



ABC de l'infection pulmonaire du greffé rénal

Emmanuel CANET

Médecine Intensive Réanimation

Nantes

Liens d'intérêts

- Aucun

Cas clinique 1

Monsieur T., 67 ans

Diabétique multicompliqué et polyvasculaire

IRCT hémodialysée depuis août 2008

1^{ère} greffe rénale le 09/08/2013, Bactrim[®], Rovalcyte[®] 3 mois

tt immunosuppresseur: cellcept[®] - prograf[®] - cortancyl[®]

Créatinine plasmatique 120 μ mol/L

09/2013 (**M1 post-greffe**) :

Cytopénie : arrêt du Bactrim[®], switch Wellvone[®]



Cas clinique 1

13/10/2014 (M14 post-greffe) :

Consultation SAU

3 jours : fièvre 40°C, dyspnée, toux sèche, pas d'expectoration

Auscultation et radiographie thoracique normales

Leucocytes	9700 (7330 PNN, 1090 Lymphocytes)
Hémoglobine	13,3
Plaquettes	320 000

Antigénurie pneumocoque	NEG
Antigénurie légionelle	NEG
Hémocultures	NEG
ECBU	Stérile
PCT	16,94µg/L

GdS	13/10
VS	AA
pH	7,46
PaCO ₂	31
HCO ₃ ⁻	21
PaO ₂	49
SaO ₂	87
Lactate	1,5

Antibiothérapie Claforan[®], hospitalisation USC

Fièvre persistante à 72 heures de l'antibiothérapie

Pas d'amélioration respiratoire, O₂ 6L/min

Age et risque infectieux

Exponentially increased risk of infectious death in older renal transplant recipients

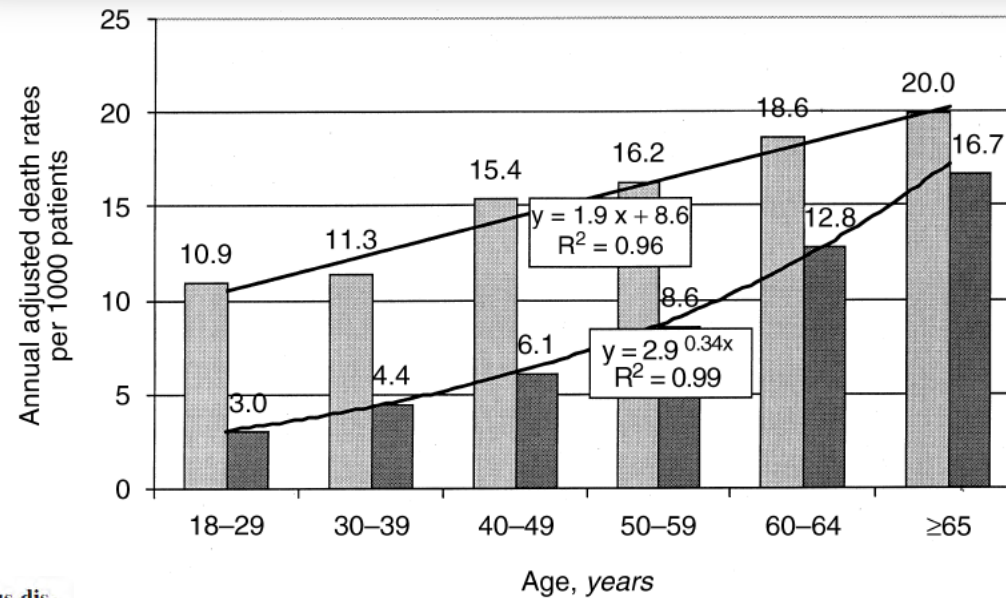
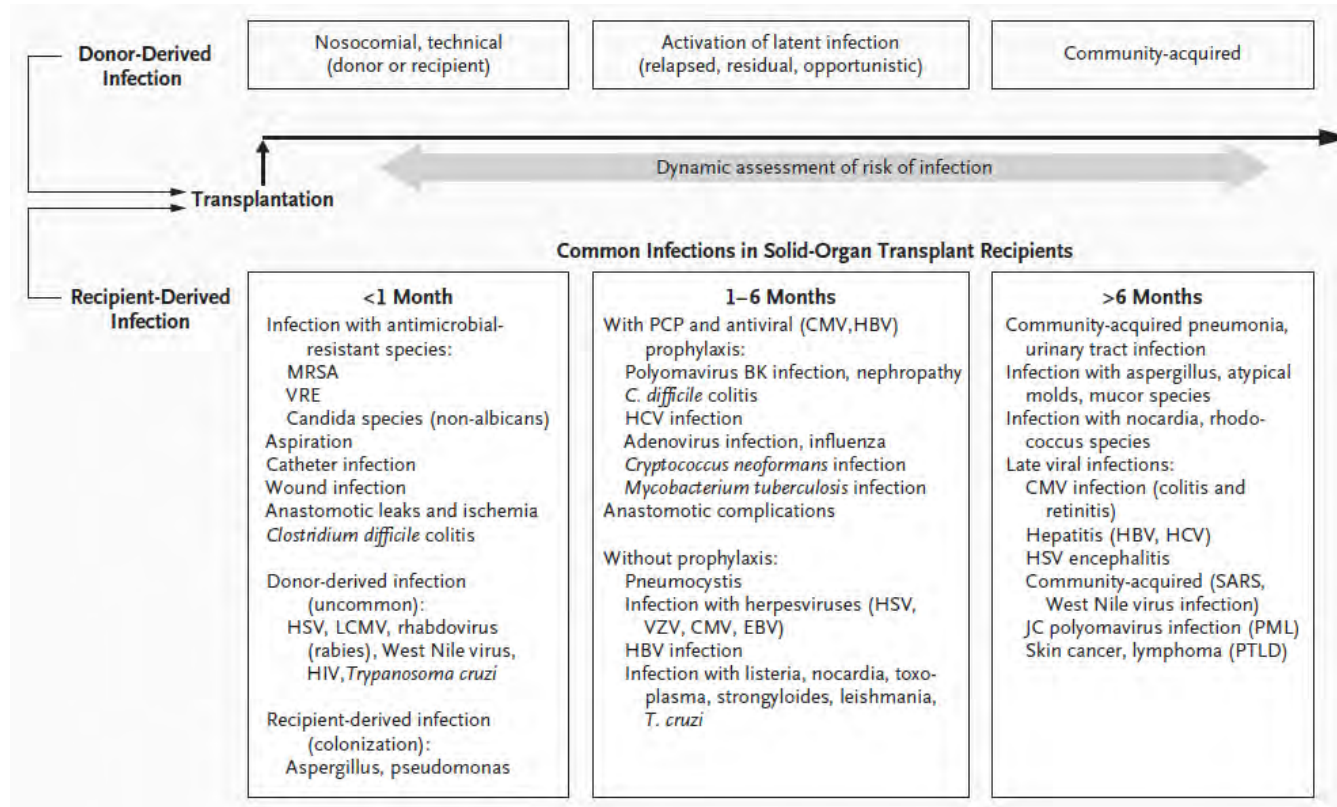


Fig. 3. Mortality secondary to infectious disease in wait-listed (□) and transplant patients (■). Annual adjusted death rates are per 1000 patients.

Meier-Kriesche, Kidney Int 2001

Délai post-transplantation



Fishman, New Engl J Med 2007, Kotloff, Am J Respir Crit Care Med 2004

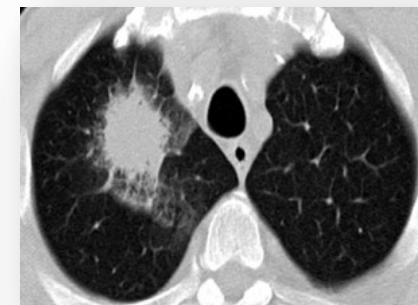
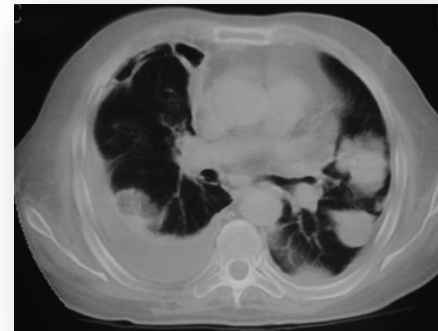
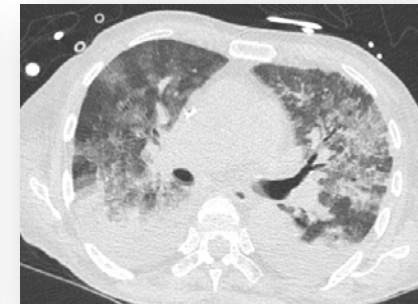
Durée des symptômes

Rate	Type of disease	
	Infectious	Non-infectious
Acute (<24 h)	Bacteria	Pulmonary edema Pulmonary hemorrhage
Subacute (1–7 days)	<i>Pneumocystis jiroveci</i>	Non-cardiogenic pulmonary edema
Chronic (>1 week)	Cytomegalovirus	
	<i>Aspergillus</i> , mucor	
	Mycobacteria	Malignancy
	Cryptococcus	Drug-induced toxicity
	<i>Nocardia</i>	Connective tissue disease

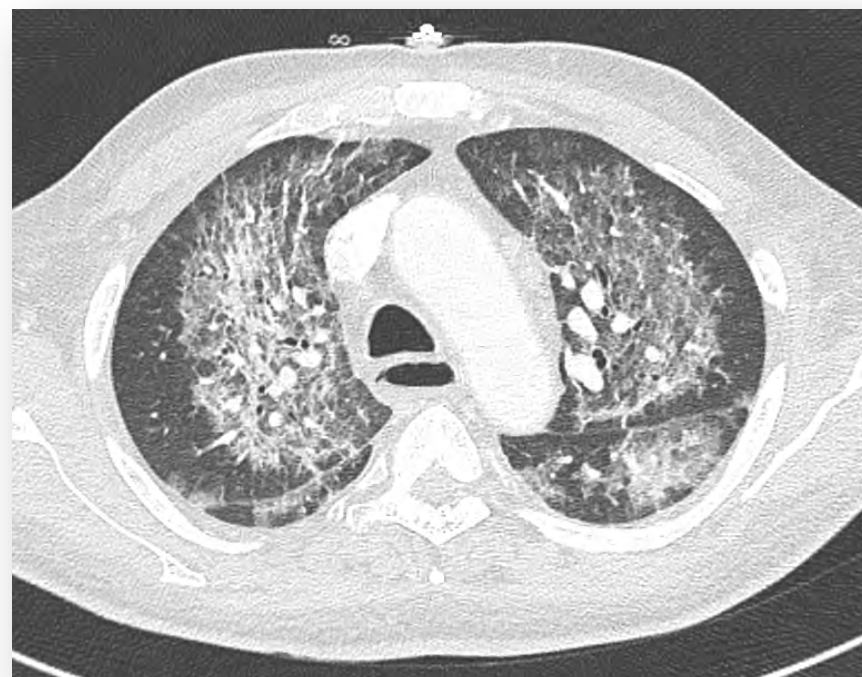
Apport du scanner thoracique

Radiographic patterns of pulmonary disease in the immunocompromised host.

Radiographic pattern	Type of disease	
	Infectious	Non-infectious
Segmental or lobar infiltrate	Bacteria Mycobacteria	Lymphoma Pulmonary infarction Radiation pneumonitis
Nodular with or without cavitation	Fungi Bacteria Septic emboli <i>Nocardia</i>	Metastatic tumor Lymphoma Connective tissue disease
Diffuse infiltrate	<i>Pneumocystis jirovecii</i> Cytomegalovirus	Pulmonary edema Pulmonary hemorrhage Idiopathic pneumonia syndrome Drug-induced toxicity Lymphangitis carcinomatosa Connective tissue disease
Mediastinal adenopathy	Mycobacteria Fungi(histoplasma, Coccidiomycosis)	Lymphoma Leukemia Metastatic tumor
Pleural effusion	Bacteria Mycobacteria <i>Nocardia</i>	Malignancy Connective tissue disease Pulmonary infarction Pulmonary edema Drug-induced toxicity



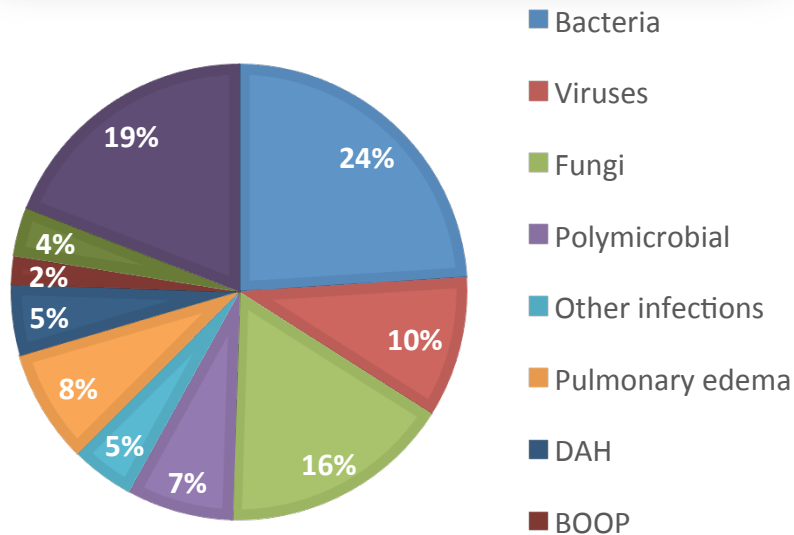
Cas clinique 1



Diagnostic invasif ou non invasif ?

Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures

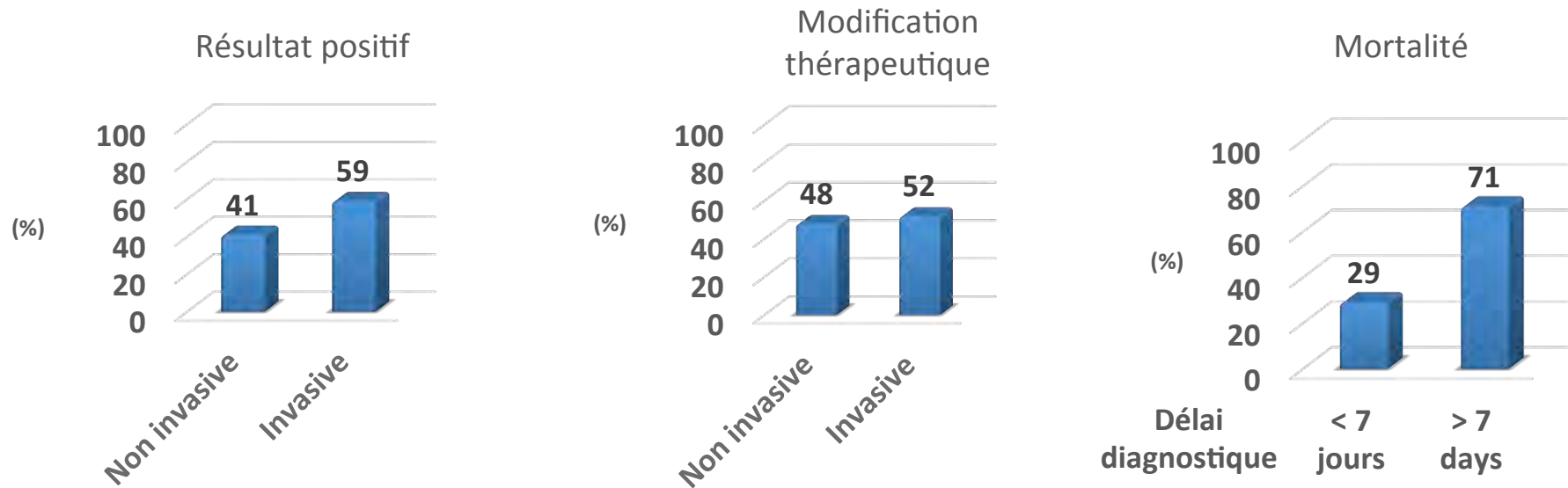
200 immunodéprimés (52 SOT)



Diagnostic technique	No positive/ no performed (%)
Blood cultures	30/191 (16%)
CMV antigen detection	11/91 (12%)
Aspergillus antigen detection	8/54 (15%)
NPW	9/50 (18%)
Sputum	27/88 (31%)
FBAS	16/28 (57%)
TBAS	35/55 (64%)
PSB	30/125 (24%)
BAL	68/135 (51%)
TBB	6/11 (55%)
VTC biopsy	2/2 (100%)

Rano, Thorax 2001

Résultats selon la stratégie



- 1) Diagnostic étiologique: 81%
- 2) Modification thérapeutique 50%
- 3) Diagnostic précoce = meilleure survie

Rano, Thorax 2001

Lavage broncho-alvéolaire

Auteur, année	Type de greffe	Patients n=	Résultat positif (n,%)
Tu, 2014	Rein	35	10 (28.6%)
Kupeli, 2011	Foie, Rein	61	34 (55.7%)
Canet, 2011	Rein	113	63 (45.5%)
Cervera, 2006	Rein, Cœur, Foie	45	30 (66.6%)
Lehto, 2005	Foie, Cœur + Foie	40	96/190 (50.5%)
Lehto, 2004	Cœur	44	18 (41%)
Starobin, 2003	Poumon, Rein, Foie, Cœur	168	82 (49%)
Reichenberger, 2001	Rein	71	63/91 (69%)
Rano, 2001	Rein, Cœur, Foie	135	68 (51%)
Chan, 1996	Poumon	83	49 (58.9%)
Sternberg, 1993	Rein	48	32 (66.6%)
Total		843	545/1013 (53.8%)

Rano, Thorax 2001
 Chan, J Heart Lung Transplant 1996
 Sternberg, Am J Med 1993
 Lehto, Transplant Int 2005
 Lehto, J Heart Lung Transplant 2004
 Starobin, Transplant Proc 2003
 Reichenberger, Transplant Infect Dis 2001

Tu, Intensive Care Med 2014
 Kupeli, Transplant Proc 2011
 Canet, Crit Care 2011
 Cervera, Diagn Microbiol Infect Dis 2006



Informations relatives à l'échantillon : Broncho-pulmonaire / L. broncho-alvéolaire
Contexte de prélèvement Suspicion infection

IMMUNOLOGIE FONGIQUE

Aspergillose

Ag galactomannane (IE) 0.04

Platelia Aspergillus EIA Biorad

Négatif : < 0.5

Positif : > 0.5

Conclusion Absence d'antigène.

EXAMEN PARASITOLOGIQUE

Recherche spécifiques après Coloration-Concentration

Pneumocystis jirovecii (MGG) Positif(ve)

Pneumocystis jirovecii (IF) Positif(ve)

Toxoplasmes (MGG) Négatif(ve)

Identification

Nombreux kystes et trophozoïtes de Pneumocystis jirovecii

LBA : valeur pronostique

Cellular Profiles of Bronchoalveolar Lavage Fluid and Their Prognostic Significance for Non-HIV-Infected Patients with *Pneumocystis jirovecii* Pneumonia

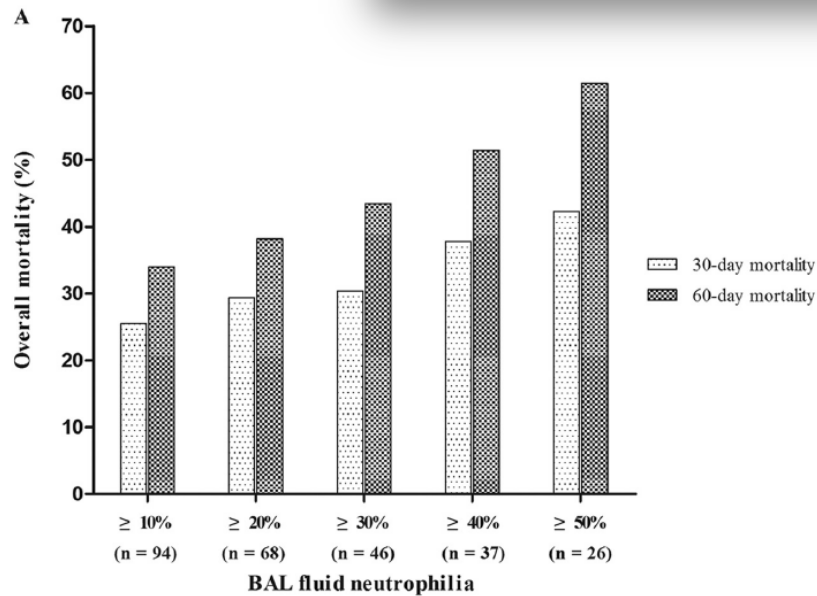


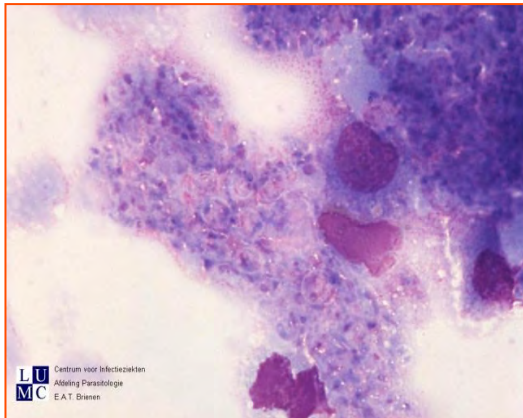
TABLE 3 Multiple logistic-regression analysis of predictors for 30-day and 60-day mortalities in non-HIV-infected patients with *Pneumocystis jirovecii* pneumonia^a

Predictor	30-day mortality		60-day mortality	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Male gender	2.52 (1.10–5.75)	0.03		
Solid-organ transplantation	0.28 (0.09–0.87)	0.03	0.20 (0.07–0.57)	0.003
APACHE II score	1.08 (1.01–1.16)	0.02	1.09 (1.03–1.17)	0.01
BAL fluid neutrophil %	1.02 (1.01–1.03)	0.03	1.02 (1.01–1.04)	0.02

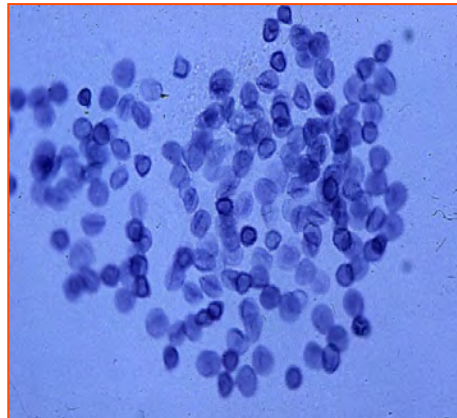
Pneumocystose

Prélèvements: LBA ou Expectorations induites

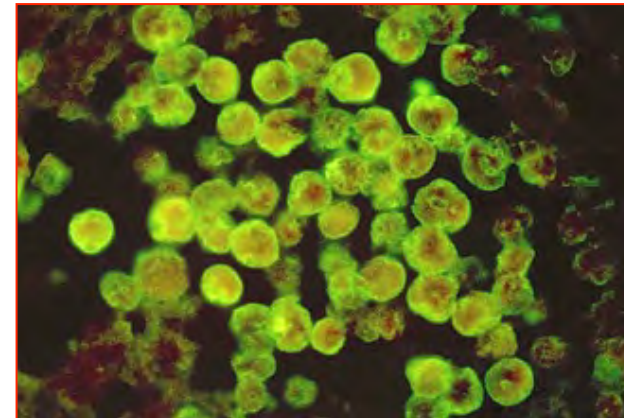
MGG



Grocott
Bleu de toluidine



Immunofluorescence



PCR, β -D-glucan

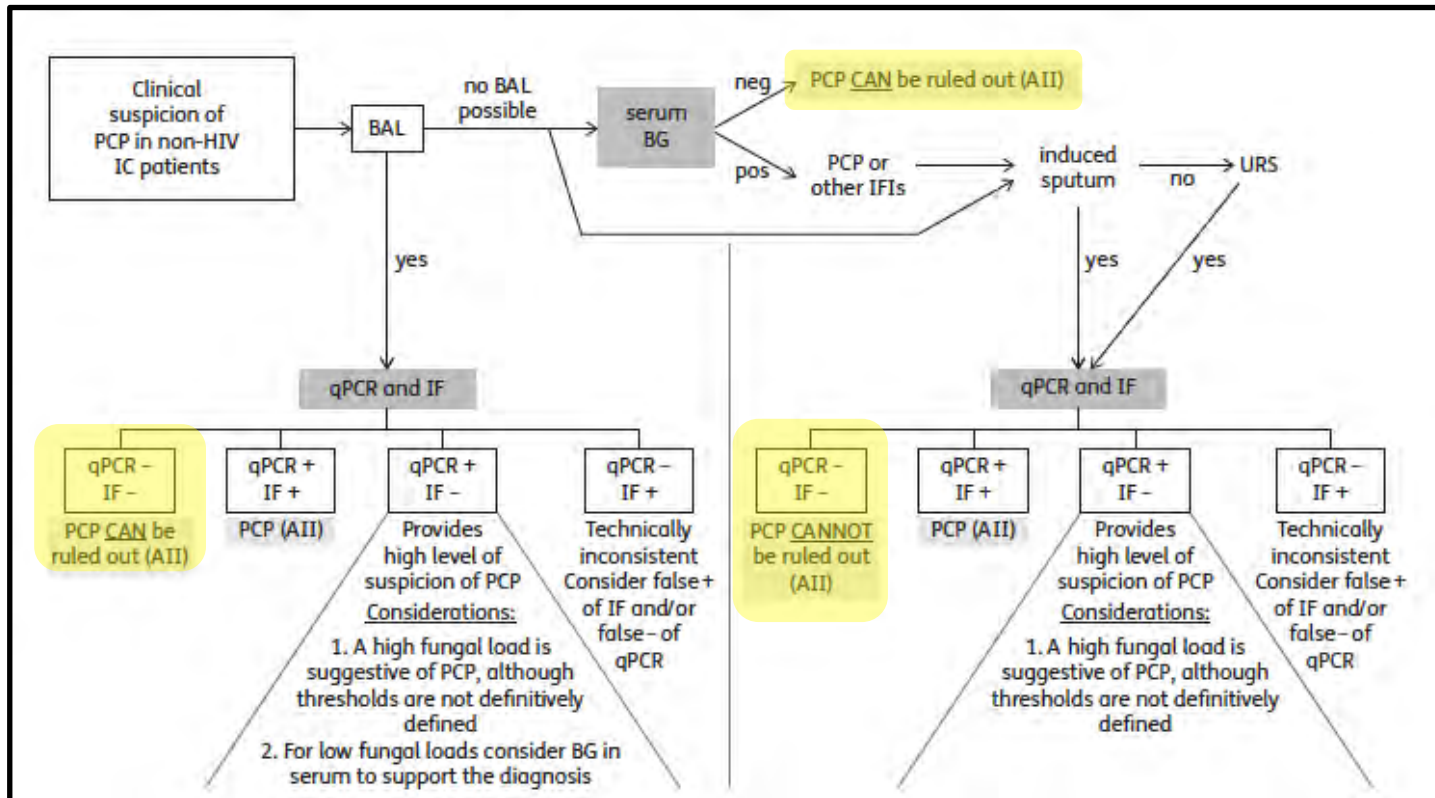
ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients

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, β -D-glucan



10/10/2014

13/10/2014

16/10/2014

22/10/2014

24/10/2014

27/10/2014

Réanimation

Intubation

Fièvre
Toux
Dyspnée

SAU

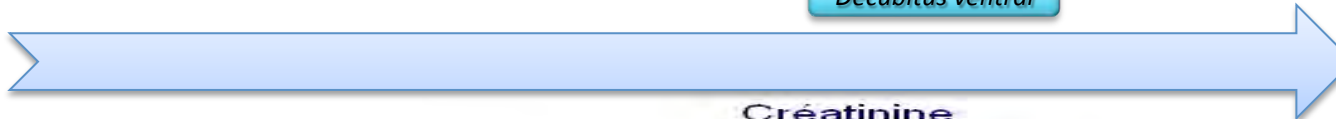


O₂

VNI

VM

Decubitus ventral



Créatinine



Pneumocystis jiroveci

Analysis of USRDS: Incidence and Risk Factors for *Pneumocystis jiroveci* Pneumonia

32 757 greffés rénaux (2000-2004)

142 pneumocystoses

Incidence 0,4%

PJP indépendamment associée à

- **Perte du greffon AHR 3,42 (2,56-4,56)**
- **Décès AHR 3,17 (2,25-4,48)**

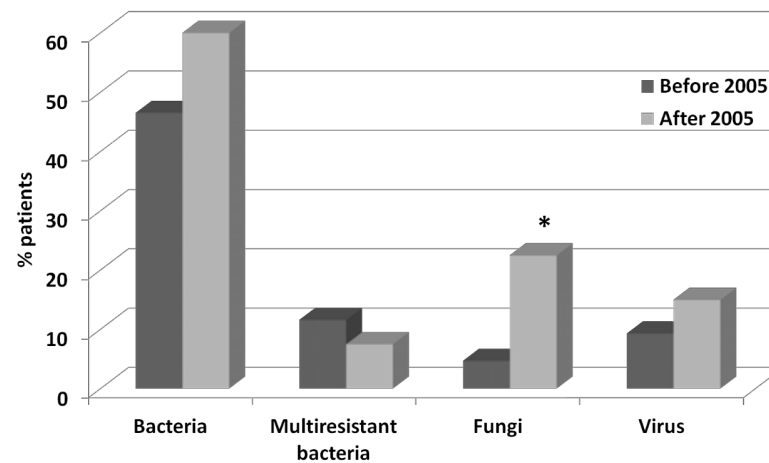
TABLE 2. Cox regression analysis results of factors associated with development of PCP (N=32,757)

Factor	Adjusted hazard ratio	95% confidence interval
Female gender	1.49	1.05–2.12
Expanded criteria donor	1.96	1.24–3.11
Donation after cardiac death	2.99	1.43–6.23
Transplant before 2002 (compared with 2002 and later)	1.46	1.00–2.12
Prior history of cancer	2.77	1.21–6.37
Medication regimen tacrolimus and mycophenolate mofetil as comparison group (AHR=1)		
Tacrolimus and sirolimus	3.60	2.03–6.39
Sirolimus and mycophenolate mofetil	2.77	1.40–5.47
Cyclosporine (Neoral) and mycophenolate mofetil	2.09	1.31–3.31
All other regimens	1.39	0.84–2.23

Pneumocystis jiroveci

Severe infections requiring intensive care unit admission in kidney transplant recipients: impact on graft outcome

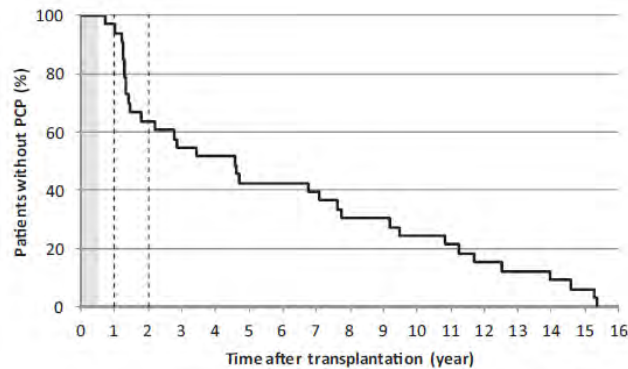
	n=83
Documentation microbiologique	55 (66%)
Infection polymicrobienne	19 (34%)
Source de l'infection	
<i>Poumon</i>	45 (54%)
<i>Urine</i>	20 (24%)
<i>Bactériémie</i>	18 (22%)
<i>Abdominale</i>	8 (10%)
Bactéries multi-R	8 (10%)



Bige, Transpl Infect dis 2014

Pneumocystis jiroveci

Risk Factors of *Pneumocystis* Pneumonia in Solid Organ Recipients in the Era of the Common Use of Posttransplantation Prophylaxis



33 *pneumocystoses* (2004-2010)

23 greffés rénaux

5 greffés hépatiques

5 greffés cardiaques

Table 5: Multivariate analysis of risk factors for the development of PCP in transplant recipients

Variable ¹	Adjusted odds ratio	95% confidence interval	p-Value
Age \geq 65 years	3.7	1.3–10.4	0.012
CMV infection in the year before D0	5.2	1.8–14.7	0.002
Regimen containing tacrolimus	0.4	0.1–1.1	0.065
Average level of lymphocytes $<$ 750/mm ³ in the 50 days before D0	3.9	1.4–10.7	0.009

Pneumocystis jirovecii

Pneumocystis jirovecii Pneumonia in Patients with or without AIDS, France

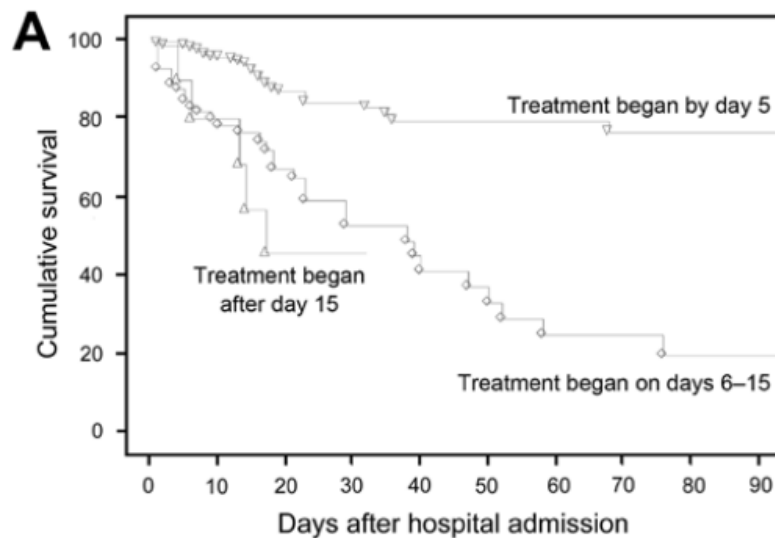


Table 3. Multivariate analysis of independent predictors of hospital death for AIDS and non-AIDS patients with PCP, France, January 1, 2007–December 31, 2010*

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)

Faut-il faire des corticoïdes ?



A CONTROLLED TRIAL OF EARLY ADJUNCTIVE TREATMENT WITH CORTICOSTEROIDS FOR *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

SAMUEL A. BOZZETTE, M.D., FRED R. SATTLER, M.D., JOSEPH CHIU, M.D., ALBERT W. WU, M.D.,

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., OTIS W. KIRKSEY, PHARM.D., AND LAWRENCE LA VOIE, PH.D.

Outcomes of Moderate-to-Severe *Pneumocystis* Pneumonia Treated with Adjunctive Steroid in Non-HIV-Infected Patients[†]

Song Mi Moon,¹ Tark Kim,¹ Heungsop Sung,² Mi-Na Kim,² Sung-Han Kim,¹ Sang-Ho Choi,³ Jin-Yong Jeong,¹ Jun Hee Woo,³ Yang Soo Kim,¹ and Sang-Oh Lee^{1*}



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, Ghba Amraoui, Ghislaine Lelen, François Lebarry, Laurent Brochard, Benoit Schlemmer, and Christian Brun-Buisson

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

Use of Adjunctive Corticosteroids in Severe Adult Non-HIV *Pneumocystis carinii* Pneumonia*

Jaiine C. Pareja, MD; Robert Garland, BRT; and Henry Kotzel, MD

Adjunctive steroid in HIV-negative patients with severe *Pneumocystis* pneumonia

Virginie Lemiale¹, Alexandre Debrumetz¹, Alexandra Delannoy², Corinne Alberti^{2,3} and Elie Azoulay^{1,3}

Etude PIC

Intérêt de la corticothérapie dans la pneumocystose grave du patient immunodéprimé non VIH.

Investigateur coordonnateur

Dr Virginie Lemiale, réanimation médicale hôpital Saint Louis, Paris

Comité de pilotage

Dr Virginie Lemiale, Pr Elie Azoulay, Dr Matthieu Resche-Rigon, Mr Lakhdar Mameri, Mr Igor Théodose (ARC du groupe Grrroh), Mme Cécile Kedzia,

Méthodologie- Analyse statistique

Dr Matthieu Resche-Rigon

Promoteur

AP-HP DRCD- hôpital Saint Louis

Unité de Recherche Clinique Lariboisière –Saint Louis

Pr Sylvie Chevret – Dr Matthieu Resche-Rigon

Attaché de recherche clinique

Coordinateur Etude Clinique : Lakhdar Mameri



Infection pulmonaire du greffé rénal

Bacterial pneumonia in kidney transplant recipients

- Pneumonie: 1^{ère} cause d'hospitalisation 1 an après la greffe
- Post-greffe : bactéries nosocomiales (Klebsielle, E Coli, Pyocyanique,...)
- > 6 mois : Pneumocoque, Haemophilus, Mycoplasme, Chlamydia
- En réanimation : Ventilation mécanique >60%, Choc 50%, Mortalité 35%
- Attention aux interactions médicamenteuses !!!

Interactions médicamenteuses

Potential interactions between CNI/mTOR inhibitors and antimicrobial agents.

Anti-infective agent	Interaction with CYP3A4	Interaction with P-gp	Adjustment of CNI/mTOR i
Azithromycin	no	Inhibition	monitor
Clarithromycin	inhibition	Inhibition	Reduce dose
Erythromycin	inhibition	inhibitor	Reduce dose
Levofloxacin	no	no	no
Ciprofloxacin	no	no	no
Rifampicin	Induction	induction	increase dose
Isoniazid	no	no	no
Ethambutol	no	no	no
TMP-SMX	no	no	no

TMP-SMX: trimethoprim-sulfamethoxazole; CYP3A4: cytochrome P450 3A4; P-gp: P-glycoprotein; CNI: calcineurin inhibitors; mTOR i: mammalian target of rapamycin inhibitor.

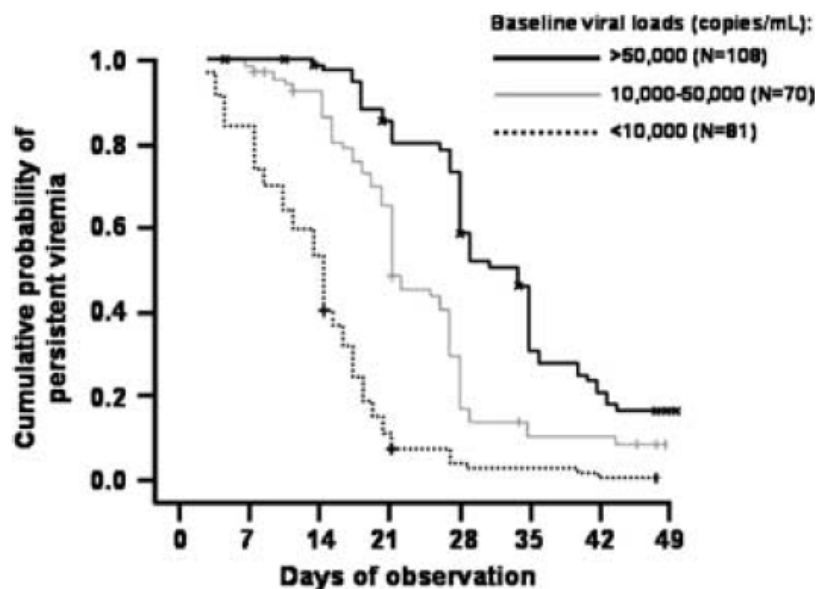
Infections virales: CMV

Infections in Solid-Organ Transplant Recipients

Type of infection	Incidence of infection (%) ^b in patients receiving:				
	Liver	Kidney	Heart	Lung/ heart-lung	Pancreas/ kidney- pancreas
Bacterial	33-68	47	21-30	54	35
CMV	22-29	8-32	9-35	39-41	50
HSV	5-44	55	1-42	10-18	6
VZV	5-10	4-12	1-12	8-15	9
<i>Candida</i> spp.	1-26	2	1-5	10-16	32
Mycelial fungi	2-4	1-2	3-6	3-19	3
<i>P. carinii</i>	4-11	5-10	1-8	15	

Patel, Clin Microbiol Rev 1997

Cytomegalovirus in Solid Organ Transplantation



☐ Résistance Ganciclovir ?

Pas d'interprétation de la virémie avant J15

Rare chez les patients recevant une prophylaxie (<5%)

Attention si charge virale initiale très élevée

Mutations CMV : UL97, UL54

Alternatives : baisse IS+++, Foscavir, Cidofovir, IgIV ?

Razonable, Am J Transplant 2013

Eid, Drugs 2010

Asberg, Am J Transplant 2007

GREPI
Groupe pour la Recherche et l'Évaluation en Pneumologie Infectieuse

6^{es}
JOURNÉES
du GREPI

Autres virus

➤ Virus communautaires

Influenza

Parainfluenza

Adenovirus

Virus respiratoire syncitial

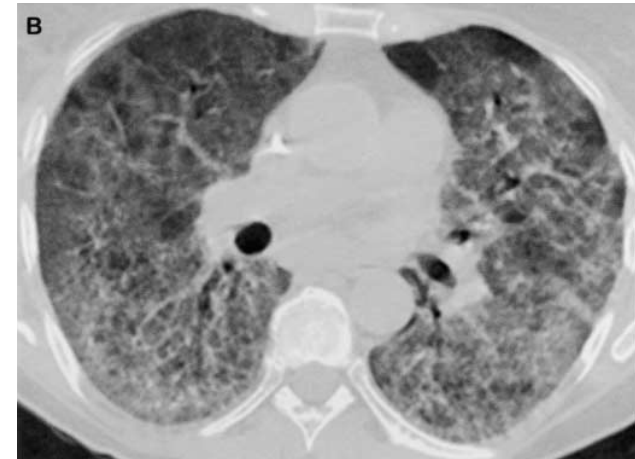
Pneumonie, bronchiolite, mortalité 0-20%

➤ « Nouveaux » virus

- 2008 : PCR multiplex

Metapneumovirus,

Bocavirus, Coronavirus, Rhinovirus, Polyomavirus



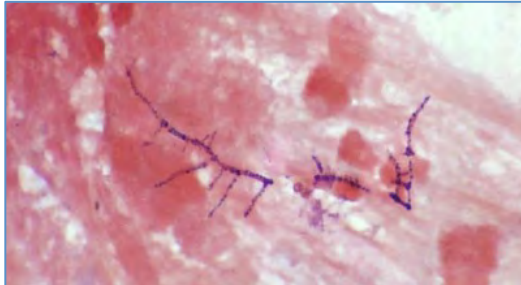
Pneumonie VRS

Kotloff, Am J Respir Crit Care Med 2004

Renaud, Curr Opin Infect Dis 2011

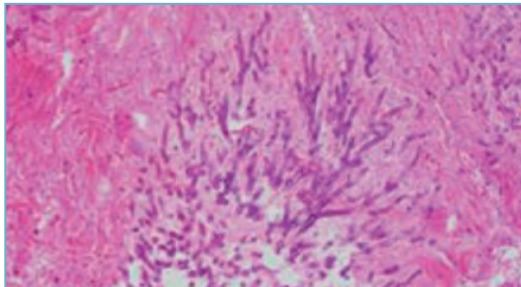
Autres opportunistes rencontrés en greffe rénale

Bactéries



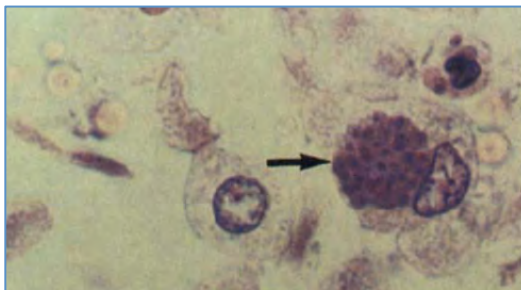
- Rhodococcus equi
- Nocardia
- Mycobactéries

Champignons



- Aspergillose
- Cryptococcose
- Mucormycose

Parasites



- Toxoplasmose

Et les immunosuppresseurs dans tout ça ?...

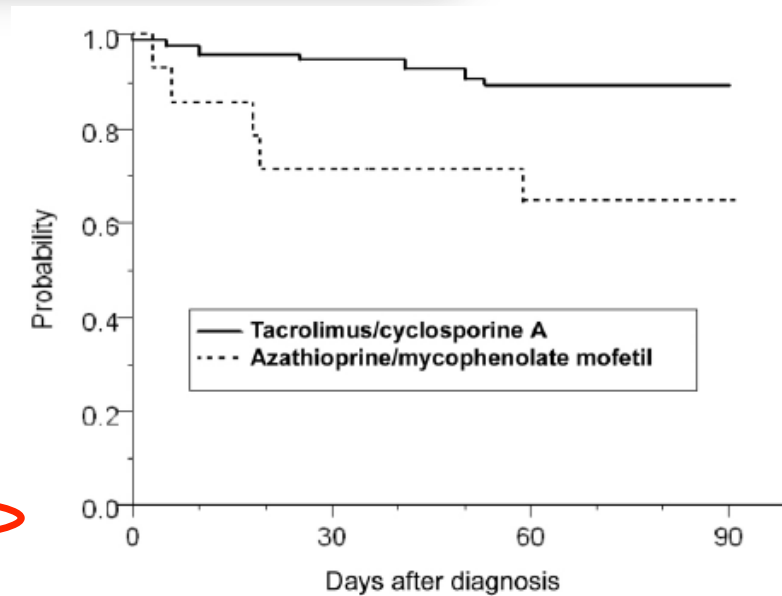
Cryptococcus neoformans in Organ Transplant Recipients: Impact of Calcineurin-Inhibitor Agents on Mortality

- 111 greffés d'organe solide
- Infection à *Cryptococcus neoformans*

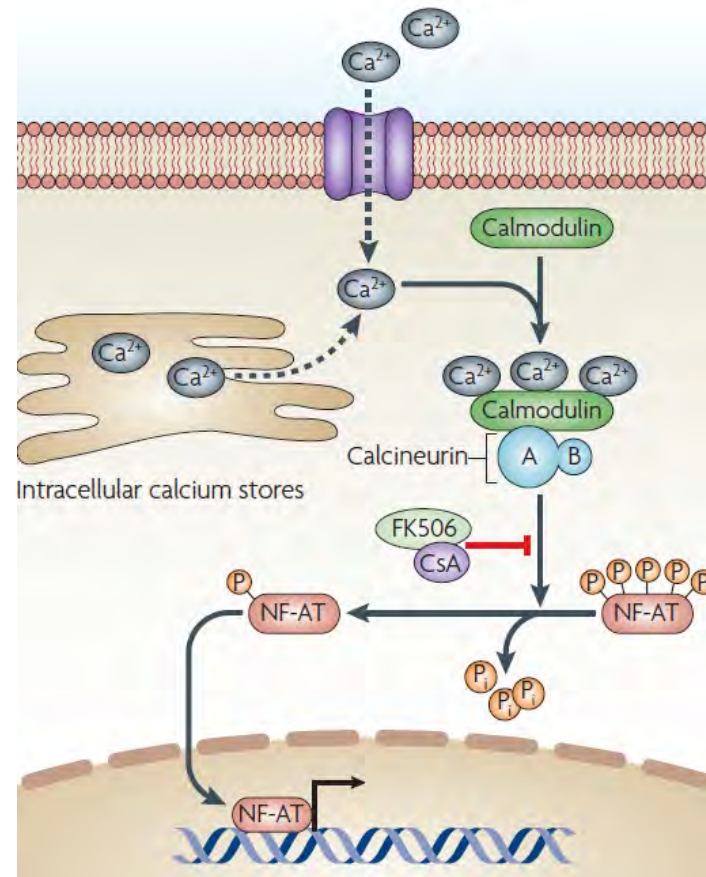
Table 4. Variables associated with mortality at 90 days in study patients, on the basis of a Cox proportional hazards analysis.

Multivariable analysis ^f		
Disseminated infection	4.13 (0.92–18.42)	.063
Receipt of a calcineurin-inhibitor agent	0.21 (0.06–0.66)	.008
Renal failure	3.14 (1.06–9.26)	.037

Singh, J Infect Dis 2007



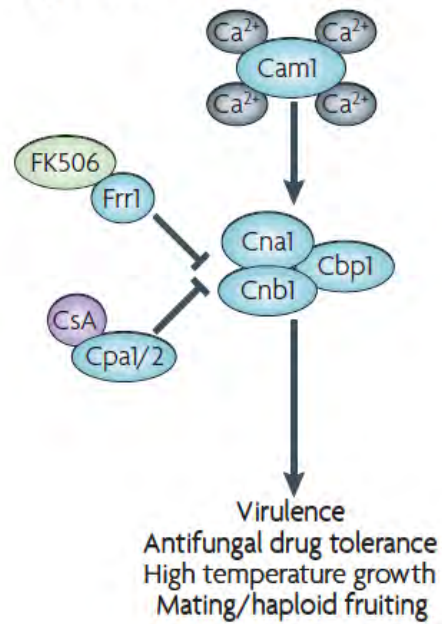
Activité antifongique des CNI ?



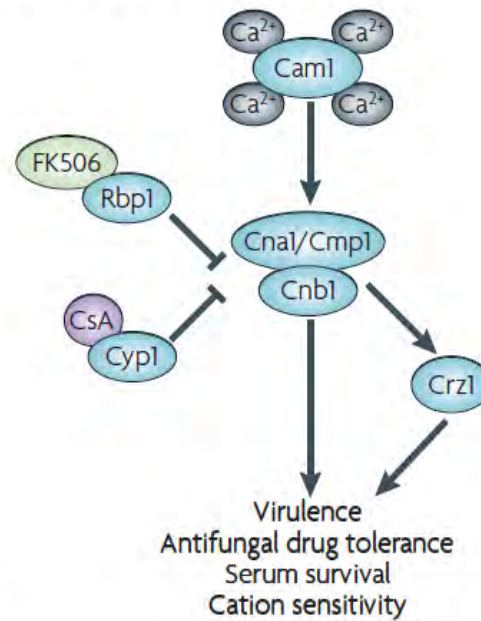
Steinbach WJ et al. Nat Rev Micr 2007

Activité antifongique des CNI ?

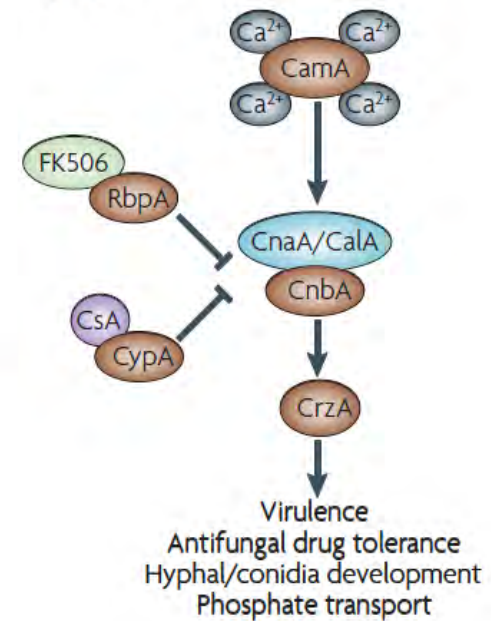
Cryptococcus neoformans



Candida albicans



Aspergillus fumigatus



Steinbach WJ et al. Nat Rev Micr 2007

Aggravation des symptômes à l'arrêt ?

Opportunistic Infection-Associated Immune Reconstitution Syndrome in Transplant Recipients

Pathogènes associés à l'IRS

- **Champignons** : *cryptococcus, aspergillus, histoplasma, candida,...*
- **Bactéries** : *mycobacterium*
- **Virus** : *CMV*

Table 1. Effect of Iatrogenic Immunosuppressive Agents in Transplant Recipients on T-helper Cell Phenotype

Agent	Th1	Th17	Th2	Tregs
Calcineurin inhibitors	↓↓	↓↓	↑/↓	No effect
Mycophenolate mofetil	↓	↓	↓	No effect
Inhibitors of mTOR	↓	↓	↓	↑↑
Corticosteroids	↓	↓	↑	↑
CD-52 antibody	↓	↓↓	↑	↑↑↑

NOTE. Data adapted from [32–42]. mTOR, mammalian target of rapamycin; Tregs, T regulatory cells.

Sun, Clin Infect Dis 2011



10 conseils pratiques

1. Admission précoce
2. Evaluation systématique de la fonction cardiaque
3. 3 étiologies fréquentes: pneumonie bactérienne, pyélonéphrite, bactériémie
4. Evaluer le risque de pneumocystose et considérer la fibro-LBA
5. Reconnaître les toxicité médicamenteuses
6. Eviction des néphrotoxiques
7. Echographie et doppler du greffon systématique
8. Doser les immunosuppresseurs
9. Discuter le G-CSF en cas de neutropénie
10. Réanimation complète compte-tenu du pronostic

Merci de votre attention...

...et venez nombreux à Nantes aux JAMIR 2018 !!!

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