Infections bactériennes et transplantations d’organes

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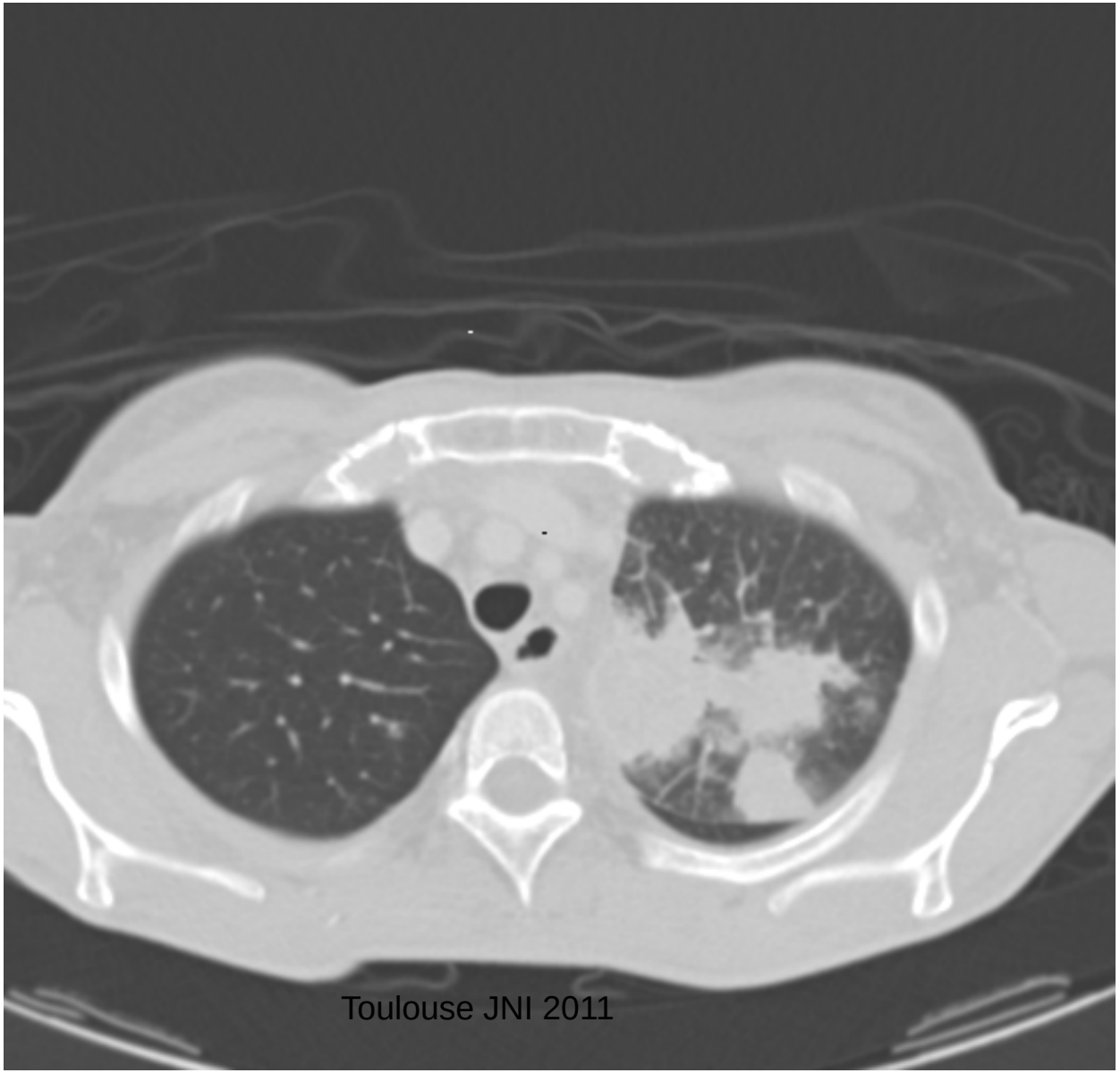
Hôpitaux de Lyon

Dossier n°1

- Patiente née novembre 1962,
- Diabète insulino-dépendant depuis 1982
- Complications (rétinopathie proliférante, néphropathie avec IRC, neuropathie périphérique, gastroparésie).
- 26/02/2006 : Première allogreffe R et P, Thymoglobuline, Prograf, CS, Cellcept puis Rapamune à partir de J8.

- 17 juin 2006, perforation duodénale et nodules spléniques : splénectomie et transplantectomie pour le P. Lymphome EBV + sur le duodenum (12 cures de Mabthera) avec diminution de l'immunosuppression.
- Aout 2006 : primo-infection à CMV et rejet traité par bolus de CS.
- 3 septembre 2007 : séances de photochimiothérapie extracorporelle (protocole).
- Avril 2009 : Cellcept est remplacé par Imurel devant une diarrhée chronique.

20 octobre 2009, hospitalisation pour un tableau pulmonaire fébrile, isolé.



LBA du 23 octobre 2009

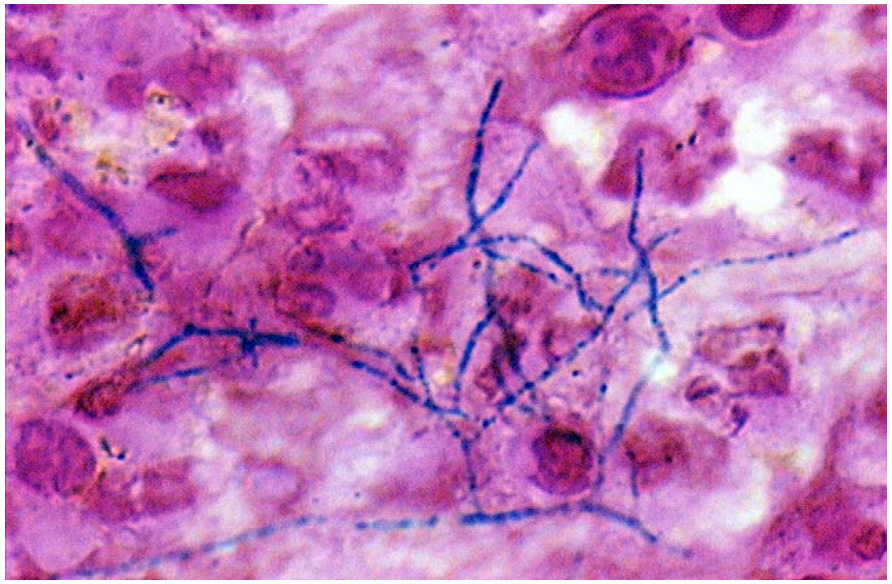
- ED : quelques bacilles gram positif
- Ziehl : négatif
- 10^5 ufc/mL *Nocardia nova*
- Sensible : céfotaxime, imipénème, amikacine, linézolide, rifampicine, cotrimoxazole
- Résistante : amox-Ac.clav, vancomycine, ciprofloxacine, tétracycline.

Evolution

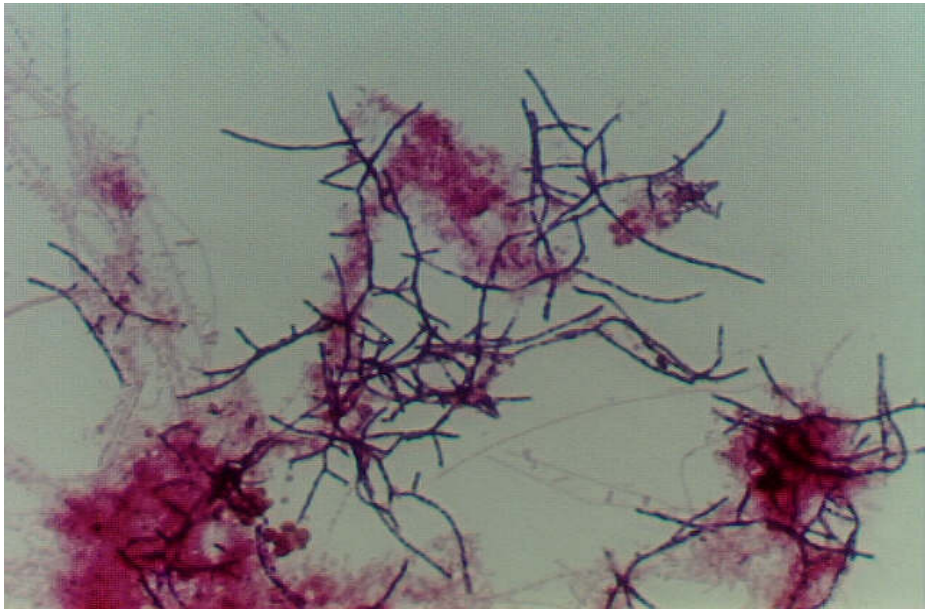
- Imipénème et amikacine, évolution favorable, réactivation de CMV
- Puis relai Bactrim Forte
- 29 mars 2010 : TDM pulmonaire quasi normalisé. Colite à CMV avec anémie, arrêt du Bactrim Forte.
- En juin 2011 : pas de récidive de la nocardiose.

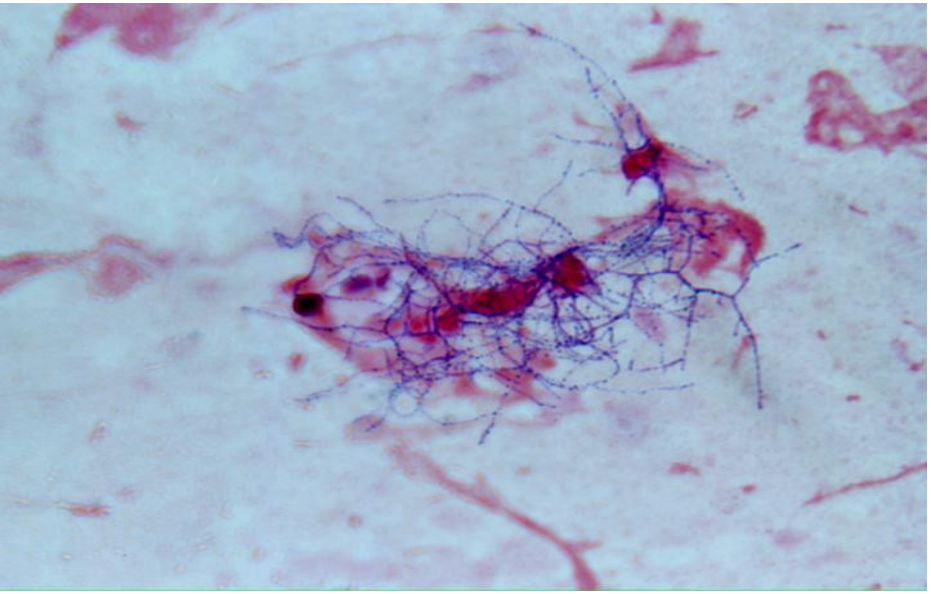
Nocardia

- *Nocardia, bactéries à Gram* positif, aérobies strictes, filamenteuses et ramifiées.
- *Nocardia et Rhodococcus appartiennent à la famille des Nocardiaceae, sont proches* des genres *Gordonia, Tsukamurella, Actinomadura, Corynebacterium et Mycobacterium.*
- *N. asteroides*, N. farcinica*, N. nova* (80 à 90% des cas) et* plus rarement *N. otitidiscaviarum, N. brasiliensis et N. transvalensis*.*



Coloration de Gram





CLINICAL MICROBIOLOGY REVIEWS, Apr. 2006, p. 259–282 Vol. 19, No. 2
0893-8512/06/$08.00+0 doi:10.1128/CMR.19.2.259–282.2006

Clinical and Laboratory Features of the *Nocardia* spp. Based on Current Molecular Taxonomy

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Plus de 80 espèces différentes de *Nocardia,*

Au moins 30 impliquées dans la pathologie humaine dont

*N. cyriacigeorgica * ,*

N. abscessus,

N. veterana et

N. paucivorans .

TABLE 1. Current validly described *Nocardia* species of human clinical significance

Species	Reference(s)	Commonly associated disease[a]		
		Primary skin	Pulmonary	Disseminated
N. abscessus	228		+	+
N. africana	82		+	
N. anaemiae	101			
N. aobensis	95			
N. araoensis	98			
N. arthritidis	96			
N. asiatica	92		+	
N. asteroides	54	+	+	+
N. beijingensis	93, 217		+	+
N. brasiliensis (formerly *Discomyces brasiliensis*, *Streptothrix brasiliensis*, *Oospora brasiliensis*, *Actinomyces brasiliensis*)	125	+		
N. brevicatena (formerly *Micropolyspora brevicatena*)	122			
N. carnea	166			
N. cyriacigeorgica[b] (formerly *N. cyriacigeorgici*)	229		+	+
N. farcinica	189		+	+
N. higoensis	97		+	+
N. inohanensis	99			
N. kruczakiae	41			
N. mexicana[c]	165			
N. niigatensis	94	+		
N. nova	192		+	+
N. otitidiscaviarum (formerly *N. caviae*)	179	+	+	+
N. paucivorans	227		+	+
N. pseudobrasiliensis	168		+	+
N. pneumoniae	98			
N. puris	231			
N. sienata (formerly *N. senatus*)	100			
N. testaceae (formerly *N. testaceus*)	100			
N. thailandica	94			
N. transvalensis	160		+	+
N. vermiculata	94			
N. veterana	80		+	
N. vinacea	101, 109			
N. yamanashiensis	99			

[a] Four or more known cases.
[b] The original spelling of the epithet in *N. cyriacigeorgici* [sic] has been corrected by the List Editor, IJSEM (126).
[c] Not validated.

Clinical Infectious Diseases 2007; 44:1307–14

Risk Factors, Clinical Characteristics, and Outcome of *Nocardia* Infection in Organ Transplant Recipients: A Matched Case-Control Study

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Etude cas contrôle (1/2)

- Janvier 1995 et décembre 2005
- 35 infections à *Nocardia* chez 5126 (0,6%) :
  - 18/512 (3,5%) en T pulmonaire
  - 10/392 (2,5%) en T cardiaque
  - 2/155 (1,3%) en T intestinale
  - 3/1717 (0,2%) en T rénale
  - 2/1840 (0,1%) en T hépatique
  - 0 pour 180 Pancréas, 297 R+P, 24 C+Poumon.
- Délai : 22/35 dans l'année et 5 plus de 5 ans

Table 2. Independent risk factors for *Nocardia* infection as determined by multivariable conditional logistic regression analysis.

Variable	OR (95% CI)	*P*
Receipt of high-dose prednisone in preceding 6 months[a]	27 (3.2–235)	.003
Elevated median calcineurin inhibitor level in preceding 30 days[b]	5.8 (1.5–22)	.012
Cytomegalovirus disease	6.9 (1.02–46)	.047

[a] Defined as ⩾20 mg of prednisone for ⩾1 month or >2 pulses of 1 g intravenous methylprednisolone.

[b] Defined as >15 μg/mL for tacrolimus and >300 ng/mL for cyclosporin.

Radiological findings	
Pulmonary[d]	
Nodule[e]	22 (63)
Infiltrate	7 (20)
Reticulonodular	1 (3)
Consolidation	13 (37)
Effusion	8 (23)
CNS[f]	
Solitary abscess	2 (6)
Multiple abscesses	1 (3)
Length of hospitalization, median days (range)	12 (2–104)
Death at 6 months after diagnosis	5 (14)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] *Nocardia* infection involving ⩾2 noncontiguous organs, the CNS, or *Nocardia* species in blood.

[b] A kidney recipient with an infected peritoneal dialysis catheter.

[c] One case each of invasive pulmonary aspergillosis, invasive lung infection with *Scedosporium apiospermum,* and esophageal candidiasis.

[d] Thirty (86%) of the case patients had an abnormal finding on chest imaging. Multiple pulmonary findings were observed for many patients; therefore, the total percentage is >100%.

[e] Five (23%) of the infections were cavitary.

[f] Seventeen (49%) of the case patients had no neuroimaging, including 2 case patients who presented with headache and fever and 1 who presented with disseminated infection.

- 80% formes pulmonaires et 20% disséminées (3 abcès cérébraux, 3 hémocultures, 1 prostatite, 1 cutanée)
- 24/35 étaient sous cotrimoxazole (médiane de 264 jours)
- *N nova* (17), *N farcinica* (9), *N asteroides* (8) et *N brasiliensis* (1).
- 97 % des souches sensibles au CTX
- 5 décès dont 4 attribuables à *Nocardia*.

Traitement

- Indications chirurgicales
- Pas toujours de corrélation entre les données *in vitro* et l'évolution clinique, adresser les souches **à l'Observatoire national des *Nocardia*, à Lyon**.
- Ceci est surtout vrai pour les abcès cérébraux (observance thérapeutique).
- Profils attendus de résistances naturelles

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TABLE 3. Antimicrobial susceptibility patterns of species of the former *Nocardia asteroides* complex, *N. brasiliensis*, *N. pseudobrasiliensis*, and *N. otitidiscaviarum*

Species	Corresponding type drug pattern	Major drug pattern characteristics
N. abscessus	I	Susceptible to ampicillin, amoxicillin-clavulanic acid, ceftriaxone, linezolid, and amikacin; most have resistant MICs for imipenem; resistant to ciprofloxacin and clarithromycin
N. brevicatena/paucivorans complex, unnamed group	II	Same as type I but kanamycin MICs low (<1 μg/ml) and susceptible to ciprofloxacin; usually resistant to gentamicin; resistant to clarithromycin
N. nova complex (*N. nova*, *N. veterana*, *N. africana*, *N. kruczakiae*)	III	Susceptible to ampicillin but resistant to amoxicillin-clavulanic acid; susceptible to erythromycin, clarithromycin, linezolid, and ceftriaxone; very low MICs to imipenem and amikacin
N. transvalensis complex	IV	Resistant to all aminoglycosides, including amikacin; susceptible to ciprofloxacin, ceftriaxone, linezolid, and imipenem; resistant to erythromycin and clarithromycin
N. farcinica	V	Resistant to ampicillin, broad-spectrum cephalosporins, and clarithromycin; resistant to aminoglycosides except amikacin; susceptible to ciprofloxacin, linezolid, and imipenem
N. asteroides complex	VI	Resistant to ampicillin, amoxicillin-clavulanic acid, clarithromycin, and ciprofloxacin; susceptible to ceftriaxone, amikacin, linezolid, and imipenem
N. asteroides type VI (unnamed), *N. cyriacigeorgica*		The ATCC type strain is susceptible to ampicillin, other drug susceptibilities are the same as for pattern VI
N. brasiliensis	NA[a]	Susceptible to minocycline, amoxicillin-clavulanic acid, carbenicillin, and sulfamethoxazole; resistant to kanamycin, cefamandole, ampicillin, ciprofloxacin, and clarithromycin
N. pseudobrasiliensis	NA	Susceptible to carbenicillin, ciprofloxacin, clarithromycin, and sulfamethoxazole; resistant to kanamycin, cefamandole, ampicillin, minocycline, and amoxicillin-clavulanic acid
N. otitidiscaviarum	NA	Susceptible to kanamycin, gentamicin, amikacin, sulfamethoxazole, and ciprofloxacin; resistant to ceftriaxone, ampicillin, amoxicillin-clavulanic acid, carbenicillin, and imipenem (often resistant to all β-lactam antibiotics)

[a] NA, not applicable.

TABLE 254-1 -- Antimicrobial Susceptibility of Selected *Nocardia* Species (% Isolates Susceptible)

Antimicrobial*	*N. asteroides*	*N. farcinica*	*N. nova*	*N. brasiliensis*	*N. transvalensis*	*N. otitidiscaviarum*
Sulfamethoxazole	96-99	89-100	89-97	99-100	90	V
Trimethoprim-sulfamethoxazole	100	100	NR	100	88	V
Ampicillin	40-93	0-5	100	14	10	NR
Amoxicillin-clavulanate	53-67	47-71	3-6	65-97	30	R
Ceftriaxone	94-100	0-73	100	88-100	50	NR
Imipenem	77-98	64-100	100	20-30	90	R
Amikacin	100	100	100	100	†82	S
Doxycycline	48-88	0-14	19-94	NR	NR	NR
Minocycline	78-94	12-96	89-100	75-90	54	S
Ciprofloxacin	38-98	68-100	0	12-30	60	R
Moxifloxacin	50	NR	NR	NR	NR	NR
Erythromycin	23-93	0-3	100	40	50	NR
Clarithromycin	42	5	NR	NR	NR	NR
Linezolid	100	100	100	100	100	100

R, resistant; V, variable susceptibility; S, sensitive; NR, not reported.

*Based on a small number of isolates. Amikacin resistance has been considered a characteristic of the *N. transvalensis* complex.

American Journal of Transplantation 2009; 9 (Suppl 4): S70–S77

Table 2: Suggested therapy for *Nocardia* infections in transplant patients

Disease	Primary therapy	Alternative‡
Pulmonary-stable	TMP-SMX**–15 mg/kg in 3–4 divided doses, either IV or PO [II-2]	Imipenem + amikacin [III] or minocycline [III] or linezolid [III]
Pulmonary-critical	Imipenem** (500 mg q6h) + amikacin** (10–15 mg/(kg day)) [III] or TMP-SMX [II-2]	Linezolid 600 mg q12h [III]
Cerebral*	Imipenem† + amikacin [III] or TMP-SMX [II-2]	Linezolid 600 mg [III] q12h or ceftriaxone [III] 2 g q12h or cefotaxime** [III] 2 g q8h or minocycline [III] 200 mg q12h
Disseminated*	Imipenem + amikacin [III] or TMP-SMX [II-2]	Ceftriaxone, cefotaxime, linezolid or minocycline [III] after initial therapy

*Based on animal studies and numerous case reports (1,2,11,15,36,44,47–56,59,61–63,65–75).

**Adjust therapeutic agents based on patient's renal function.

†Meropenem (1 gram q8h) may be an alternative agent depending on species. [III]

‡The use of alternative regimens should be governed by antimicrobial susceptibility testing. This table is a only a guide and choice of treatment depends on antimicrobial susceptibility, severity of condition and immunosuppression of the patient and allergy history. Alternate agents, such as amoxicillin-clavulanate, ceftriaxone, fluoroquinolones and macrolides may be effective [III] but there is insufficient information to support their use as initial therapy. These agents should be considered only if standard therapy is ineffective.

Note: Sulfonamides may be substituted for TMP-SMX.

Durée des traitements

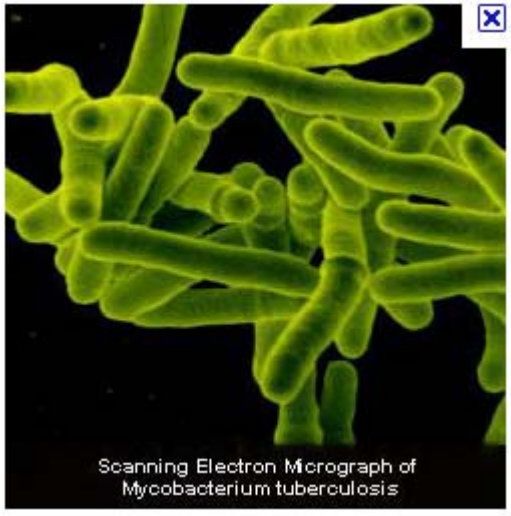
- **1 à 3 mois**, lésion cutanée (plus pour les mycétomes).
- Au moins **6 mois**, pour les localisations pulmonaires.
- Au moins, **12 mois** pour les abcès cérébraux avec suivi d'1 an à l'arrêt.
- Traitement **suspensif** journalier discutable.
- **Prophylaxie** journalière par CTX.

Dossier n°2

- Patient né le 09/09/1961,
- Greffé hépatique en 2003 sur cirrhose virale C et éthylique,
- Récidive de cirrhose virale C, ascite réfractaire imposant un TIPS en juillet 2010,
- 8 mois plus tard, nouvelle décompensation récidivante de l'ascite (exsudative, 70% de lymphocytes).

- Baisse de l’état général, amaigrissement de 8 kg, toux avec quelques hémoptysies.
- Voyages fréquents au Maroc,
- Pas de fièvre, quelques lésions cutanées non spécifiques.
- Quantiféron positif à 5, IDR est à 15 mm, le TDM pulmonaire normal (CD4+ 55%/588).
- Aspect feuilleté du péritoine péri-hépatique

- PBH : réinfection virale C du greffon, ED, PCR BK, culture négatifs
- BK négatifs dans l'ascite (3), crachats (4), fibroaspiration et LBA.
- Tuberculose péritonéale probable:
  - 22/04/2011 : RMP (600 mg), INH (200 mg), EMB (1200 mg) et ofloxacine (400 mg).
  - Advagraf (1,5 mg), posologie multipliée par 3



- Incidence de l'infection : 20 à 70 fois supérieure à celle de la population générale.
- La prévalence suit celle du pays:
  - 0,45 %, 16146 T rénaux (14 centres, 20 ans) E Canet (2011)
  - 12,4 -15,2%, T rénaux , (Rubina Naqvi, 2010)

Clinical Infectious Diseases 2009; 48:1276–84

Table 2. Frequency of tuberculosis among solid-organ transplant recipients.

Variable	Solid-organ transplantation type					
	Overall	Pulmonary	Cardiac	Renal	Hepatic	Renal-pancreatic
Prevalence, %						
Literature[a]	1.2–6.4[b]	2–6.5	1–1.5	0.5–15	0.7–2.3	…
GESITRA	0.45	1.15	0.26	0.35	0.47	0.85
Incidence, cases per 10^5 inhabitants per year (95% CI 95): GESITRA	512 (317–783)	2072 (565–5306)	255 (6.5–1421)	358 (144–728)	541 (269–1065)	1204 (30.5–6710)

NOTE. Data from the Network for the Study of Infection in Transplant recipients (GESITRA) are from 2008.

[a] Data are from [1–4].

[b] Data shown are for developed countries; the prevalence in countries where tuberculosis is highly endemic was 15%.

Tuberculose latente

- Dépister le candidat à la greffe
  - Histoire, contacts, voyages…
  - IDR, à refaire 15 jours si anergie
  - Quantiféron ou Spot-test
  - Eliminer une tuberculose-maladie (clinique, radiologie et BK des prélèvements respiratoires…)

HAS novembre 2007

- IDR post-transplantation si non faite avant :
  - IDR est positive si supérieure à 5 mm,
  - Si IDR négative, refaire à 2 semaines.
- Prophylaxie par isoniazide de 6 ou 9 mois :

- antécédents de tuberculose active sans traitement adapté ;
- radiographie pulmonaire d'un patient avec séquelles de tuberculose, non traité antérieurement ;
- greffe d'un organe d'un donneur IDR +;
- greffés aux contacts prolongés avec un patient qui a développé une tuberculose;
- greffé avec positivation de son IDR.

Table 3. Risk factors for tuberculosis (TB) after transplantation.

Risk factor
Immunosuppressive therapy[a]
OKT3 or anti-T lymphocyte antibodies (III)
Intensification of immunosuppression associated with graft rejection (II)
Cyclosporine A vs. azathioprine plus prednisone (II)
Mycophenolate mofetil and tacrolimus vs. azathioprine, cyclosporine, and prednisone (III)
History of exposure to *Mycobacterium tuberculosis*
Positive PPD test result (III)
Radiological evidence of previous untreated TB (III)
Clinical condition
Chronic renal insufficiency or hemodialysis (kidney transplantation; II)
Diabetes mellitus (II)
Hepatitis C virus infection (kidney transplantation; III)
Chronic liver disease (III)
Other coexisting infections: profound mycoses, cytomegalovirus, or *Pneumocystis jiroveci* or *Nocardia* pneumonia (III)

NOTE. Roman numerals indicate the degree of evidence (table 1). PPD, purified protein derivative.

[a] No information was available on recently introduced immunosuppressors, such as sirolimus, everolimus, or monoclonal antibodies (daclizumab and basiliximab).

Traitement de la tuberculose latente

- Idéalement : débuter avant la greffe,
- Isoniazide (300 mg/jour) et vitamine B6 pendant durée totale de 9 mois.
- Toxicité hépatique (arrêt si plus de 3 à 5 N)
- Rifampicine (+/- INH) pendant 4 mois,
- Rifampicine et PZA : 2 mois.
- INH-EMB-PZA (2 mois) et INH (7 mois) (impossibilité d'éliminer tuberculose-maladie, en attente de la négativité des recherches)

Traitement de la tuberculose latente : greffe hépatique

- Attendre la greffe pour traiter
- Risque accru de toxicité hépatique (PBH)
- Yehia (Liver Transplant. 2010,16:1129-35)
  - Cirrhose compensée : traiter avant (possible)
  - Cirrhose décompensée : attendre la greffe
  - Levofloxacine et EMB (6 mois).

Traitement de la tuberculose –maladie chez le transplanté d’organe

Table 4. Tuberculosis (TB) treatment options, recommended doses, alternative dosing regimens, and drug interactions and contraindications.

Situation	Initial treatment	Maintenance treatment
Patients with localized, nonsevere forms of TB, without suspicion or evidence of resistance to isoniazid	Avoid the use of rifamycins; if rifamycins are used, the levels of immunosuppressors should be closely monitored, and the dose of cyclosporine or tacrolimus should be increased (A-II); if treatment is started early, it is not necessary to reduce the level of immunosuppression (C-III)	Isoniazid and ethambutol (or pyrazinamide) are recommended for 12–18 months (C-III); the incorporation of a third drug, such as pyrazinamide or levofloxacin,[a] could reduce this period to 12 months (C-III)
Severe forms or disseminated forms of TB or suspicion or evidence of resistance to isoniazid[b]	Consider adding rifampicin or rifabutin to the regimen (B-III)[c]	Complete treatment with isoniazid and rifampicin or rifabutin for at least 9 months
Multidrug-resistant TB or when there is some limitation for the use of the aforementioned drugs	If isoniazid and rifamycins cannot be used, induction treatment should include 4–6 drugs, including injectable antimicrobials (e.g., streptomycin,[d] amikacin, kanamycin, or capreomycin), linezolid, or other second-line drugs (C-III)[e]	The absence of isoniazid and rifamycin in the initial treatment makes it difficult to calculate the duration of treatment and the types of drugs to be used; therapy should be individualized

[a] Prolonged use of fluoroquinolones can be associated with arthralgias, and the combination of pyrazinamide and levofloxacin is poorly tolerated by the digestive system.

[b] If isoniazid cannot be used, induction and maintenance treatment that includes 4 drugs for at least 18 months is recommended (C-III).

[c] Use of rifampicin or rifabutin would require an increased dose of cyclosporine or tacrolimus and closer monitoring of the levels of these drugs (A-II). Resistance to rifampin is almost systematically associated with cross-resistance to rifabutin and rifapentine; therefore, these drugs are not suitable alternatives (D-II).

[d] In cases of resistance to streptomycin, there is no cross-resistance with other injectable drugs (e.g., amikacin, kanamycin, and capreomycin); however, cross-resistance between amikacin and kanamycin is universal. The combination of injectable drugs is not recommended because of their intolerance and the association of adverse effects (D-II).

[e] There is no experience with the use of intermittent regimens which, therefore, are not recommended for the management of multidrug-resistant TB, with the of injectable drugs after a period of at least 2–3 months of daily therapy (D-II).

American Journal of Transplantation 2009; 9 (Suppl 4): S263–S266

- Effet inducteur du CYP 3A4 par rifampicine:
  - Avec les inhibiteurs de la calcineurine
    - Augmentation des posologies par 3 ou 5 du tacrolimus et de la ciclosporine A
  - Avec les inhibiteurs de mTor
  - Rifabutine (300 mg/jour) : moins inducteur +++
  - Dosages des IS et des antituberculeux
- Pas d'interaction avec les autres traitements
- http://pharmacoclin.hug-ge.ch/_library/pdf/cytp450.pdf

Durée du traitement

- Pas moins de 12 mois si absence RMF
- Pas moins de 9 mois si schéma conventionnel
- Résultats :
  - T rénale (E Canet, 2011)
    - Mortalité de 6,1%
    - Survie du greffon à 10 ans (67%/64%)
  - T hépatique (JC Holty, 2009)
    - Mortalité de 31% (suivi de 25 mois, rejet+++)

Conclusions

- Problèmes de diagnostic étiologique et recherches multiples systématiques
- Toxicités médicamenteuses cumulées
- Interactions médicamenteuses
- Intérêt des traitements prophylactiques
- Nécessité de la collaboration multidisciplinaire des équipes.

Je vous remercie pour votre attention