

Pneumocystose pulmonaire

Cours DES pneumologie

Ile de France

Phase Socle

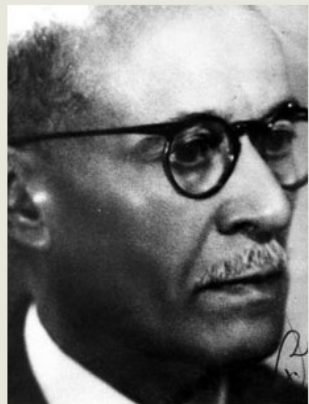
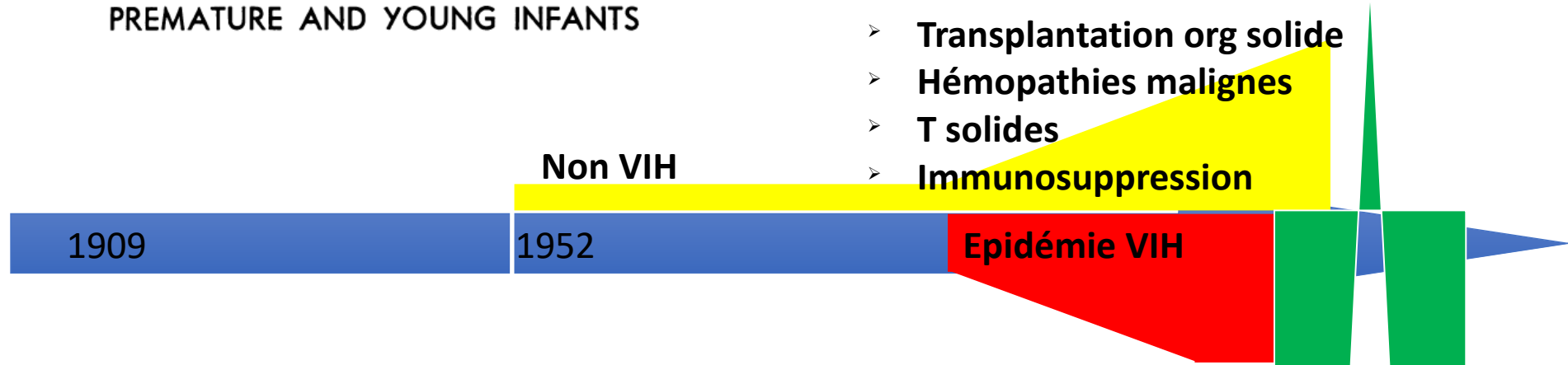
31/01/2020

Antoine Roux

(Hôpital Foch)

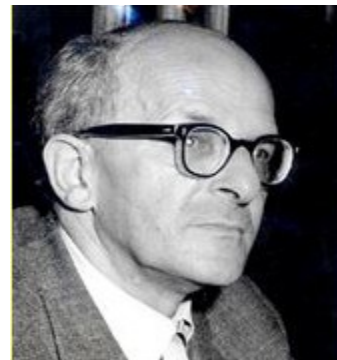
Introduction

PNEUMOCYSTIS CARINII—ETIOLOGIC AGENT OF INTERSTITIAL PLASMA CELL PNEUMONIA OF PREMATURE AND YOUNG INFANTS

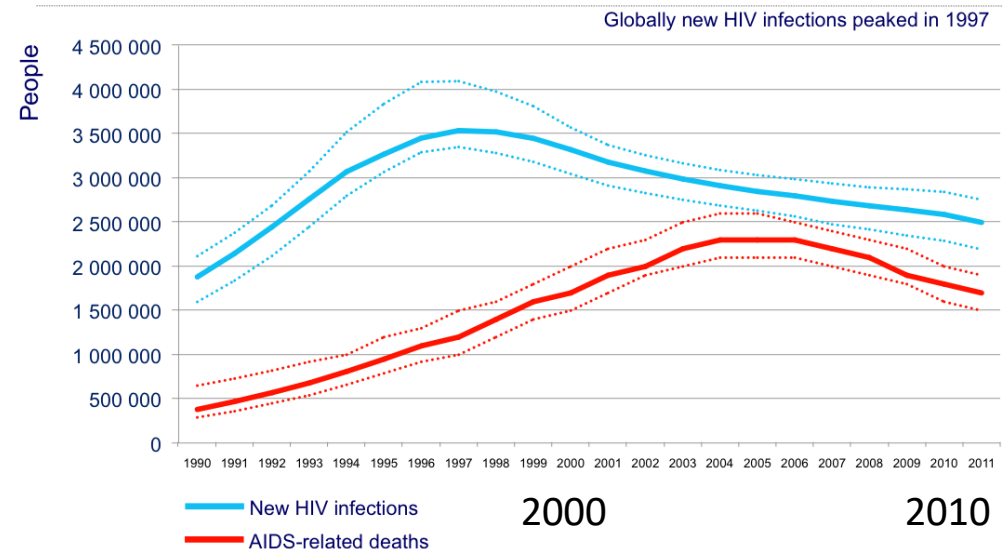


Antonio Carini

Vs. Chagas



Otto Jerovec



Présentations cliniques

Clinique non spécifique

- Toux (8-70)/DE (24-80%)/F°(50-80%)
- Crépitants/normale (20%)
- AA → O2 → SDRA
- Choc: autre infection



Terrain

VIH vs. Non VIH



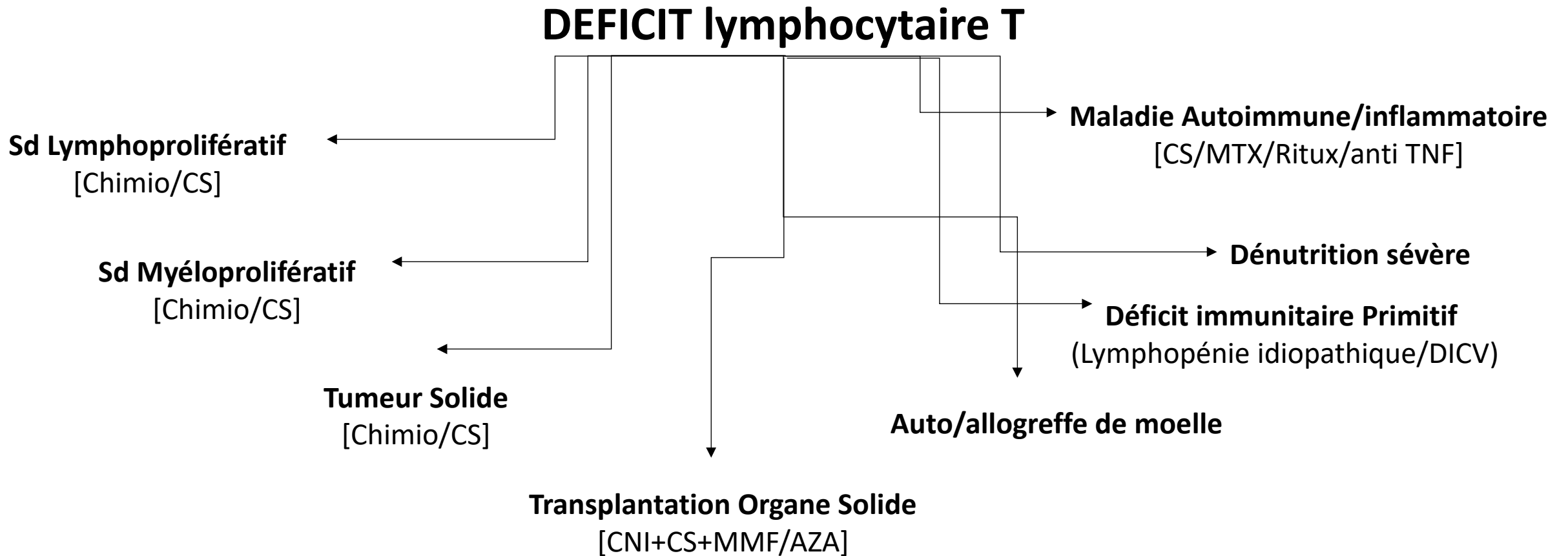
Absence de prophylaxie

Particularités VIH vs. Non VIH

- Durée des symptômes plus courte pour non VIH (#4-5jrs vs. 21jrs)
- Non VIH plus graves au diagnostic:
 - Admission en réa (35% vs. 50%)
 - VNI (8% vs. 16%)
 - VM (11% vs. 30%)
 - Choc (2 vs. 7%)
- Début du traitement plus tardif pour non VIH

Terrains

- VIH CD4<200/mm³, infection inaugurale (30%)
- Non VIH



Terrains- Incidences

Incidence de pneumocystose pulmonaire chez les patients d'oncologie en fonction du type de cancer.

	Cases	Number of patients	Incidence (%)
Lymphomas	34	9907	0.34
Acute lymphoblastic leukemia	5	2929	0.17
Other types of leukemia	16	5023	0.32
Solid malignancies and corticosteroids	30	26085	0.11
Brain malignancies and corticosteroids	21	3098	0.68
Allogeneic bone marrow transplantation	22	1348	1.63

Incidence de la pneumocystose pulmonaire au cours de différentes pathologies auto-immunes ou inflammatoires.

Disease	Incidence (%)	References
Granulomatosis with polyangiitis	8–12	[1]
Periarteritis nodosa	6.5	[1,4]
Polymyositis and dermatomyositis	2.7	[9]
Systemic lupus erythematosus	2	[10]
Rheumatoid arthritis	0.1–0.3	[1]

Incidence de la pneumocystose pulmonaire chez des transplantés d'organe en l'absence de prophylaxie.

Organ transplanted	Incidence (%)
Kidney	0.6–14
Liver	3–11
Heart	2–41
Heart-lung/lung	6.5–43

Drug	Action	PJP incidence (%)
Infliximab (Remicade®)	Anti-TNF α	0.3
Etanercept (Embrel®)	Anti-TNF α	0.1
Adalimumab (Humira®)	Anti-TNF α	0.3
Tocilizumab (RoActemra®)	Anti IL6	0.2
Abatacept (Orencia®)	Anti CD 28	0.1

Main drugs associated with pneumonia (PJP).

Principaux médicaments associés avec la survenue de pneumocystose pulmonaire.

Corticosteroids

Alkylating agents

Cyclophosphamide

Temozolomide

Antibiotics

Bleomycin

Anticalcineurins

Cyclosporine

Tacrolimus

Antimetabolites

Cytarabine

Fluorouracil

Methotrexate

Purine analogs

Azathioprine

Cladribine

Fludarabine

TNF α inhibitors

Adalimumab

Etanercept

Infliximab

Monoclonal antibodies

Abatacept

Alemtuzumab

Rituximab

Miscellaneous

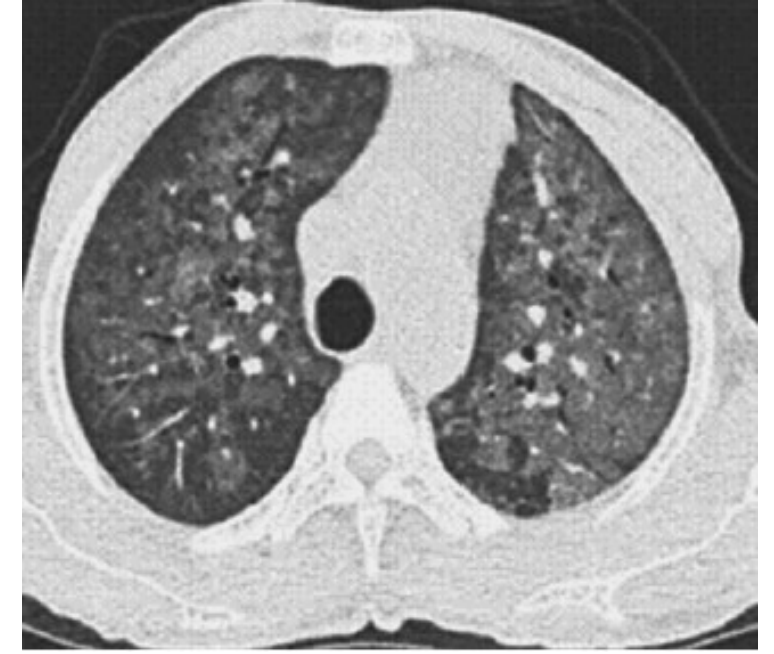
Sirolimus

Tocilizumab

Aspects radiologiques= non spécifiques

Radio de thorax

- Atteinte alvéolo-interstielle
- peri hilaire
- « Normale » (20-30%)



TDM thoracique

Le plus fréquent

- Verre dépoli,
- Diffus, prédominance apicale
- bilatéral
- « crazy paving »
- (Fibrose)

Rares mais « classiques »

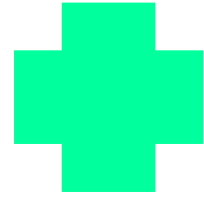
- Kystes (VIH>>non VIH)
- pneumothorax
- Séquelle Fibrose
- (Nodules)

PCP pas le premier Dg si

- Condensations
- Micronodules
- Nodules

Diagnostic

Clinique+ imagerie
non spécifique



Terrain



Absence
de prophylaxie



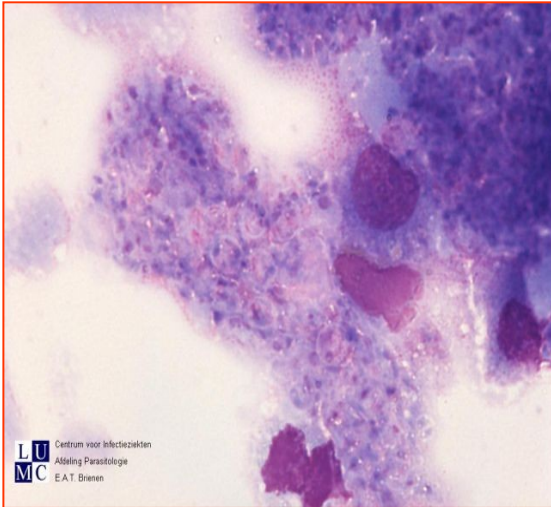
- 1/ évoquer le Diagnostic
 - 2/ gamme diagnostic
 - 3/ documentation microbiologique
- (patient avec Dg ont un meilleur pronostic)

Diagnostic microbiologique

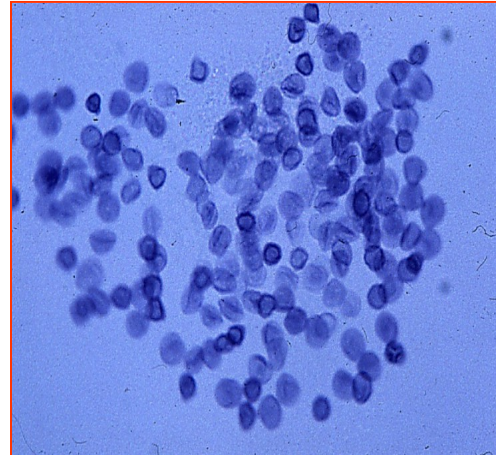
Prélèvements

- LBA+++
- Expectorations induites

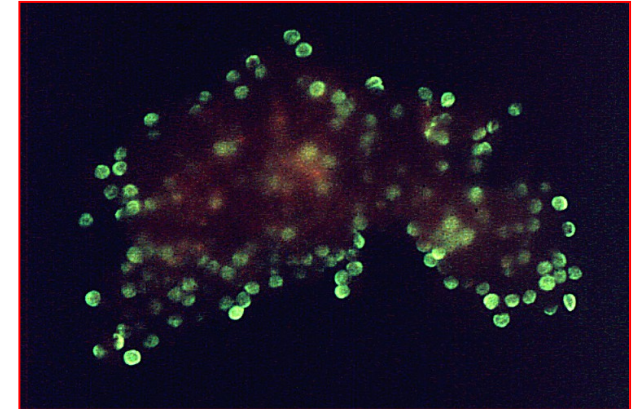
Colorations Classiques= MGG



Colorations Spécifiques= Grocott/ BTO



Immunofluorescence

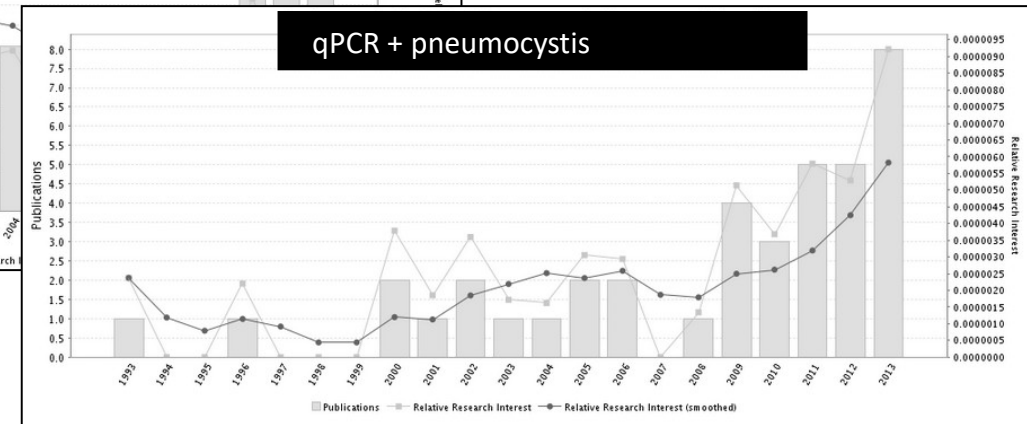
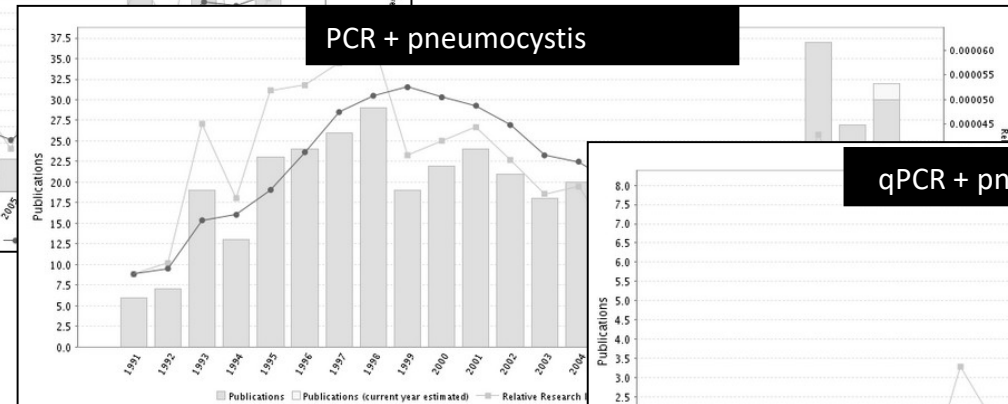
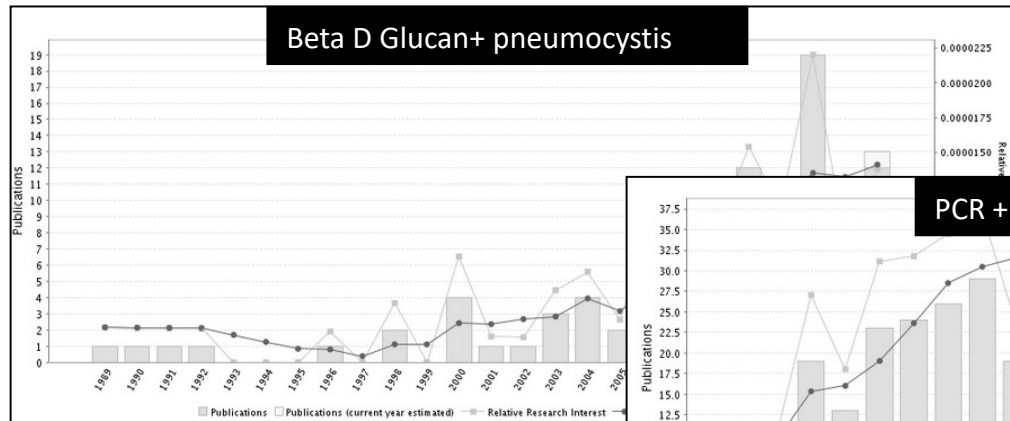


Performance diagnostique des Techniques classiques

- Suffisant pour VIH
- Insuffisant pour non VIH (formes paucikystiques)

« nouveaux outils »: qPCR et betaD glucan

1° publications → BDG= 1989/ PCR= 1991/ PCRq= 1993-96



« Nouveaux outils »: qPCR

Microbiologistes convaincus

- Permet quantification de la charge fongique
- Cibles: gène glycoprotéine de surface/ sous unité ribosomale
- Sensibilité de détection+++ → permet détection sur prvlt non invasifs

TABLE 2. Pooled test performance of the studies included in our meta-analysis of the diagnosis of PCP using PCR

Study subjects or method	No. of articles	No. of studies	SEN	SPE	PLR	NLR	AUC ^b
Whole population	13	20	0.99 (0.96–1.00) ^a	0.90 (0.87–0.93)	10.2 (7.8–13.4)	0.01 (0.00–0.04)	0.98 (0.96–0.99)
AIDS population	10	16	0.99 (0.98–1.00)	0.91 (0.86–0.95)	11.5 (6.9–19.3)	0.01 (0.00–0.03)	0.99 (0.98–1.00)
Non-AIDS population	5	8	0.99 (0.33–1.00)	0.92 (0.90–0.94)	12.2 (9.6–15.6)	0.01 (0.00–2.10)	0.95 (0.93–0.97)
BALF PCR	8	11	1.00 (0.98–1.00)	0.88 (0.82–0.92)	8.0 (5.4–11.7)	0.01 (0.00–0.02)	1.00 (0.98–1.00)
OW PCR	4	5	0.76 (0.60–0.87)	0.93 (0.88–0.96)	10.4 (5.4–19.8)	0.26 (0.14–0.47)	0.94 (0.92–0.96)

^a Shown are pooled values with 95% confidence intervals in parentheses.

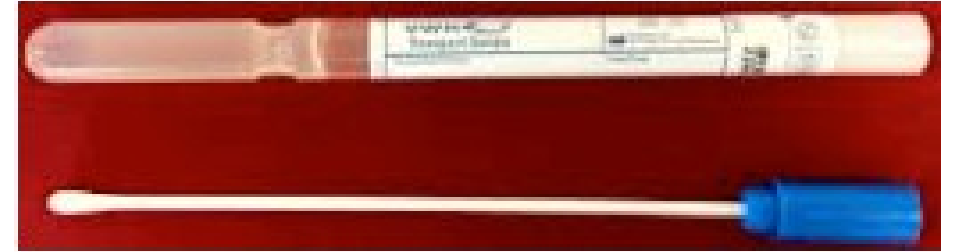
^b AUC, area under the summary receiver operating characteristic curve.

LU, JCM, 2011

- Intérêt de la VPN
- PCR= très sensible= différencier colonisation/maladie → seuil
- Standardisation

qPCR: Approche non invasive

- Expectoration induite
- Ecouvillon rhinopharyngé
- Aspiration rhinopharyngé
- Lavage oro pharyngé



- Accessibilité
- Rapidité exécution
- Moindre dangerosité (mais étude minimax...) *Azoulay, 2009*
- Autres recherches (virologie/germes intracellulaires)
- Réduction des couts
- Perd information sur cellularité LBA/diagnostic différentiel
- 20-30% de co infection

« Nouveaux outils »: beta D Glucan

Kit	Manufacturer	FDA approved	Crab species	Cut off value
Fungitell	Associates of Cape Cod (U.S.)	Yes	<i>Limulus polyphemus</i> (colorimetric)	60–80 pg/mL
Endostafe-PTS glucan	Charles River Laboratories (U.S.)	No	<i>Limulus polyphemus</i> (colorimetric)	10–1000 pg/mL
Fungitec G-MK	Seikagaku Biobusiness (Japan)	No	<i>Tachypleus tridentatus</i> (colorimetric)	20 pg/mL
β-glucan test	Waco Pure Chemical Industries (Japan)	No	<i>Tachypleus tridentatus</i> (turbidimetric)	11 pg/mL
BGSTAR β-glucan test	Maruha (Japan)	No	<i>Tachypleus tridentatus</i> (colorimetric)	11 pg/mL

Intérêt d'un résultat négatif

MAIS

- populations très différentes
- Méthodologies insuffisantes

“Méta-analyse”, 14 études

Karageorgopoulos Clin Microb Infect 2013

Se=95%/ SP=86%/RVP=6,9/ RVN= 0,06

« Nouveaux outils »: beta D Glucan

Infectious

- Gram negative infection (Pseudomonas Aeruginosa, Alcalagines sp)
- Other fungall infection
 - In HIV patient:* Cryptococcosis (rarely positive), histoplasmosis, oesophageal candidiasis
 - In non HIV patient:* Invasive Aspergillosis, systemic candidiasis

Other medical condition

Mucositis, neutropenia (excluding Gram negative infection and IFI)

Therapeutic

Albumin perfusion [50]
Immunoglobulin [50]
Antibiotics [111]
Haemodialysis [51],
use of cellulose membrane in extracorporeal eparation,
certains gauzes on mucosal or serosal surface [51]
administration of blood products produced through cellulose filters [51]

- Lipemic blood samples
- Hemolyzed blood samples
- Certain fungi that lack significant levels of (1-3)- β -D-glucan such as *Zygomycetes*, *Cryptococcus neoformans*, and *Blastomyces dermatitidis*.

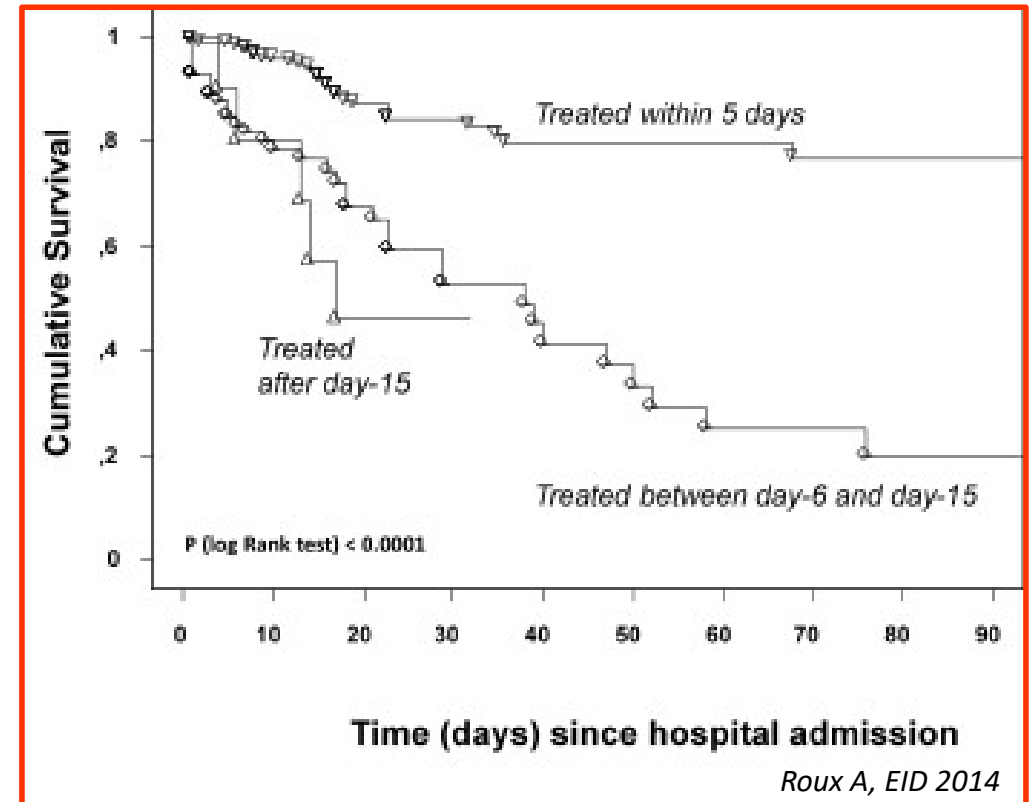
Pronostic

Gravité

- Admission en réa= 50%
- VM= 30%
- Mortalité
 - 4%-10% pour VIH
 - 20-40% non VIH
 - >80% si VM

Facteurs de risque de mortalité

Variable	Odds ratio
VIH+	OR 0.33, 95% CI [0.12-0.92]
Transplantation d'organe	OR 0.08, 95% CI [0.02-0.31]
Age	OR 1.04/a, 95% CI [1.02-1.06]
Allogreffe de CSH	OR 8.6, 95% CI [1.40-53.02]
Besoin d'O2 dès l'admission	OR 4.06, 95% CI [1.44-11.5]
Besoin de VM	OR 16.70, 95% CI [7.25-38]
Délai de traitement	OR 1.11/j, 95% CI [1.04-1.18]



Traitement curatif

- INITIATION du traitement dès la suspicion SANS attendre les prlvts ni les résultats
- ≥ 14 jrs

Drug	Dose	Route	Comments
Trimethoprim–sulfamethoxazole	15–20 mg/kg 75–100 mg/kg daily in divided doses	Oral or intravenous	First choice
Primaquine plus clindamycin	30 mg daily 600 mg three times daily	Oral	Alternate choice
Atovaquone	750 mg two times daily	Oral	Alternate choice
Pentamidine	4 mg/kg daily 600 mg daily	Intravenous Aerosol	Alternate choice

Traitement curatif- Corticothérapie adjuvante.

Contexte HIV	Contexte non HIV			
<ul style="list-style-type: none">• ECR• Bozette, NEJM, 1990, n=333 (PaO₂>75))• Gagnon, NEJM, 1990, n=23 (PaO₂<75)• Diminution insuffisance respiratoire +mortalité	<ul style="list-style-type: none">• Etudes rétrospectives• Résultats contradictoires			
	<table border="1"><tr><td>mortalité <i>Pareja, 1998</i> <i>Inoue, 2019</i></td><td>Ø effet <i>Delclaux, CID, 1999</i> <i>Moon, 2011</i></td><td>↑mortalité <i>Lemiale, 2013</i></td></tr></table>	mortalité <i>Pareja, 1998</i> <i>Inoue, 2019</i>	Ø effet <i>Delclaux, CID, 1999</i> <i>Moon, 2011</i>	↑mortalité <i>Lemiale, 2013</i>
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Protocoles proposés

- **Bozette: Prednisone**
40mg x2/J 5jrs
puis 40mg/J pdt 5jrs
puis 20mg pdt 5jrs
- **Gagnon (72hrs du tt ATB)**
Methylprednisone 40mg x4/J, 7jrs
- **Pareja: Prednisone**
≥ 60mg/J
- **Moon, Prednisone**
40mg x2/J pdt 5jrs
- **PHRC: Methylprednisone**
Day 1 to 5 : 30mg twice per day
Day 6 to 10 : 30mg per day
Day 11 to 21 : 20mg per day

Traitement préventif

HIV: CD4<200

Non HIV: cf Terrain

- *PCP que chez des patients sans prophylaxie avec mortalité 30-50%*
- Si prophylaxie avait été interrompue reprendre après intensification IS

Table 1. Drugs for Prophylaxis against Pneumocystis Pneumonia.

Drug	Dose	Route	Comments
Trimethoprim–sulfamethoxazole	1 double-strength tablet daily or 1 single-strength tablet daily 1 double-strength tablet 3 times per week	Oral	First choice Alternate choice
Dapsone	50 mg twice daily or 100 mg daily	Oral	Ensure patient does not have glucose-6-phosphate dehydrogenase deficiency
Dapsone plus pyrimethamine plus leucovorin	50 mg daily 50 mg weekly 25 mg weekly	Oral	
Dapsone plus pyrimethamine plus leucovorin	200 mg weekly 75 mg weekly 25 mg weekly	Oral	
Pentamidine	300 mg monthly	Aerosol	
Atovaquone	1500 mg daily	Oral	Give with high-fat meals, for maximal absorption

Traitement préventif

Should Prophylaxis for *Pneumocystis carinii* Pneumonia in Solid Organ Transplant Recipients Ever Be Discontinued?

Steven M. Gordon, Steven P. LaRosa,* Sujith Kalmadi, Alejandro C. Arrolliga, Robin K. Avery, Laura Truesdell-LaRosa, and David L. Longworth

From the Departments of Infectious Diseases and Pulmonary Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio

Gordon, 1999

- 4,8/1000, Tpulm>>Trénale
- 8x plus de risque de PCP pdt la 1° année

- 36% des PCP sont après 1an
- PAS de pcp sous prophylaxie
- Cout/eff ++ vs pas de prophylaxie et PCP

© 2011 John Wiley & Sons AS
Transplant Infectious Disease, ISSN 1398-2273

Pneumocystis jirovecii pneumonia is rare in renal transplant recipients receiving only one month of prophylaxis

Anand, 2011

- 4 PCP/1352 patients
- <1mois, Trénale

American Journal of Transplantation 2013; 13: 272-279
Wiley Periodicals Inc.

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doi: 10.1111/ajt.12119

Special Article

Pneumocystis Pneumonia in Solid Organ Transplantation

AST recommandation 2013

- 6-12mois
- sauf Tpulm/intestin: long cours

ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients

Preventing exposure

Most cases of PCP occur from reactivation of latent infection, although cases of person-to-person transmission have been reported.²⁻⁴ Few healthcare facilities require respiratory precautions with respect to patients infected with PCP, but it seems reasonable that severely immunocompromised patients should avoid contact with patients with documented PCP (C-III).

- Réduction du risque=91% (RR=0,09) chez AL et HSCT
- 15 patients à traiter pour éviter 1 PCP
- Réduction de la mortalité 83% (RR= 0,17)
- 1° ligne BF/ 2° Ligne= Atovaquone/Dapsone/Pentacarinat
- COMBIEN DE TEMPS??
 - ≥6mois ou plus si prolongation de l'IS
 - « Recurrent PCP is rare provided that secondary prophylaxis is continued until the end of immunosuppression. »

Questions non résolues

- Place des BDG? de la qPCR/approche non invasive?
- Chez qui arrêter la prophylaxie?
- Cas groupés; isolement?
- Colonisation vs. Maladie?
- Corticothérapie adjuvante?
- Hétérogénéité des patients non VIH?

Merci de votre attention

PCR, qPCR, BDG

ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients

J Antimicrob Chemother 2016; **71**: 2386–2396

Table 1. Recommended diagnosis of PCP in adult patients with haematological malignancies and stem cell transplant recipients (it is not recommended that PCP diagnosis should rely only on clinical criteria or imaging)

Specimen/technique	Recommended usage	Strength of recommendation	Quality of evidence
Diagnostic specimen			
BAL fluid	allows detection of multiple aetiologies	A	II
other (non-invasive specimens ^a)	alternative specimen to BAL	B	II
Diagnostic technique			
Respiratory samples			
immunofluorescence assays	most sensitive microscopic diagnostic method	A	II
real-time quantitative PCR	routine diagnosis allowing quantification	A	III
	exclusion of PCP by negative result in BAL only	A	II
Serum			
β -D-glucan	detection in serum as a contributive diagnostic tool	A	II
	exclusion of PCP by negative result	A	II
genotyping using multilocus sequence markers	investigation of suspected outbreaks	A	II
detection of dihydropteroate synthase mutations	not recommended in case of treatment failure	B	II

^aIncludes induced sputa, sputa and upper respiratory samples (nasopharyngeal aspirates, nasal or oral washes).

PCR, qPCR, BDG

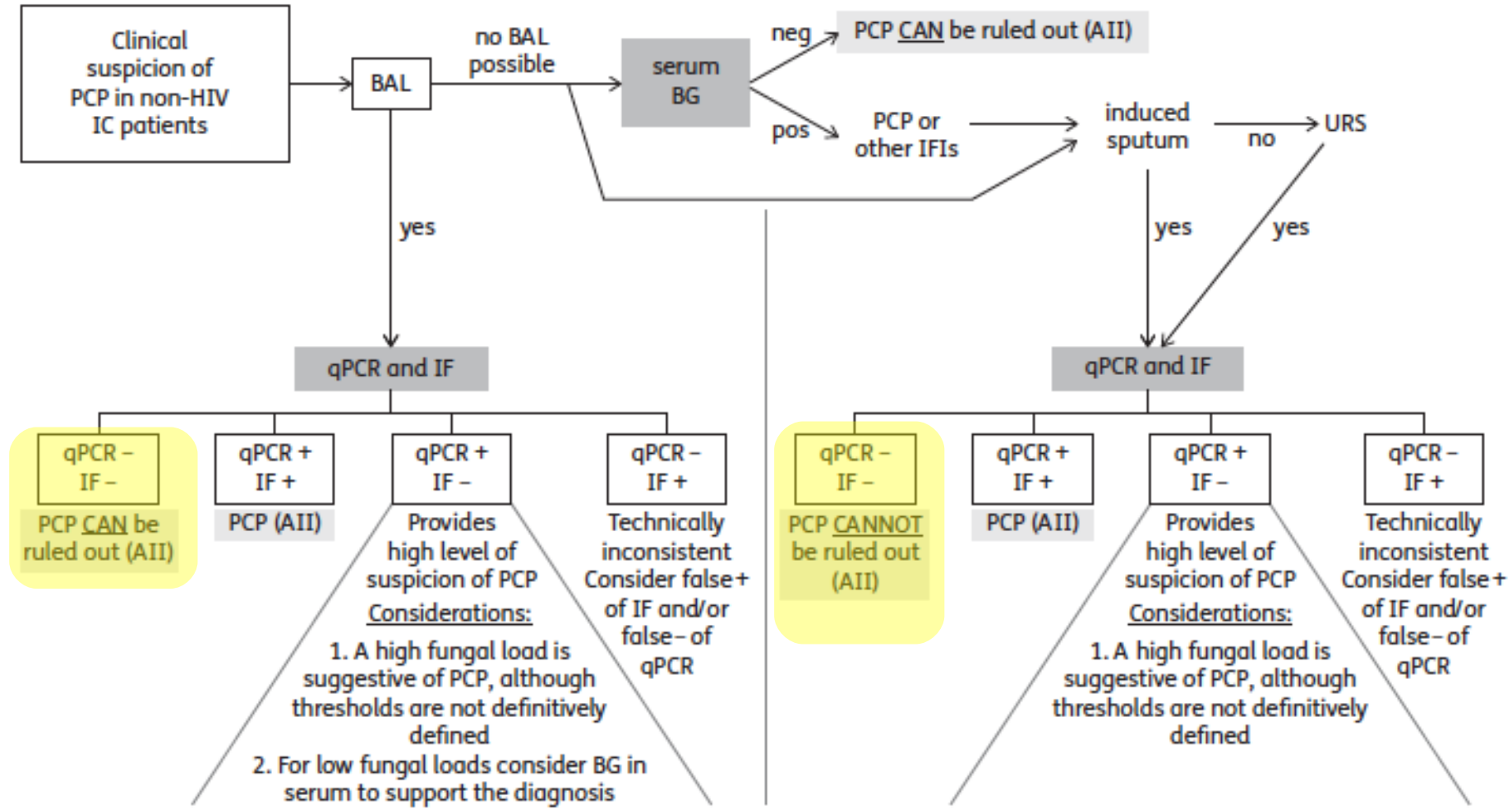


Figure 1. Flow chart for the diagnosis of *Pneumocystis pneumonia* in non-HIV immunocompromised (IC) patients. Biological tests are highlighted in dark grey and recommendations in light grey. BG, β -D-glucan; A-II, level of recommendation; IFI, invasive fungal infection.

PCR, qPCR, BDG

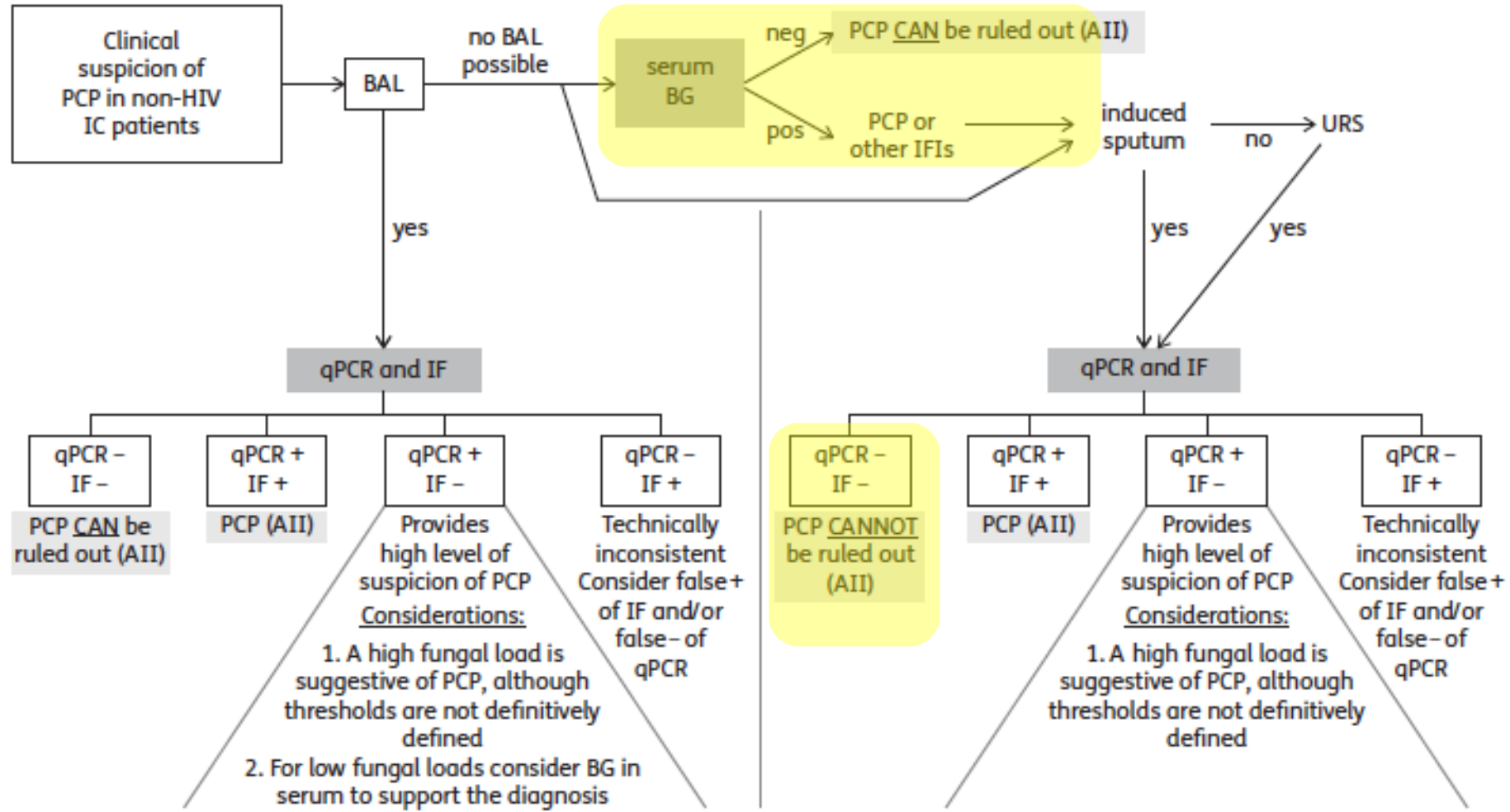


Figure 1. Flow chart for the diagnosis of *Pneumocystis pneumonia* in non-HIV immunocompromised (IC) patients. Biological tests are highlighted in dark grey and recommendations in light grey. BG, β -D-glucan; A-II, level of recommendation; IFI, invasive fungal infection.

Pneumocystose- TRAITEMENT CURATIF

ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients

J Antimicrob Chemother 2016; **71**: 2405–2413

doi:10.1093/jac/dkw158 Advance Access publication 12 May 2016

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	IIIr
		pentamidine iv 4 mg/kg/day	C	IIIr
		primaquine + clindamycin 30 mg/day oral + 600 mg \times 3/day iv or oral	C	IIIr
		atovaquone 750 mg \times 2 (or 3)/day oral	C	IIIr

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 \times 3) per day	B	IIIr
		pentamidine iv 4 mg/kg/day	B	III
		TMP/SMX (15–20 mg/kg/day) + caspofungin (70–50 mg/day)	C	IIIu
		echinocandin alone	D	IIIu

Transmission

Réactivation endogène

D'une infection

latent/colonisation

Sérologie frqt positive

PJ retrouvé chez sujets
sains (PCR)

Transmission aéroportée interpersonnelle

À partir de sujet sains/malades

Présence de PJ dans l'air

Cas groupés

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-012-1586-x

ARTICLE

***A Pneumocystis jirovecii* pneumonia outbreak in a single kidney-transplant center: role of cytomegalovirus co-infection**

R. U. Pliquett • A. Asbe-Vollkopf • P. M. Hauser •

Modèles animaux

→ Transmission interindividuelle

Cas groupés chez l'homme

→ 30-40% ≥1 souches /patient

→ Durée d'incubation = 2 mois??

→ Transmission interindividuelle

Nosocomial *Pneumocystis jirovecii* Pneumonia: Lessons From a Cluster in Kidney Transplant Recipients

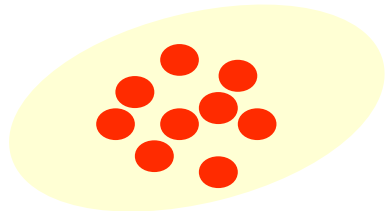
Lisa M. Phipps,¹ Sharon C.-A. Chen,^{2,3,4} Kathy Kable,¹ Catriona L. Halliday,² Carolina Firacative,^{2,3,4}
Wieland Meyer,^{2,3,4} Germaine Wong,¹ and Brian J. Nankivell^{1,5}

A Cluster of *Pneumocystis* Infections Among Renal Transplant Recipients: Molecular Evidence of Colonized Patients as Potential Infectious Sources of *Pneumocystis jirovecii*

Solène Le Gal,^{1,3} Céline Damiani,^{7,8} Amélie Rouillé,¹ Anne Grall,⁴ Laetitia Tréguer,⁴ Michèle Vimaux,¹ Elodie Moalic,^{1,3}
Dorothée Quinio,^{1,3} Marie-Christine Moal,⁴ Christian Berthou,^{2,5} Philippe Saliou,⁶ Yann Le Meur,^{2,4} Anne Totet,^{7,8} and
Gilles Nevez^{1,3}

Cas groupés

Cas groupés

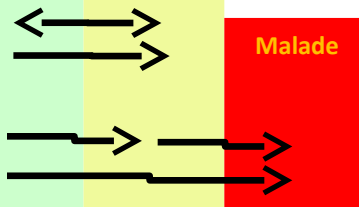


- Transmission/circulation?
- Isolement malade/à risque?

Histoire naturelle

A risque
Non colonisé

A risque
colonisé



Génotypes dans la population générale?



● Identification du génotype

Génotypage sur gène cible

→ Identité sur un gène ≠ identité génome

→ Différence sur gène cibles = cluster différent/mutation

« Without definitive data, formal recommendations regarding infection control in the hospital or healthcare clinic cannot yet be made », *AJT, 2013, Martin*