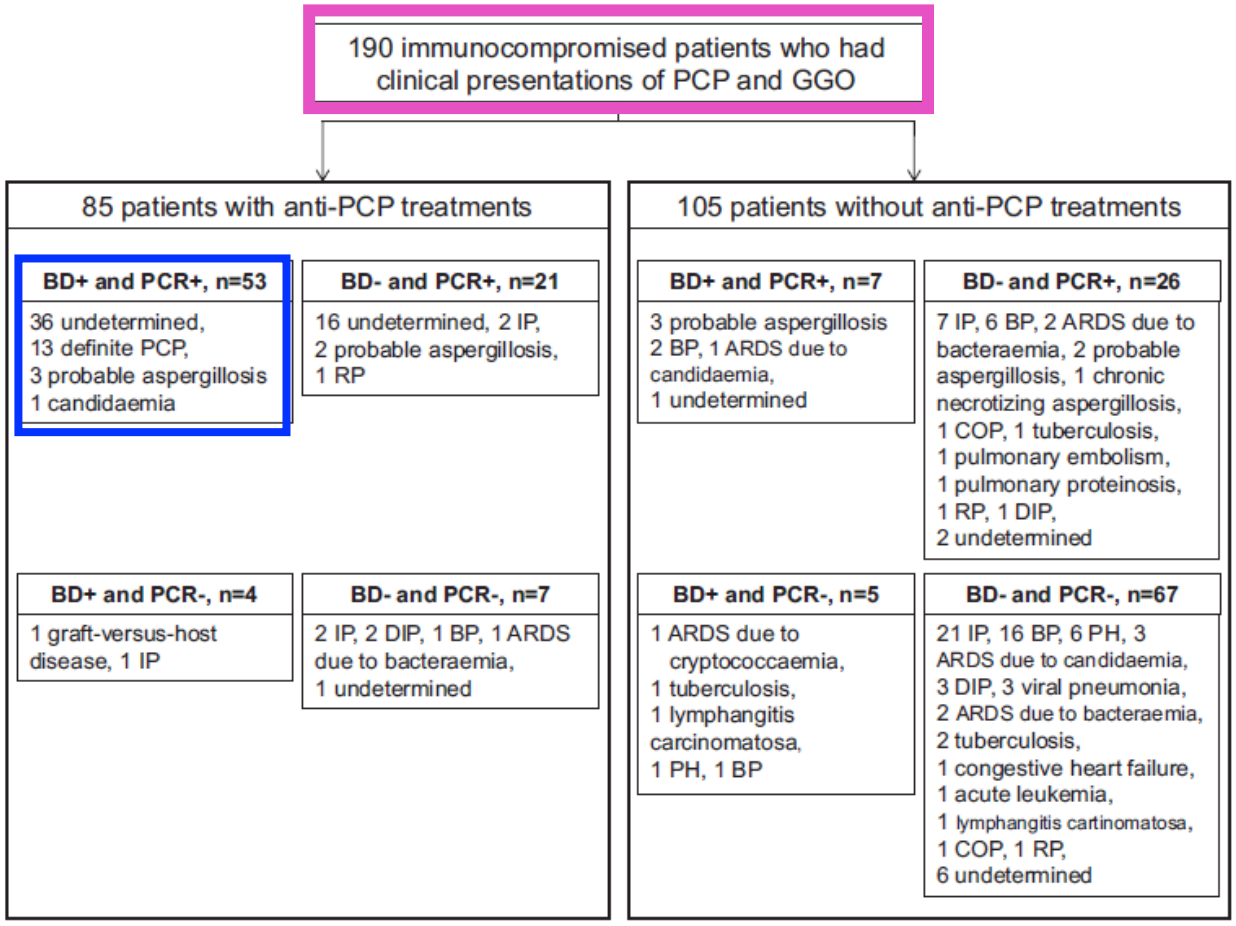
Bustin et al. Clinical Chemistry 2009, 55(4): 611-622

B-D-Glucan

- Plusieurs méthodes commercialisées
  - Fungitec G-Test MK
  - B-D-Glucan Test Wako
  - B-G Star kit
  - **Test Fungitell, pg/ml de sérum <31 pg/ml à > 500 pg/ml**
- Pas Spécifique du Pneumocystis
- Ne détecte pas certaines espèces fongiques (*Cryptococcus,* les zygomycètes comme *Absidia*, *Mucor* et *Rhizopus*, et *Blastomyces dermatitidis)*
- Faux positifs: matériel étranger, coton ou compresses chirurgicales, certains antibiotiques, bactériémies, albumine, IgIV, hémodialyse…

DIAGNOSTIC

Pneumocystis polymerase chain reaction and blood (1→3)-β-D-glucan assays to predict survival with suspected *Pneumocystis jirovecii* pneumonia



Kyoto 2008-2011

colorations sur LBA ou IS

+

WAKO BD glucan

+

Single-round **PCR** large sous unité rRNA mitochondriale, et

Matsumara et al. J Infec Chemother 20 (2014) 109-114

DIAGNOSTIC

Thirty-day mortality rates among patients who were suspected of having *Pneumocystis* pneumonia.

Characteristics	30-day mortality rate (number of deaths/total patients)				*P*-value
	Total	PCP treatment +		PCP treatment −	
All patients	21.6% (41/190)	20.0% (17/85)		22.9% (24/105)	0.72
β-D-glucan-positive	10.1% (7/69)	10.5% (6/57)		8.3% (1/12)	1.00
β-D-glucan-negative	28.1% (34/121)	39.3% (11/28)		24.7% (23/93)	0.15
Positive PCR	15.0% (16/107)	12.2% (9/74)		21.2% (7/33)	0.25
Definite PCP	0.0% (0/13)	0.0% (0/13)		— (0/0)	—
Other than definite PCP	17.0% (16/94)	14.8% (9/61)		21.2% (7/33)	0.57
Negative PCR	30.1% (25/83)	72.7% (8/11)		23.6% (17/72)	0.002

All definite PCP patients were positive by PCR.
PCP, *Pneumocystis* pneumonia.

Matsumara et al. J Infec Chemother 20 (2014) 109-114

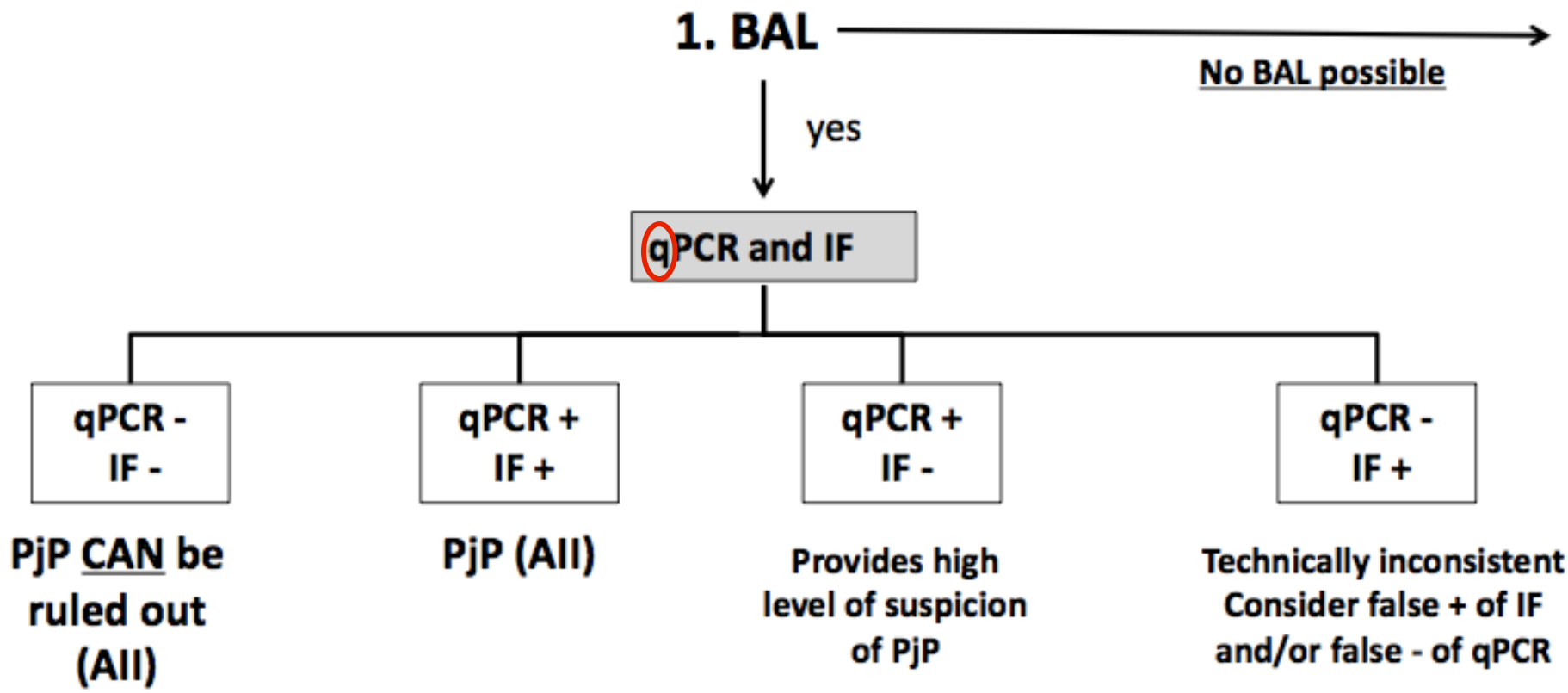
DIAGNOSTIC

72

Factors associated with 30-day mortality in patients receiving anti-*Pneumocystis* pneumonia treatments without microscopic detection of *P. jirovecii* by stepwise multivariate analysis.

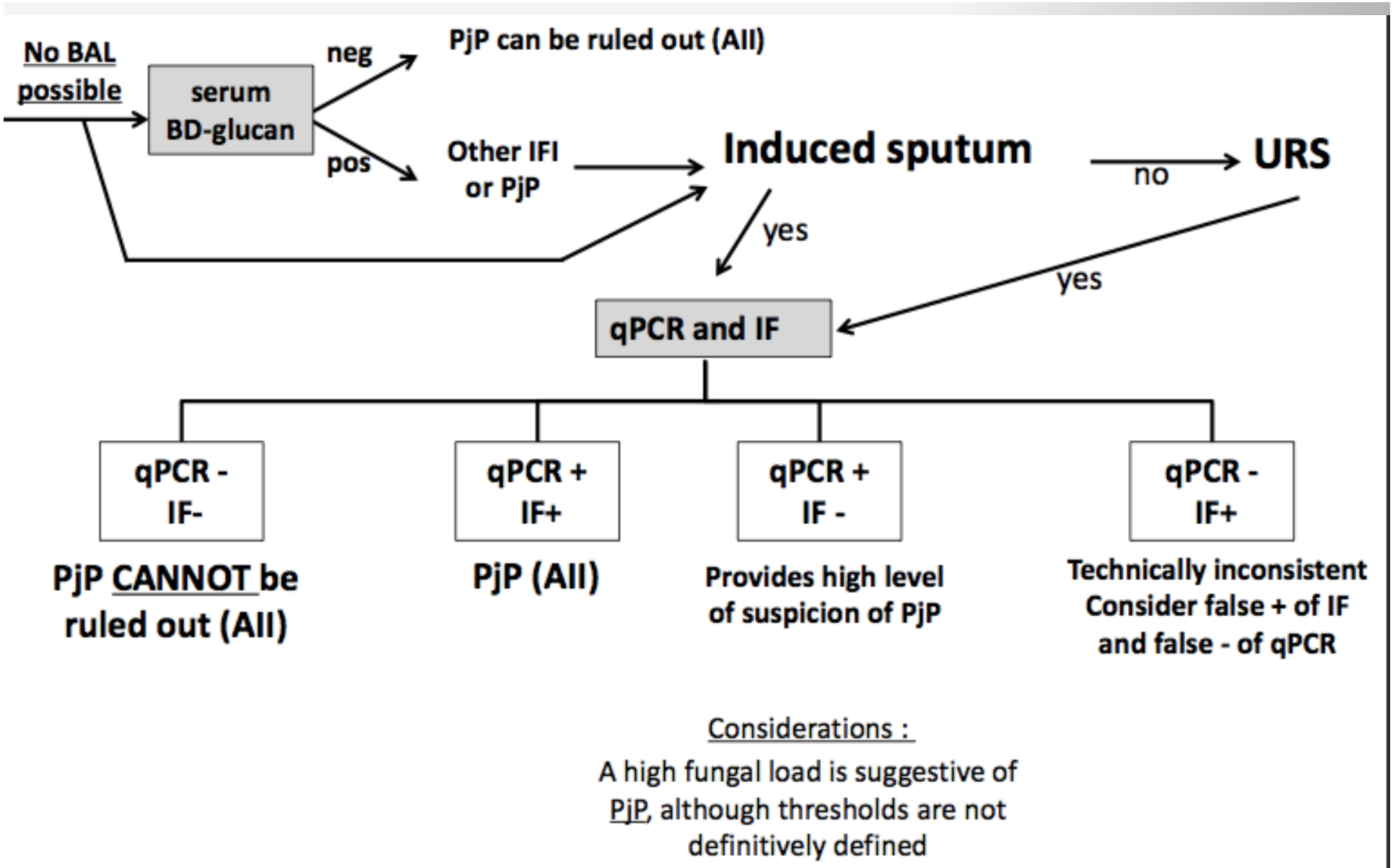
Characteristics	OR (95% CI)	*P*-value
SOFA score, per 1 point	1.42 (1.08–1.88)	0.01
Pneumocystis PCR	0.14 (0.02–0.74)	0.02
Positive β-D-glucan	0.25 (0.06–1.02)	0.05

Matsumara et al. J Infec Chemother 20 (2014) 109-114



Considerations :

- A high fungal load is suggestive of PjP, although thresholds are not definitively defined
-For low fungal loads consider BD-glucan in serum to support the diagnosis


No BAL possible
serum BD-glucan
neg
pos
PjP can be ruled out (AII)
Other IFI or PjP
Induced sputum
no
URS
yes
yes
qPCR and IF
qPCR - IF-
qPCR + IF+
qPCR + IF -
qPCR - IF+
PjP CANNOT be ruled out (AII)
PjP (AII)
Provides high level of suspicion of PjP
Technically inconsistent Consider false + of IF and false - of qPCR
Considerations :
A high fungal load is suggestive of PjP, although thresholds are not definitively defined

Traitement

Table 3
Medications for treatment of pneumocystis pneumonia

Medication	Dose	Route	Evidence for Resistance	Comments
TMP-SMX	TMP: 15–20 mg/kg SMX: 75–100 mg/kg Divided into three or four doses daily	Oral or Intravenous	DHPS mutations	First choice
Pentamidine	4 mg/kg daily	Intravenous	Clinical resistance suspected	Alternate choice
TMP plus dapsone	TMP: 5 mg/kg three times daily Dapsone: 100 mg/day once daily	Oral	DHPS mutations	Alternate choice
Atovaquone	750 mg two times daily	Oral	Mutations of coenzyme Q binding site	Alternate choice
Primaquine plus clindamycin	Primaquine: 30 mg daily Clindamycin: 600 mg three times daily	Oral	None documented	Alternate choice
Adjunctive glucocorticoids	Prednisone: 40 mg twice daily for 5 days 40 mg once daily for 5 days 20 mg once daily for 11 days	Oral	NA	Recommended for patients who have HIV with a room air $Pao_2 \leq 70$ mm Hg or alveolar–arterial oxygen gradient ≥ 35 mm Hg

Abbreviations: DHPS, Dihydropteroate synthase; NA, Not applicable; TMP, Trimethoprim, TMP-SMX, Trimethoprim-sulfamethoxazole.

Krajicek et al. Clin Chest Med 2009

Traitement

CORTICOSTEROIDS AS ADJUNCTIVE THERAPY FOR SEVERE *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

A Double-Blind, Placebo-Controlled Trial

SUZANNE GAGNON, M.D., AHMAD M. BOOTA, M.D., MARGARET A. FISCHL, M.D., HORST BAIER, M.D.,

Table 2. Occurrence of Clinical End Points According to Treatment Group.

23 patients VIH+!

END POINT	CORTICOSTEROID (N = 12)	PLACEBO (N = 11)	P VALUE*
	no. (%)		
Survival to discharge	9 (75)	2 (18)	<0.008
Respiratory failure	3 (25)	9 (82)	<0.008
Completion of antibiotic therapy	10 (83)	4 (36)	<0.024

*By the Mantel–Haenszel chi-square test.

THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 22, 1990

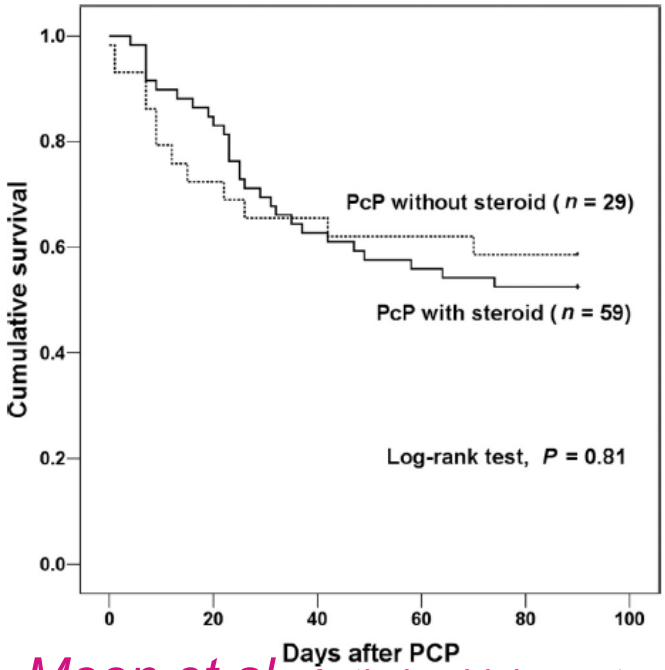
Corticosteroids as Adjunctive Therapy for Severe *Pneumocystis carinii* Pneumonia in Non–Human Immunodeficiency Virus–Infected Patients: Retrospective Study of 31 Patients

Christophe Delclaux, Jean-Ralph Zahar, Gibba Amraoui, Ghislaine Leleu, François Lebargy, Laurent Brochard, Benoit Schlemmer, and Christian Brun-Buisson

From Service de Réanimation Médicale, Hôpital Henri Mondor, Créteil, and Service de Réanimation Médicale, Hôpital Saint Louis, Paris, France

Our observations in non-HIV-infected immunocompromised patients with severe PCP, most of whom had hematologic disorders, suggest that corticosteroid therapy at least does not have the dramatic effect observed in AIDS patients, in whom it may prevent the need for mechanical ventilation or death. However, a potential beneficial effect of CAT cannot be excluded in some non-HIV-infected patients; this effect could be masked in this heterogeneous population by clinical presentation (more acute illness), microbiological and pathophysiological features (fewer organisms), or underlying immunosuppression.

Etudes rétrospectives	N	Faible dose	Forte Dose	Pas de corticoïde	
		N (Mortalité)			p
Pareja	30	14 (36%)	16 (44%)	0	NS
Roblot	60	35 (43%)		25 (20%)	NS
Moon	88	59 (30%)		29 (34%)	NS
Lemiale	139	35 (20%)	72 (29,2%)	32 (25%)	NS



Moon et al. *Antimicrobial agents and chemotherapy* 2011

Table 5—*Clinical Outcomes in Non-HIV-Infected Patients With PCP*

	Low-Dose Steroid (n=14)	Increased High-Dose Steroid (n=16)
Medical service	8	10
Surgical service	6	6
Daily steroid dose at the time of diagnosis of PCP, mg; mean±SD	16.0±10	18.4±16
Daily steroid dose following the diagnosis of PCP, mg; mean±SD	23.3±5.2	135±235
ICU admission required, No.	9	13
Duration, d; mean±SD	15.8±8	8.5±7*
Intubation required, No.	8	12
Duration, d; mean±SD	18.0±21	6.3±6*
Supplemental O_2 requirement*	14	16
Duration, d; mean±SD	32.2±33	10.0±4†
Duration of hospitalization, d; mean±SD, d; mean±SD, all patients	29.4±27	20.8±20
Time to discharge for survivors, No.,	9	9
d; mean±SD	36.3±33	15.4±5†
Mortality, overall in-hospital, No. (%)	5 (36)	7 (44)
Respiratory failure	1	3
Sepsis	2	4
Myocardial infarction	1	–
Intracranial hemorrhage	1	–

Pareja et al. Chest 1998

Traitement

Table 1 | **Metabolic treatment targets for *Pneumocystis* pneumonia**

Agent	Therapeutic use	Prophylactic use	Primary molecular target	Evidence of resistance
Trimethoprim-Sulfamethoxazole	First choice	First choice	DHPS/DHFR	DHPS mutations
Primaquine/ Clindamycin	Second choice	Not used	Uncertain/ protein synthesis inhibition	None documented
Pentamidine	Alternative choice	Aerosolized; rarely used	DNA synthesis	Clinical resistance suspected
Atovaquone	Alternative choice* (mild–moderate infection)	Alternative choice	Cytochrome *b* complex	Mutations of co-enzyme Q binding site
Dapsone/ Trimethoprim	Alternative choice‡	Dapsone alone or Dapsone with Pyrimethamine and Leucovorin	DHPS/DHFR	DHPS mutations
Corticosteroids (adjunctive)	For moderate–severe disease (given in addition to antifungals)	Not used; can induce PCP	$CD8^+$ T cells and many other inflammatory cells and processes	None documented
Trimetrexate plus Leucovorin	Salvage therapy	Not used	DHFR	None documented
Caspofungin	Animal and anecdotal human data only	Not used	GSC1	None documented

*Administer with high-fat meals to maximize absorption. ‡Must be certain patient does not have glucose-6 phosphate dehydrogenase (G6PD) deficiency as haemolysis can occur with G6PD deficiency. DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthase; GSC1, glucan synthetase; PCP, *Pneumocystis* pneumonia.

Thomas et Limper Nature 2007

Prophylaxie

General patients

Prednisone at least 20 mg for >4 weeks if patient has underlying immunosuppressive disorder or COPD [12, 107]

Cancer

Receiving corticosteroids [47]

Alemtuzumab during and for at least 2 months after treatment and CD4 >200 cells/ml [47]

Temozolomide and radiation therapy and until CD4 is >200 cells/ml [47]

Fludarabine and T-cell-depleting agent (e.g., cladribine) until CD4 >200 cells/ml [47]

All patients while receiving anti-leukemic therapy [47]

Connective tissue diseases

Wegener's granulomatosis treated with cyclophosphamide, especially if also receiving corticosteroids [55, 56]

Primary systemic vasculitis treated with corticosteroids and steroid-sparing agent (e.g., methotrexate) [113]

ANCA-associated vasculitis treated with cyclophosphamide and corticosteroids [114]

Rheumatoid arthritis treated with TNF-α inhibitors especially if on corticosteroids or other intensive immunosuppression [66]

Connective tissue diseases treated with prednisolone >20 mg per day or equivalent doses of corticosteroid for more than 2 weeks [111]

Hematopoietic stem cell transplantation

Allogeneic stem cell recipients for at least 180 days [47]

Autologous peripheral blood stem cell transplant recipients for 3–6 months after transplant [47]

All recipients for 6 months [104]

Recipients receiving immunosuppressive therapy or with chronic graft-versus-host disease (GVHD) for >6 months or the duration of immunosuppression [104]

Solid organ transplantation

Solid organ transplant recipients for at least 6–12 months after transplant [106]

Renal transplant recipients for a minimum of 4 months after transplantation [108]

Renal transplant recipients for 3–6 months after transplantation and at least 6 weeks during and after treatment for acute rejection [107]

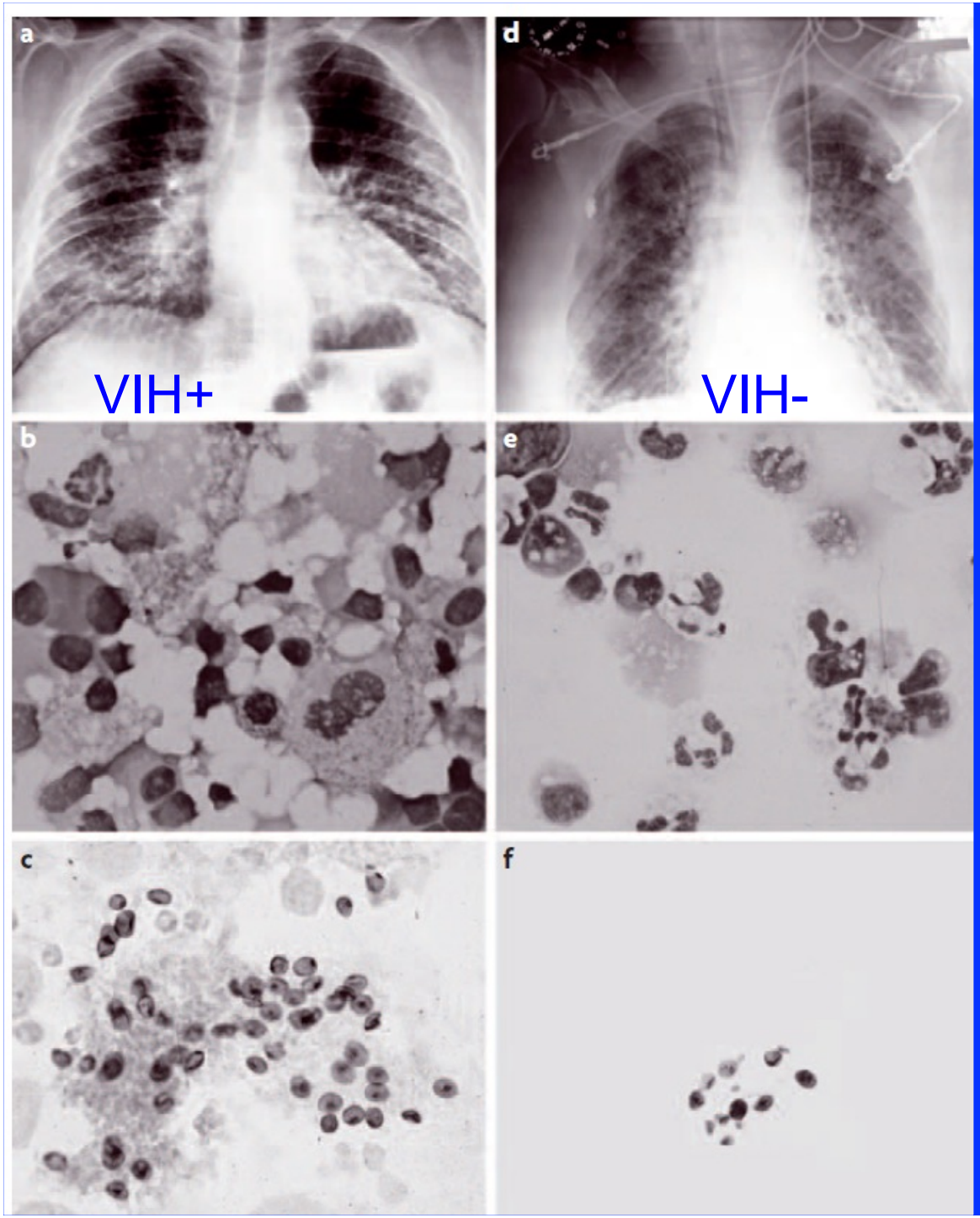
Inflammatory bowel disease

Patients receiving TNF-α inhibitors especially if on corticosteroids or other intensive immunosuppression [70]

Tasakuda et Tokuda J Infect Chemother 2013 18:793-806

PcP différences VIH+/VIH-

VIH +	VIH-
•Incidence en diminution	•Incidence en augmentation
•CD4 < 200	•Immunodépression complexe
•Prophylaxie primaire: clair	•Prophylaxie primaire…
•Souvent peu de comorbidité	•+ âgés et + Comorbidités Cancer
•Clinique typique 2-3 semaines Toux sèche dyspnée croissante	•Clinique installation + rapide, « PAC », difficultés diagnostiques
•TDM Verre dépoli +++	•TDM Verre dépoli, condensations
•LBA + de Lymphocytes + de kystes (LBA >10% PNN mauvais pronostic)	•LBA + de PNN, moins de pneumocystes, coinfections
	•Mortalité élevée…
•Mortalité faible (10-15%) depuis:	•CT adjuvante délétère? Études rétrospectives
•CT adjuvante dont l'efficacité est démontrée	
•Tt 21 jours	•Tt 14 jours



Clinique, physiopathologie pronostic

VIH+ ≠ VIH-

b: LBA inflammatoire: riche en L et macrophages, peu de PNN

e: PNN +++

c: nombreuses formes kystiques

f: peu de kystes

Thomas et Limper Nature 2007

Am J Hosp Palliat Care. 2013 Sep 30. Yamaguchi T et al

PcP in Patients treated with **Long-Term Steroid Therapy for symptom palliation**: **A neglected Infection in Palliative Care.**

1 Département de Medecine interne japonais.

3 cas de PcP
Diagnostic : **clinique + PCR positive sur crachats induits**
2 décès

« Therefore, it is important to consider PCP **prophylaxis** for high-risk patients and to diagnose PCP early and provide appropriate treatment to alleviate PCP-related symptoms
and avert **unnecessary shortening of a patient's life expectancy** »

Merci pour votre attention

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