DES Infectiologie 2023

Module Infections du SNC

Infections à *Nocardia* spp. et fongiques en quelques messages

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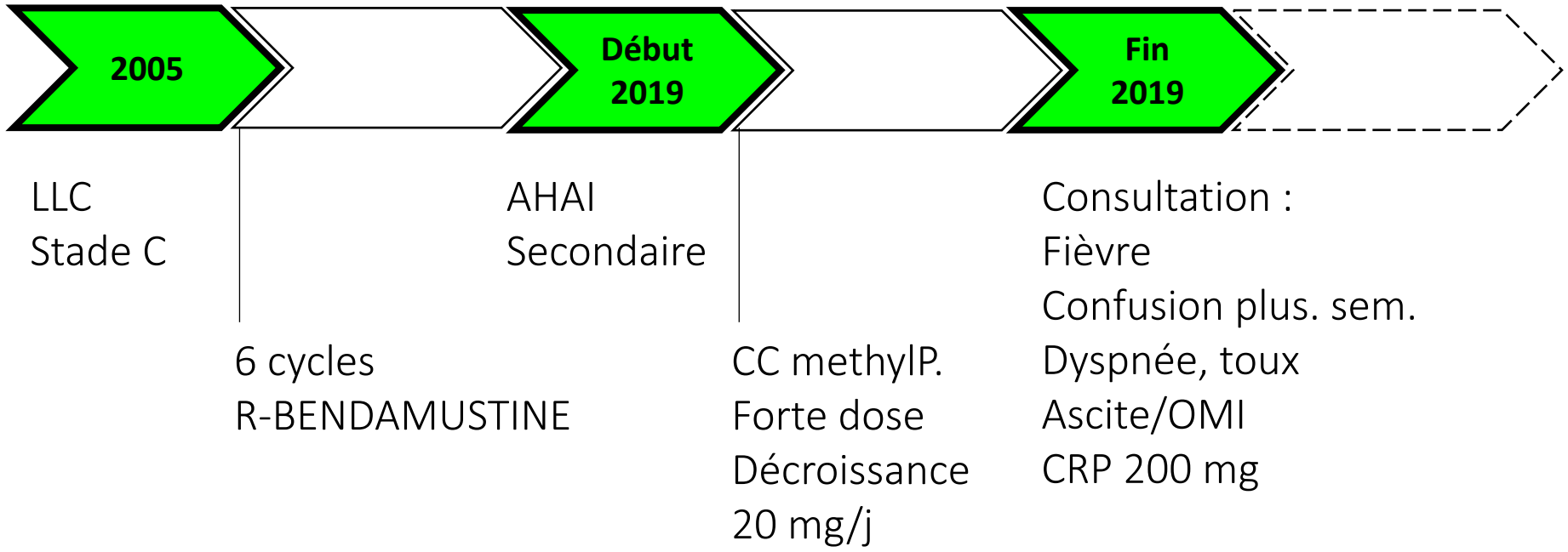
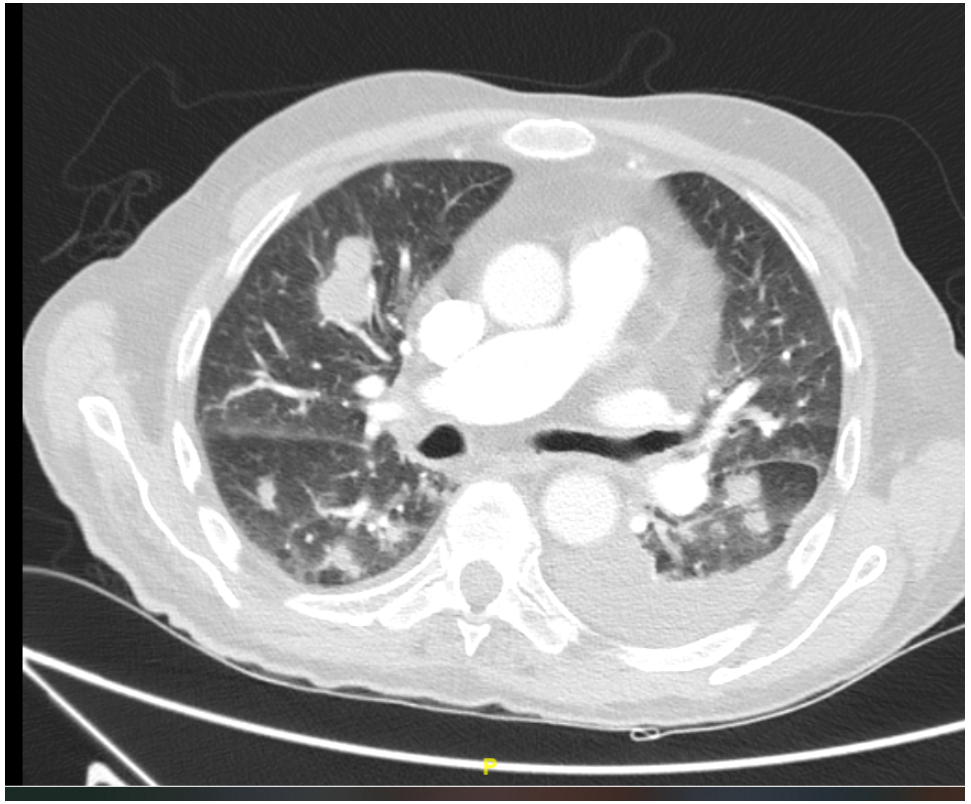
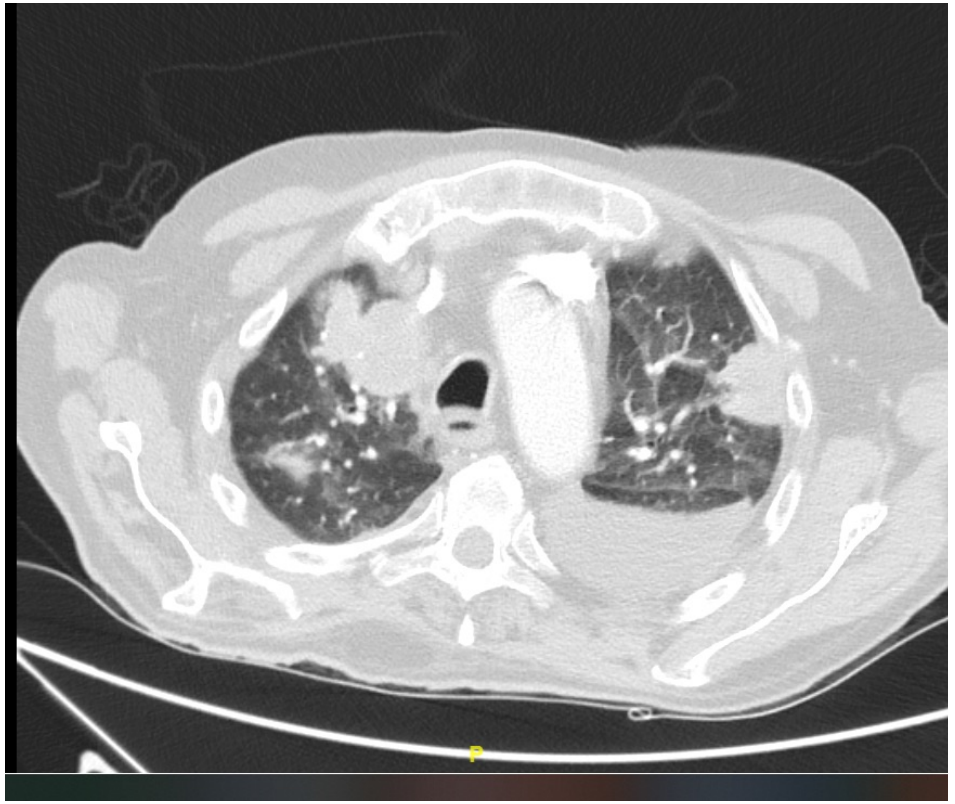
Vignette clinique Mr. BU. Ed. 14/05/1933

Habitat rural

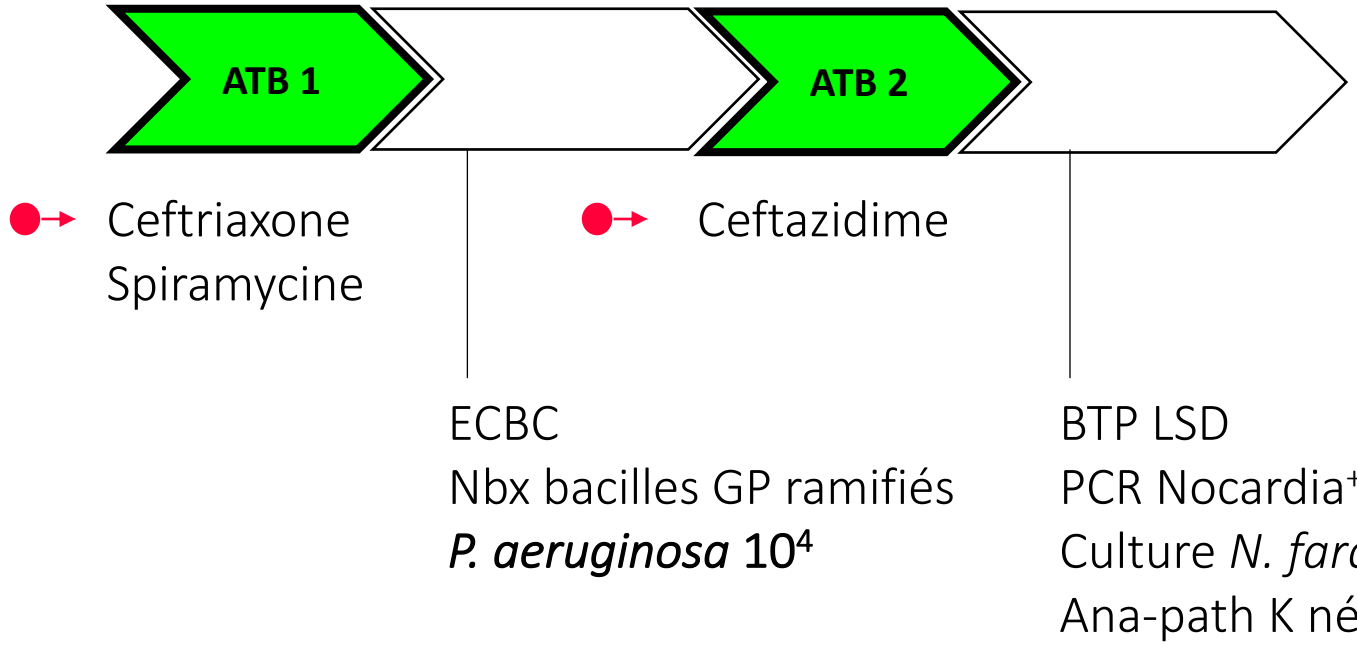






Compte rendu TDM TAP: aspect de lâcher de ballon pulmonaire associé à des condensations parenchymateuses bilatérales et un épanchement pleural gauche. Étage sous-diaphragmatique : Multiples nodules de carcinose péritonéale, avec aspect «scalloping » (indentation) splénique et hépatique. Pas de primitif évident.

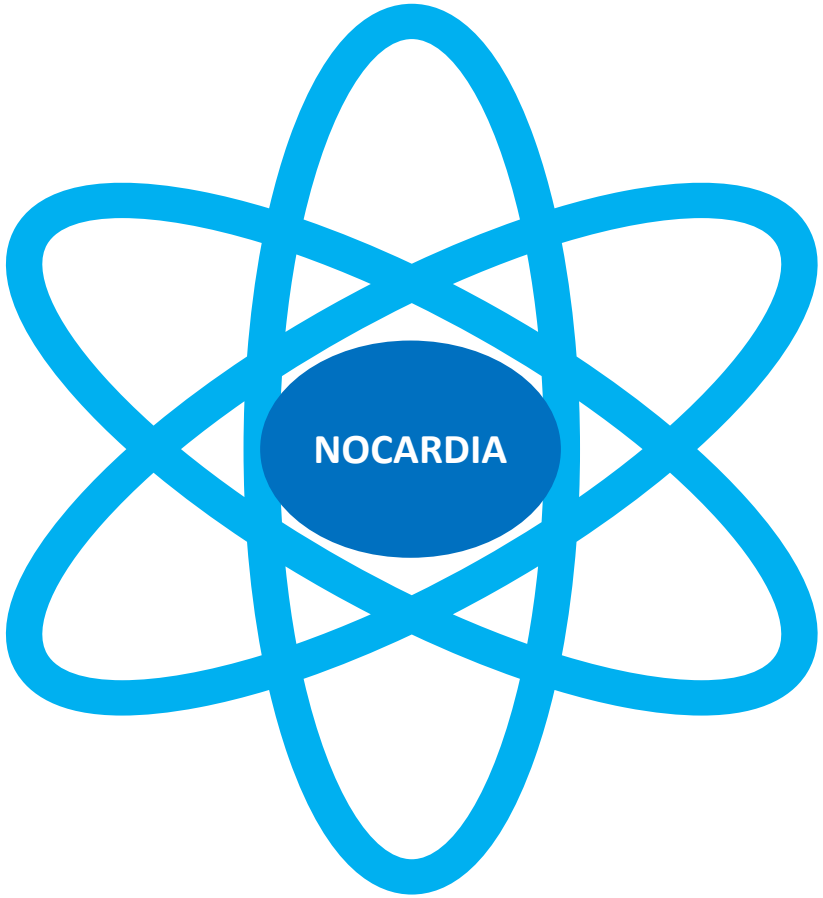
Vignette clinique Mr. BU. Ed. 14/05/1933



TERRAIN
STATUT IMMUNITAIRE ?

MANAGEMENT – PRONOSTIC

CLINIQUE
LOCAL/DISSÉMINÉ ?



TRAITEMENT ANTIBIOTIQUE

MICROBIOLOGIE

SCREENING d'IMAGERIE

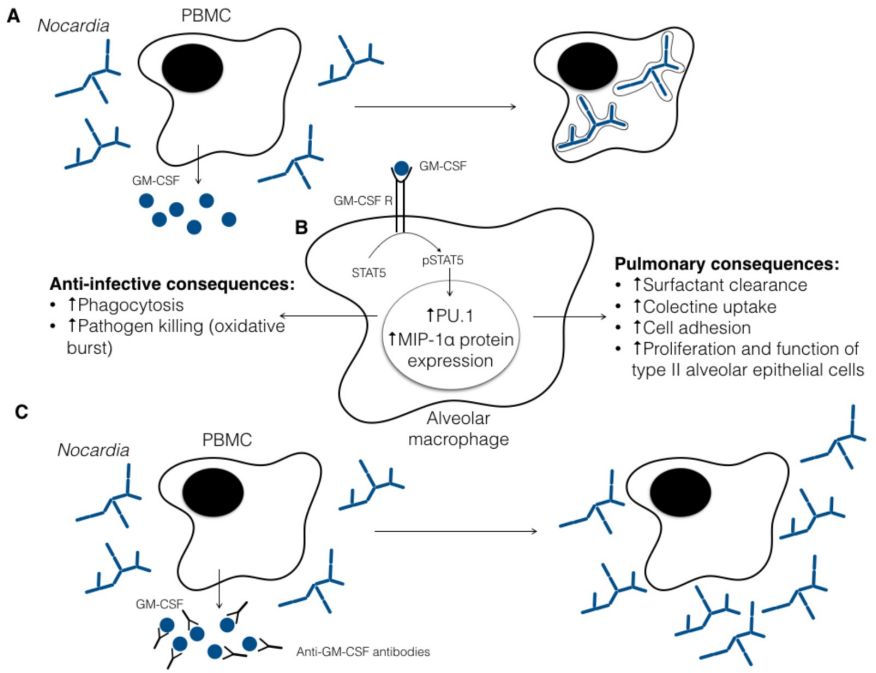
Terrain – Statut immunitaire

Dysimmunité/Immunodépression

TOS (poumons, cœur)
Transplantation CSH
Hémopathies
Cancer
Maladies auto-immunes
CC long cours
Maladies pulm. Chnq (10-58%)
VIH < 10%
Déficit immunitaire primitif rare (auto-Ac)

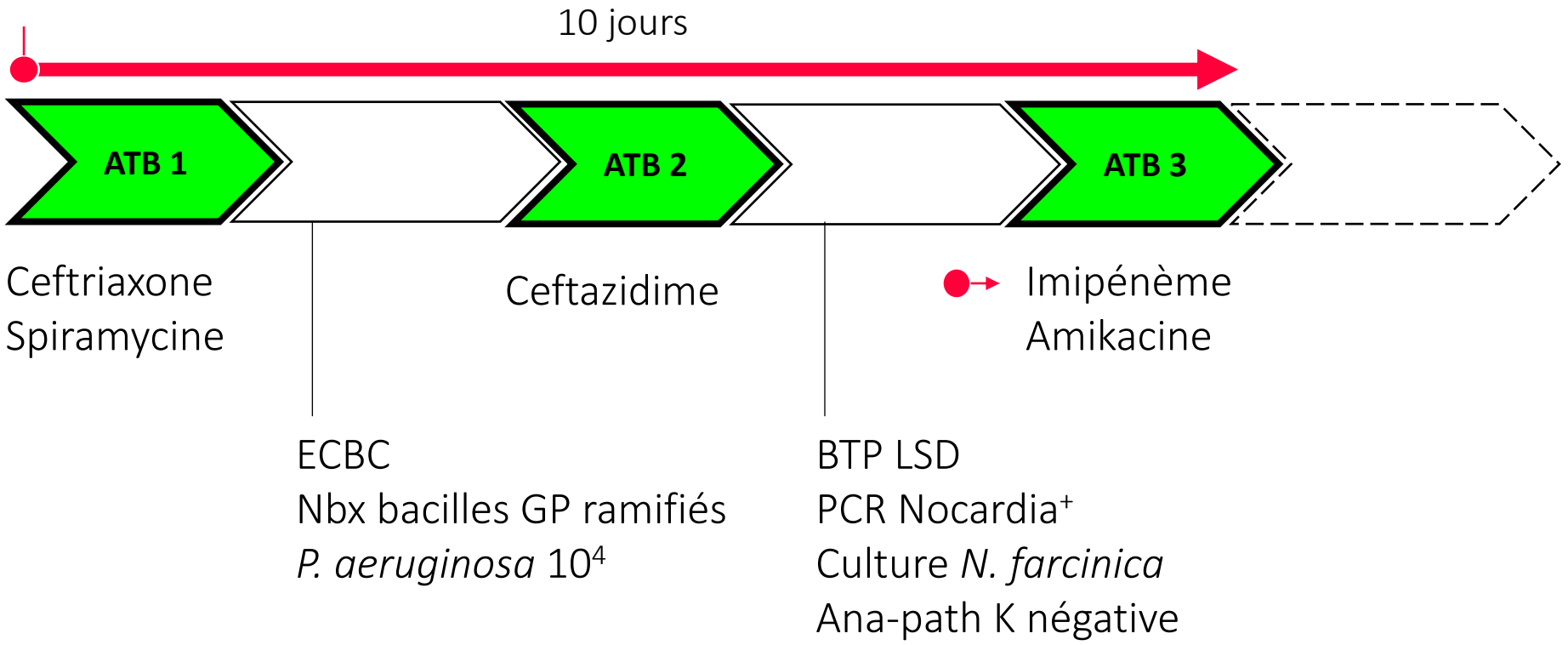
Immunocompétence

18-45%
Diabète, OH
Inoculation traumatique



Rosen LB et al., Nocardia-induced granulocyte macrophage colony-stimulating factor is neutralized by autoantibodies in disseminated/extrapulmonary nocardiosis. Clin Infect Dis. 2015 Apr 1;60(7):1017-25.

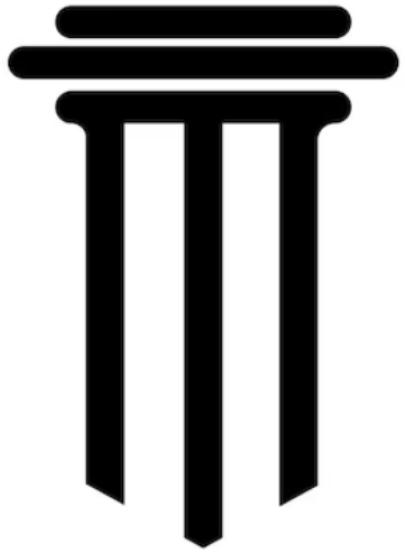
Vignette clinique Mr. BU. Ed. 14/05/1933



Clindamycine

Doxycycline

Cotrimoxazole



cine

Clarithromycine

icline

Pristinamycine

Quelle(s) est/sont la/les propositions exactes à propos de l'activité des antibiotiques sur *Nocardia* spp. ?

A – l'amikacine est quasi constamment active
B – Quand une C3G testée est active, cela vaut pour toute la classe
C – l'imipénème est inactif dans 1/3 des cas
D – le linezolide est quasi constamment actif
E – la ciprofloxacine et la moxifloxacine sont constamment actives

Quelle(s) est/sont la/les propositions exactes à propos de l'activité des antibiotiques sur *Nocardia* spp. ?

A – l'amikacine est quasi constamment active (95-100%)

B – Quand une C3G testée est active, cela vaut pour toute la classe (dissociation de classe)

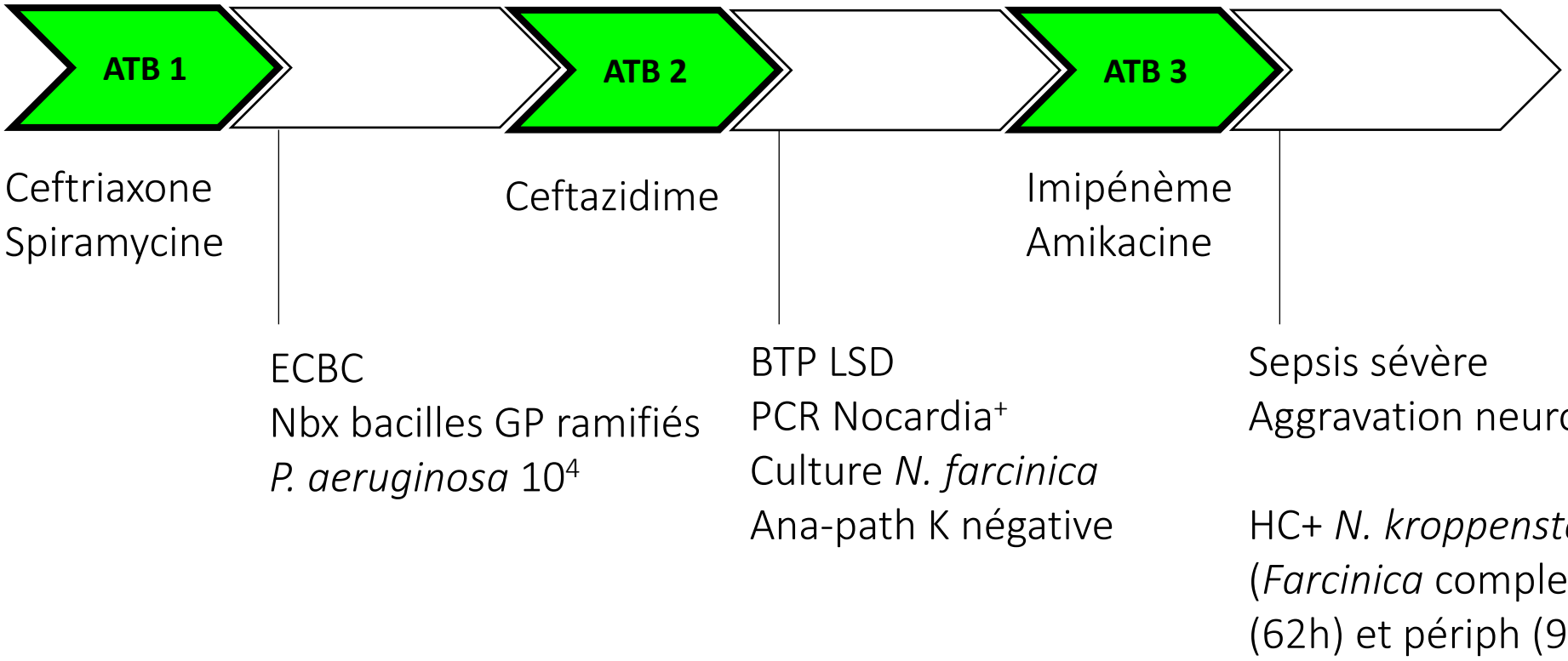
C – l'imipénème est inactif dans 1/3 des cas (dissociation de classe)

D – le linezolide est quasi constamment actif

E – la ciprofloxacine et la moxifloxacine sont constamment actives

Message 1: identification d'espèce systématique ---- > un antibiogramme avec la détermination des CMI par méthode de dilution pour chaque molécule est indispensable en cas d'infection à *Nocardia* spp.

Vignette clinique Mr. BU. Ed. 14/05/1933



Explication(s) ?

Breakpoints (mg/L)	S	R
AMK	≤8	≥16
AMC	≤8/4	≥32/16
CRO	≤8	≥64
CIP	≤1	≥4
CLR	≤2	≥8
DOX	≤1	≥8
IMI	≤4	≥16
LZD	≤8	
MIN	≤1	≥8
MXF	≤1	≥4
RFP	≤1	≥4
trimethoprim-sulfamethoxazole	≤2/38	≥4/76

AMC, amoxicillin-clavulanic acid; AMK, amikacin;; CIP, ciprofloxacin; CLR, clarithromycin; CRO, ceftriaxone; DOX, doxycycline; IMI, imipenem; LZD, linezolid; MIN, minocycline; MXF, moxifloxacin; RFP, rifampin.

Ili Margalit, Clin Microbiol Infect 2021;27:550

	Nocardia kroppenstedtii *CMI (mg/l)*
Amoxicilline + Ac.Clavulanique	S (8)
Ceftriaxone	I (16)
Céfépime	R (> 32)
Imipénème	R (32)
Tobramycine	I (8)
Amikacine	S (< 1)
Clarithromycine	R (> 16)
Doxycycline	I (4)
Minocycline	I (2)
Ciprofloxacine	S (0.5)
Moxifloxacine	S (0.5)
Cotrimoxazole	S (1)
Linézolide	S (< 1)
Cefotaxime (Etest)	R CMI : > 32
Tedizolide (Etest)	V CMI : 0.75
Meropeneme (Etest)	I CMI : 8

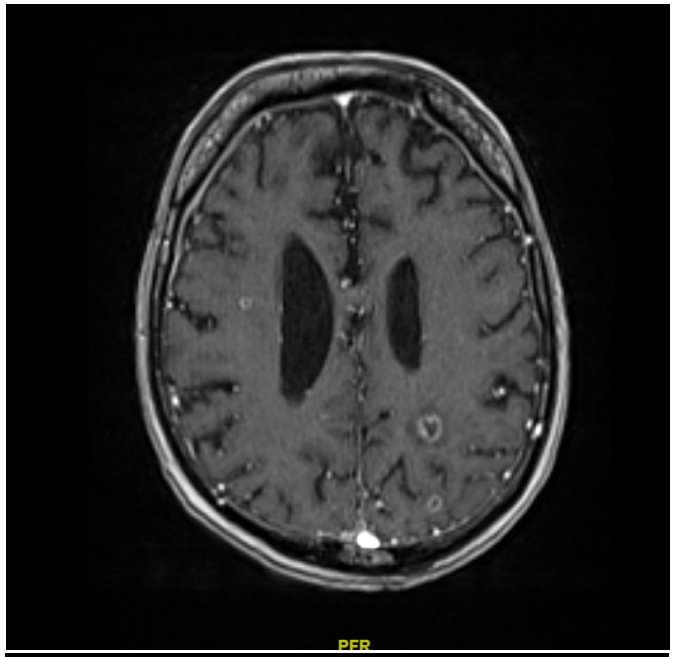
↘20%

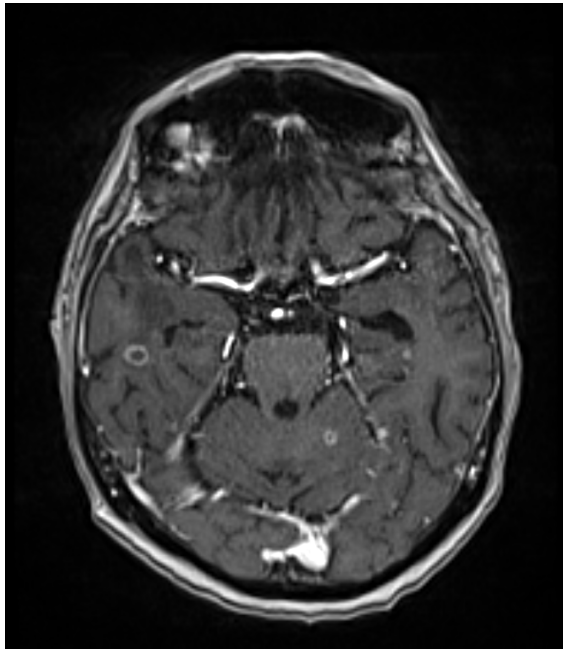
Message 2:

Activité quasi constante (> 95%) triade : Cotrimoxazole/Linezolide/Amikacine

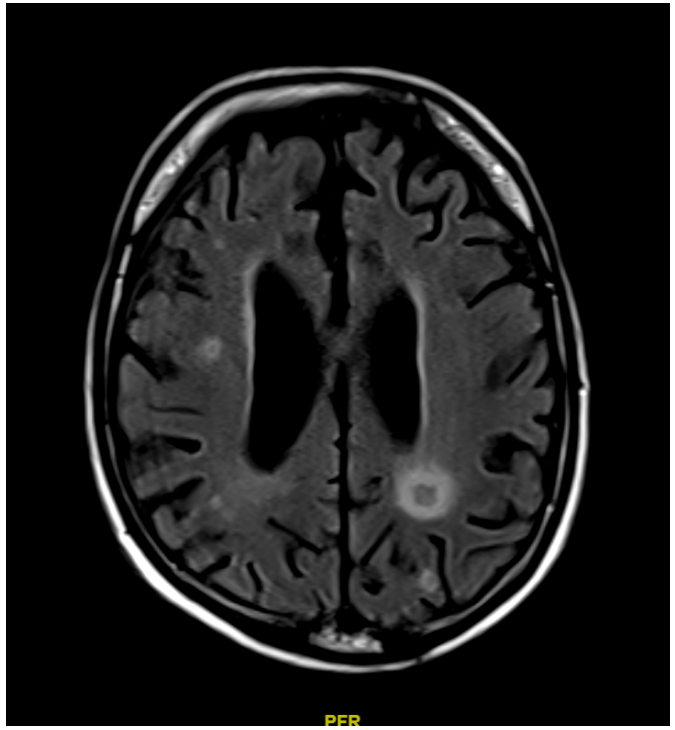
B-lactamines/FQ : inconstamment actives/dissociation de classe

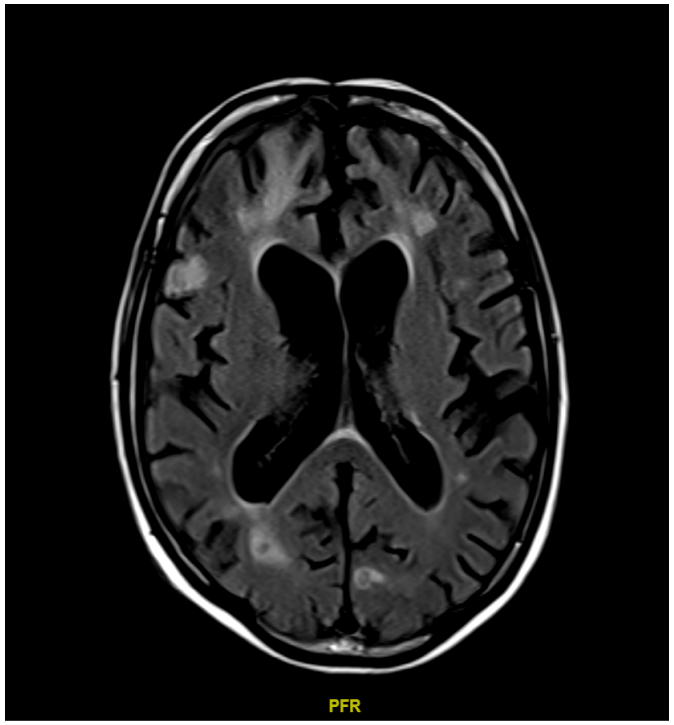
T1 gado



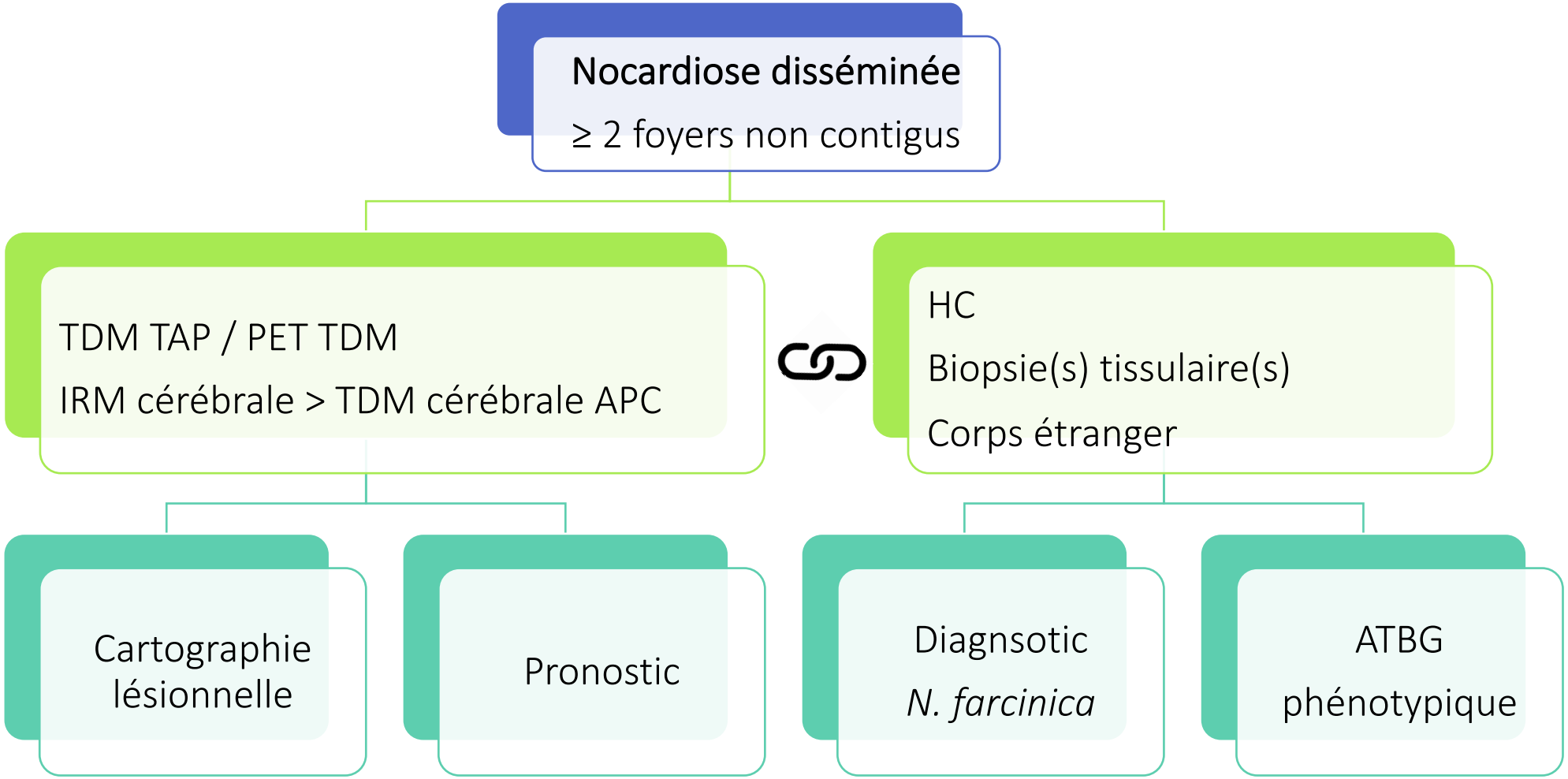


T2 FLAIR



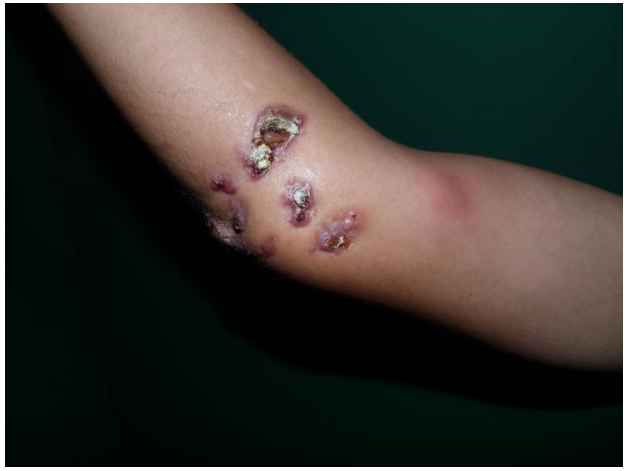


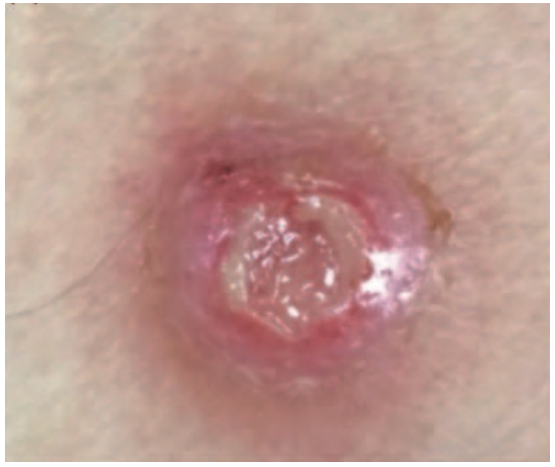
IRM cérébrale: multiples prises de contraste annulaires de taille variable disséminées de l'ensemble du parenchyme cérébral aux étages sus et sous-tentoriel compatible avec des abcès. Le plus volumineux en regard de la corne occipitale du ventricule latéral gauche mesuré jusqu'à 10.7mm.



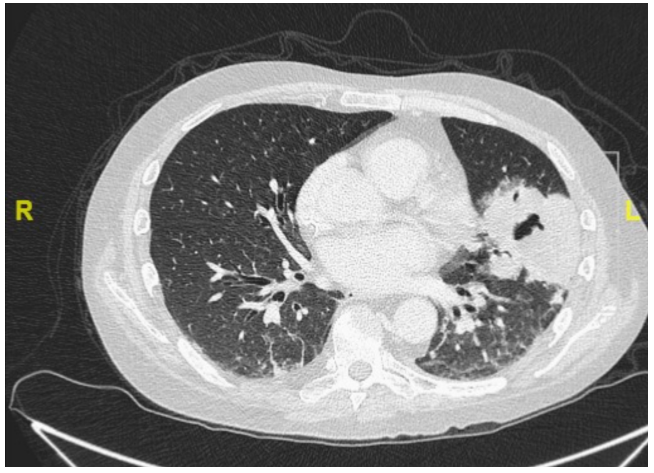
Message 3: imagerie pulmonaire et cérébrale systématique en cas d'infection à *Nocardia* spp. (seule exception possible: nocardiose cutanée primaire de l'immunocompétent)

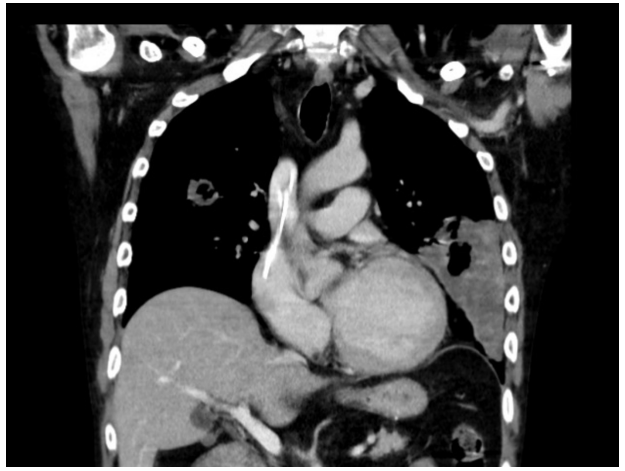
PTM



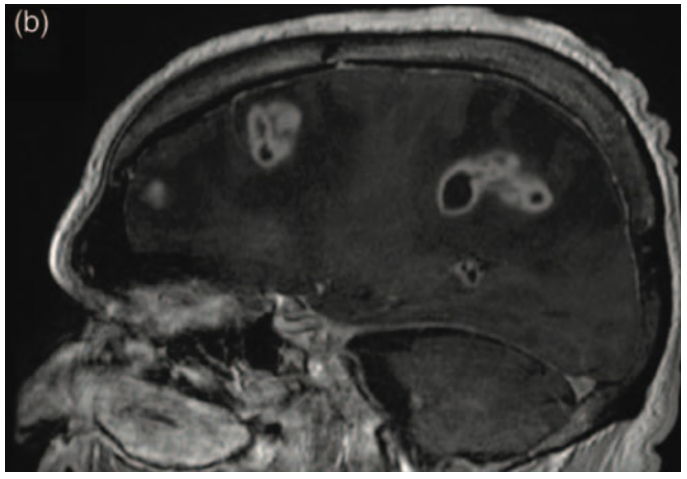


Poumons



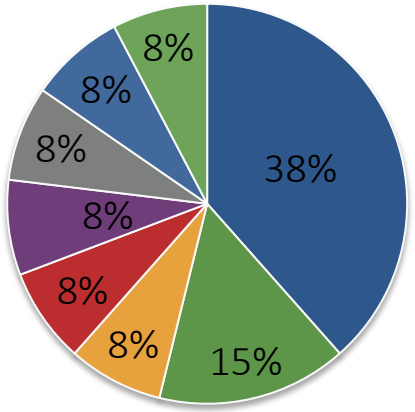


SNC

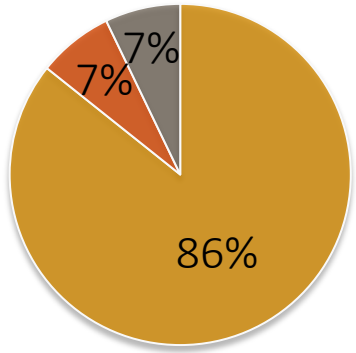


Images CHU de Lyon
Coussement J et al. Curr Opin Infect Dis 2017, 30:545 – 551

Co-infections bactériennes
n=14/53 (26.4%)



Co-infections fongiques
n=12/53 (22.6%)



S. aureus
P. aeruginosa
Legionella spp
Streptococcus
Acinetobacter
Serratia spp
Actinomyces
Staph. blanc
Aspergillus
Geotrichum
Fusarium

Message 4:
Co-infections 20-50% des cas
Une infection bactérienne peut en cacher une autre

Soueges S. et al. J Infection 2022

Nocardiosis extent	Primary skin	Isolated pulmonary	Dissemination* without CNS involvement	CNS involvement
Initial treatment (i.e., before species identification and AST results)	Trimethoprim-sulfamethoxazole ** Possible alternative: LZD**	Trimethoprim-sulfamethoxazole ± IMI or AMK or CRO or CTX** Possible alternatives: LZD ± IMI or CRO or CTX** Monotherapy (e.g., with trimethoprim-sulfamethoxazole) is probably appropriate in selected patients with non-severe pulmonary nocardiosis	Trimethoprim-sulfamethoxazole ± IMI or AMK or CRO or CTX** Possible alternatives: LZD ± IMI or CRO or CTX**	Trimethoprim-sulfamethoxazole with IMI ± AMK**† Possible alternative: LZD with IMI**

Characteristics	TMP–SMX	IMP	AMK	LZD	CTX	CRO
Oral bioavailability	~80%	NA	NA	~100%	NA	NA
C_{CSF}/C_{serum}	~50%	~10%	~20–30%	~80%	~10–50%	~10%
Main side effects[c]	Myelosuppression, nephrotoxicity[c]	Neurotoxicity[c]	Nephrotoxicity, ototoxicity[c]	Myelosuppression, neurotoxicity, lactic acidosis[c]		
Adjust on renal function	Yes	Yes	Yes	No[d]	Yes	No

Coussement J et al. Curr Opin Infect Dis 2017, 30:545 – 551
Ili Margalit, Clin Microbiol Infect 2021;27:550

Maintenance therapy	**If initial treatment was a multi-drug regimen with intravenous agents: continue for 2-6 weeks** Therapeutic modifications based on response to therapy, microbiology results, and patient specificities			
Switch to oral therapy (if indicated, when the clinical response is favorable)	trimethoprim-sulfamethoxazole** (possible alternatives: minocycline or AMC**)			trimethoprim-sulfamethoxazole**
Total duration of antimicrobial therapy	**3-6 months** (shorter durations may be appropriate for immunocompetent patients)	**6 months** (3-4 months may be appropriate for selected patients with good response to therapy and treatment complicated by side-effects)	**6-12 months** (depending on response to therapy and individual specificities)	**9-12 months** (possibly longer)
Secondary prophylaxis	**Not indicated in immunocompetent patients (very low risk of relapse)** trimethoprim-sulfamethoxazole secondary prophylaxis** may be considered in immunocompromised patients (if well tolerated)			

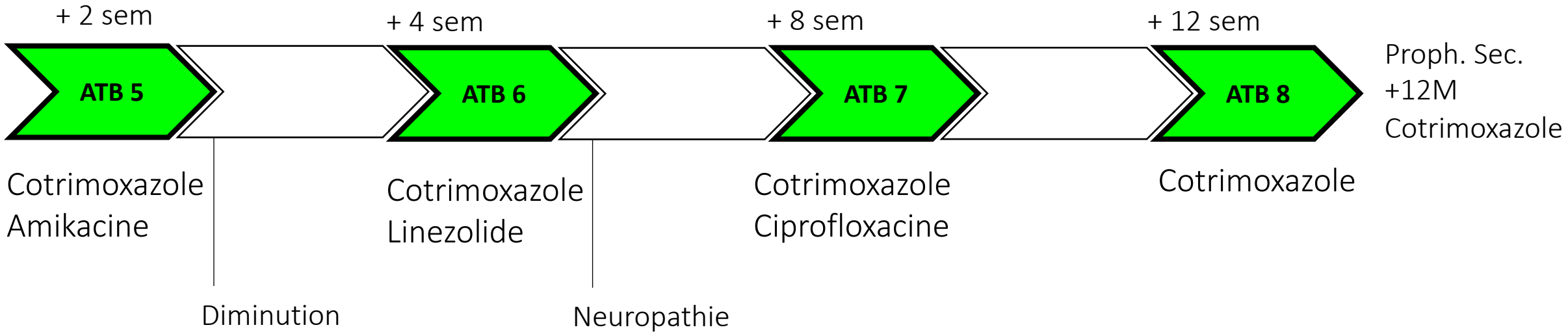
**Treatment regimens: trimethoprim-sulfamethoxazole: 10–20 mg trimethoprim/kg/day (possibly lower dose in patients with primary skin nocardiosis), secondary prophylaxis: daily oral at least 800/160 mg (unclear effectiveness, and breakthrough nocardiosis described while on 800/160 mg once daily[17]); linezolid: IV, oral: 600 mg twice daily; minocycline: oral: 100-300 mg twice daily; AMK: IV: 20-30 mg/kg/day; CRO: IV: 2000 mg once daily or twice daily if CNS involvement; CTX: IV: 2000 mg three times daily or 4000 mg three times daily if CNS involvement; IMI: IV: 500 mg four times daily. Dose adjustment for renal function is required for the following drugs: trimethoprim-sulfamethoxazole, AMK, CTX, IMI.

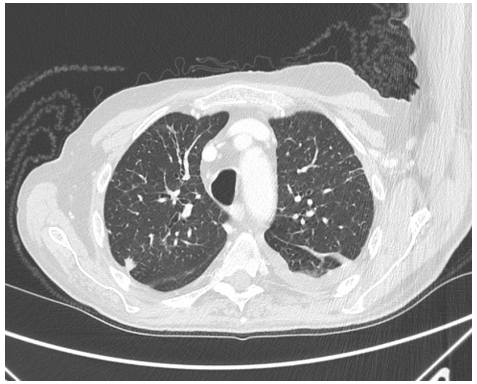
****Nocardia* identification and susceptibility testing should be done by an experienced laboratory. Based on CLSI guidelines, the recommended method for antibiotic susceptibility testing is the determination of minimal inhibitory concentration by broth microdilution (see Table 2).

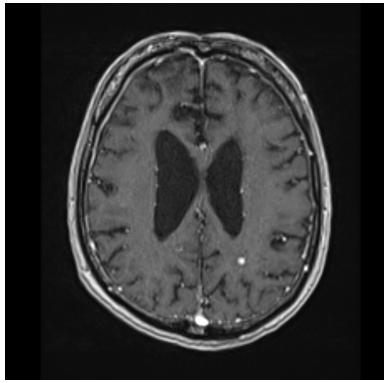
† The addition of amikacin may be discussed despite limited CNS penetration, as ~1/3 of *Nocardia* isolates are resistant to imipenem (see details in main text).

AMC=amoxicillin-clavulanic acid; AMK=amikacin; AST=antibiotic susceptibility testing; CNS=central nervous system; CRO=ceftriaxone; CT=computerized tomography; CTX=cefotaxime; IMI=imipenem; IV=intravenous; LZD=linezolid; MRI=magnetic resonance imaging.

Vignette clinique Mr. BU. Ed. 14/05/1933







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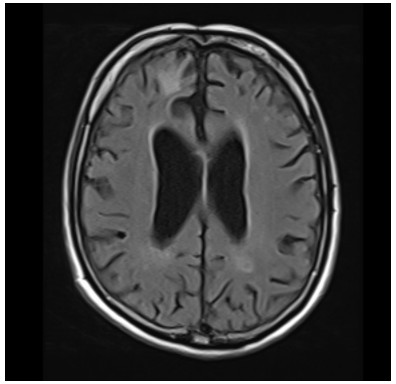

T2 FLAIR

NOCARDIOSE
POINTS CLÉS

PRESENTATION CLINIQUE
Pseudo-carcinomateuse/crytique
Nodules tissulaires pulmonaires et extra-pulmonaires
Inflammatoire

LOCAL vs. DISSÉMINATION
≥ 2 organs non contigus
Poumons, peau/tissus mous, SNC, séreuses, EI

MICRBIOLOGIE
Identification d'espèce
Antibiogramme/CMI/méthode de dilution/molecule
Co-infection(s) 20-25%

PRONOSTIC
Réduction immunosuppression
Drainage neuro-chir abcès
Extraction corps étranger
Mortalité si atteinte SNC 20-40%

TERRAIN
Immunodéprimés: TOS,HSCT, hémopathies, K, CC
Immunocompétents : 20%

IMAGERIE
Body scan
IRM cérébrale
PET TDM

ANTIBIOTHERAPIE
Pilier : cotrimoxazole (> 95%)
Valeurs sures : AMK, oxazolidinones (> 95%)
Sur ATBG: β-lactamines, FQ
Prophylaxie primaire/secondaire

References

Clinical Microbiology and Infection 27 (2021) 550–558

Contents lists available at ScienceDirect

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Narrative review

How do I manage nocardiosis?

Ili Margalit [1, 2, *], David Lebeaux [3, 4], Ori Tishler [5], Elad Goldberg [2, 5], Jihad Bishara [1, 2], Dafna Yahav [1, 2], Julien Coussement [6, 7]

Journal of Infection 85 (2022) 130–136

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Original Article

Prognosis and factors associated with disseminated nocardiosis: a ten-year multicenter study

Sarah Soueges [a], Kevin Bouiller [b,c], Elisabeth Botelho-Nevers [d,e,f], Amandine Gagneux-Brunon [d,e,f], Catherine Chirouze [b,c], Veronica Rodriguez-Nava [g,h], Oana Dumitrescu [g,i], Claire Triffault-Fillit [a], Anne Conrad [a,i], David Lebeaux [j,k], Elisabeth Hodille [g], Florent Valour [a,i], Florence Ader [a,l,*]

Clinical Infectious Diseases

MAJOR ARTICLE

Outcome and Treatment of Nocardiosis After Solid Organ Transplantation: New Insights From a European Study

David Lebeaux,[1] Romain Freund,[2,3] Christian van Delden,[4,5] Hélène Guillot,[6] Sierk D. Marbus,[7] Marie Matignon,[8] Eric Van Wijngaerden,[9] Benoit Douvry,[10] Julien De Greef,[11] Fanny Vuotto,[12] Leïla Tricot,[13] Mario Fernández-Ruiz,[14] Jacques Dantal,[15] Cédric Hirzel,[5,16] Jean-Philippe Jais,[2,3] Veronica Rodriguez-Nava,[17] Frédérique Jacobs,[18] Olivier Lortholary,[1] and Julien Coussement;[18] for the European Study Group for *Nocardia* in Solid Organ Transplantation[a]

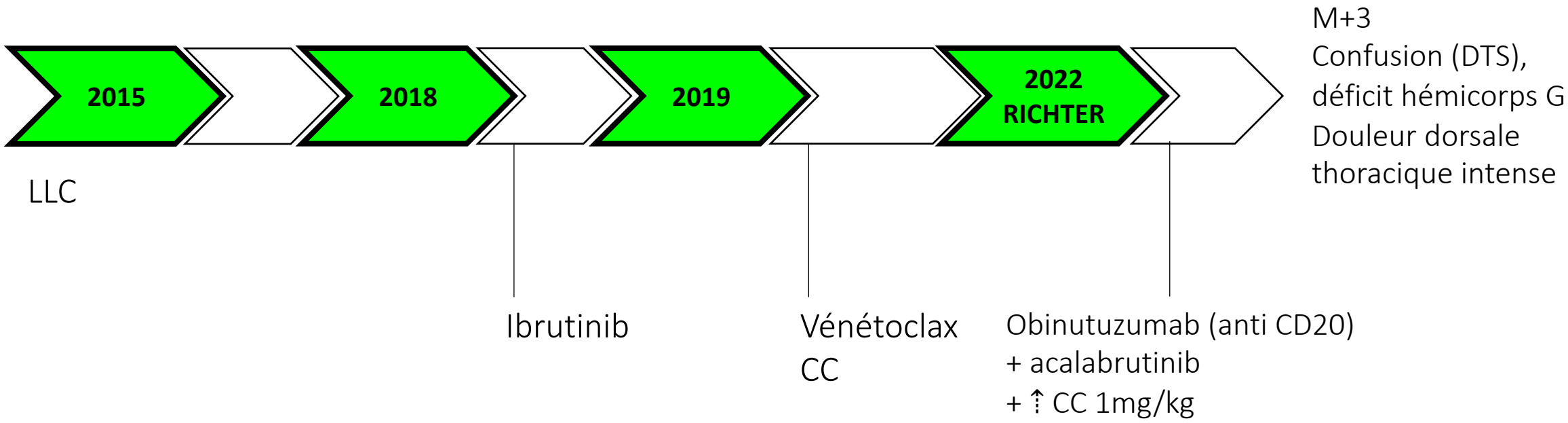
Clinical Infectious Diseases

MAJOR ARTICLE

Nocardia Infections in Hematopoietic Cell Transplant Recipients: A Multicenter International Retrospective Study of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation

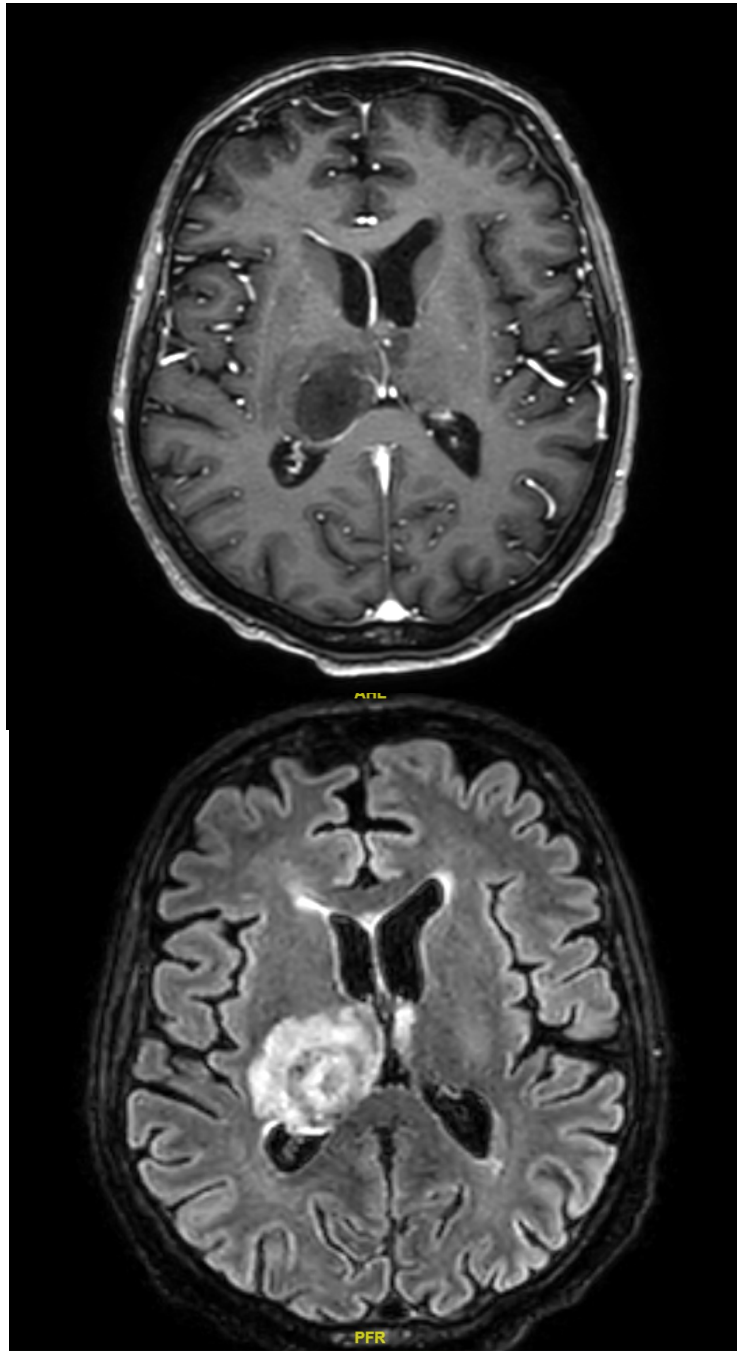
Diana Averbuch,[1,a] Julien De Greef,[2,a] Amelie Duréault,[3,a] Lotus Wendel,[4] Gloria Tridello,[5] David Lebeaux,[6,7] Malgorzata Mikulska,[8] Lidia Gil,[9] Nina Knelange,[4] Tsila Zuckerman,[10] Xavier Roussel,[11] Christine Robin,[12] Alienor Xhaard,[13] Mahmoud Aljurf,[14] Yves Beguin,[15] Amandine Le Bourgeois,[16] Carmen Botella-Garcia,[17] Nina Khanna,[18] Jens Van Praet,[19] Nicolaus Kröger,[20] Nicole Blijlevens,[21] Sophie Ducastelle Leprêtre,[22] Aloysius Ho,[23] Damien Roos-Weil,[24] Moshe Yeshurun,[25,26] Olivier Lortholary,[27,28] Arnaud Fontanet,[29,30] Rafael de la Camara,[31] Julien Coussement,[32,33,b] Johan Maertens,[34,b] and Jan Styczynski[35,b] European Study Group for Nocardia in Hematopoietic Cell Transplantation

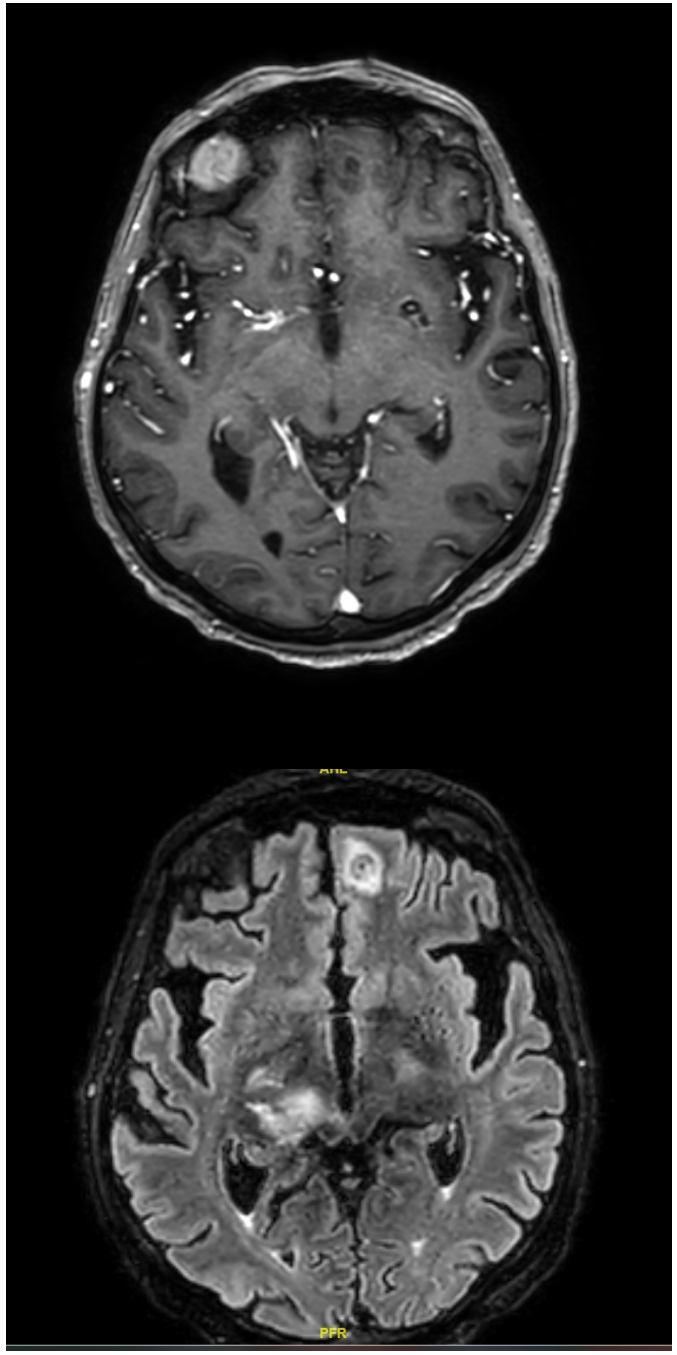
Vignette clinique Mr. TAR. Ri. 13/06/1956



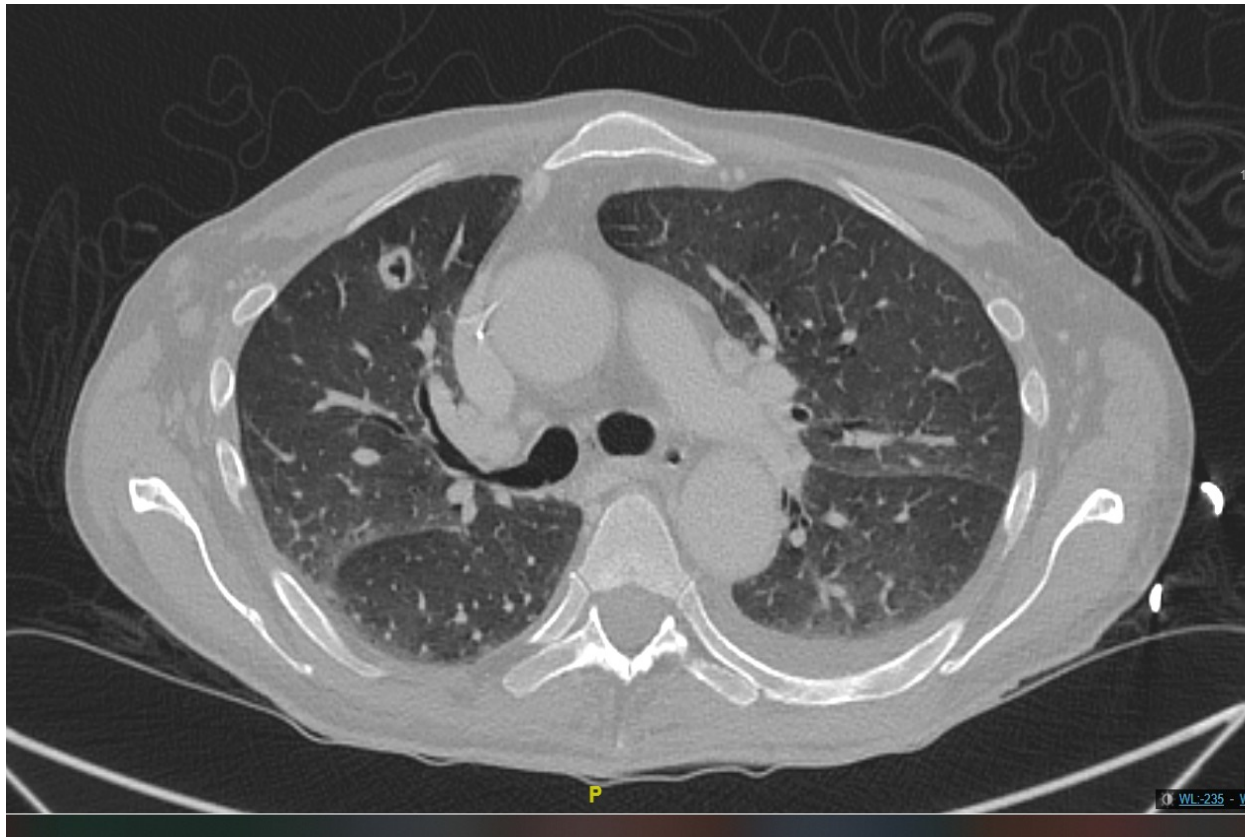
T1 gado

T2 FLAIR





IRMc : multiples lésions focales, pseudo-nodulaires particulièrement visibles en flair : 1) lésion thalamique droite (23 mm); 2) lésion de la commissure antérieure gauche (13 mm); 3) lésion thalamique gauche de (13 mm); 4) lésion frontale antérieure gauche (10 mm)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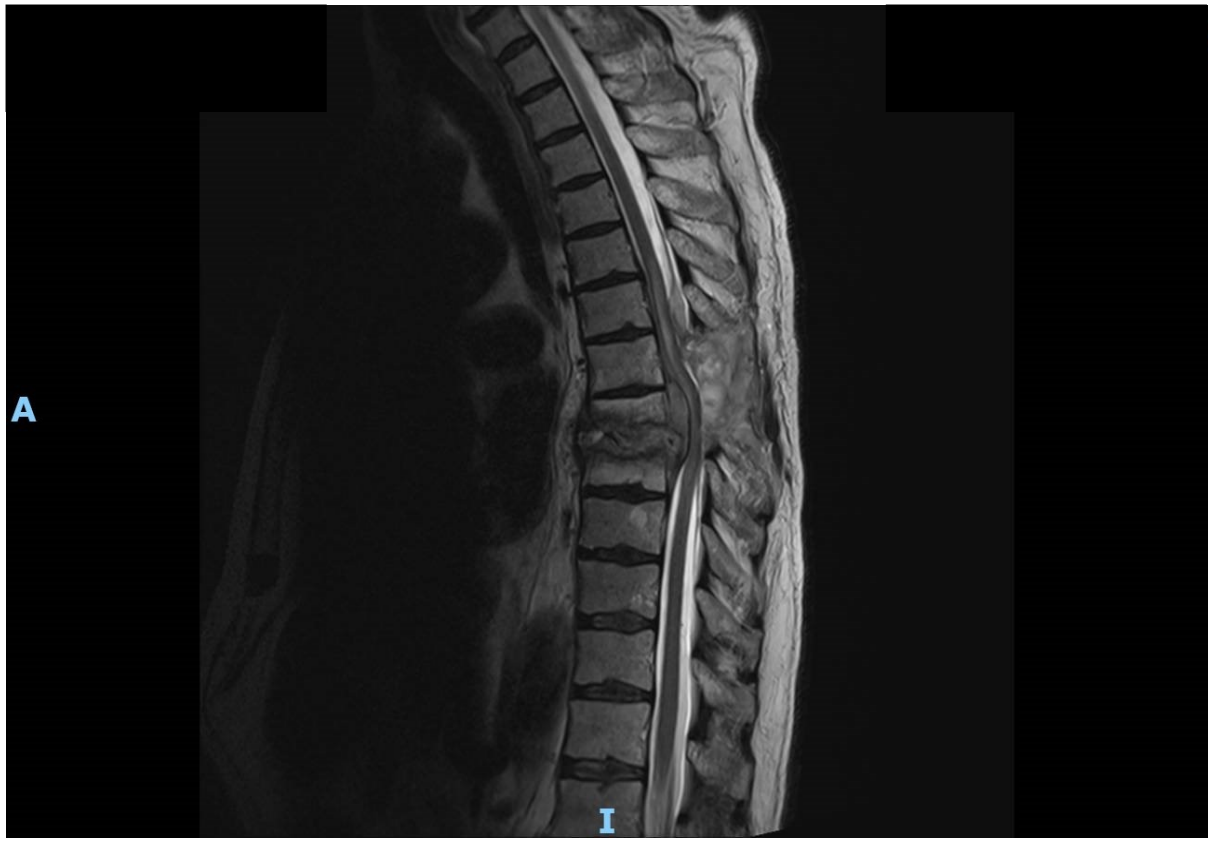

A
I

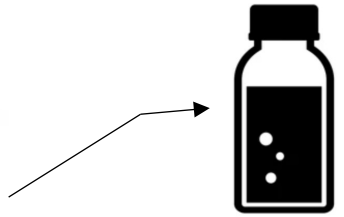
La(les) infection(s) nodulaire(s) du SNC des immunodéprimés (hors VIH) ?

Contextualiser^{++} – Temporalité$^{++}$

HC AA^{+++} (pyogènes, opportunistes)
PCR Toxoplasmose
PCR *Aspergillus*
PCR Mucorales
+/- PCR *Listeria*
+/- PCR *Nocardia*

Ag cryptocoque
Ag GM
βD glucanes

HC MTBC/NTM (sur contexte)



Examen direct – culture (pyogènes)
Kit syndromique LCS (?)

PCR *Listeria*
PCR *Nocardia*
PCR Toxoplasmose
PCR *Aspergillus*
+/- PCR Mucorales

Ag cryptocoque
Ag GM
βD glucanes (non validé)
Ex. direct + culture MTBC/NTM
+/- PCR mycobactérie (1 à 2 mL)

Message 1: screening large, exhaustif, méthodique
En désespoir de cause : biopsie cérébrale
(Ana-path, ex. direct/cultures, PCR)

----- > PL pour récolte LCS

GB 28/mm^3,

92% de PNN soit 26/mm^3, 2% de lymphocytes, 6% de monocytes/macrophages

GR 12/mm^3,

Protéinorachie 0.67g/L,

Glycorachie 4.1 mmol/L (glycémie capillaire 8.7 mmol/L)

Ag GM positif 1.54

PCR Aspergillus positif

Culture fongique stérile,

Examen direct BK négatif, PCR non amplifiée

Ag GM positif 4.61
βD glucanes > 523pg/mL

Les mécanismes par lesquels l'IFI filamenteuse cérébrale arrive?

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Commentary

Cerebral aspergillosis in the era of new antifungals: The CEREALS national cohort study Nationwide CEREbral Aspergillosis Lesional study (CEREALS)

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Dissémination hématogène
Patients les plus jeunes
Hémopathies, TOS
Ag GM et PCR *Aspergillus* souvent positifs sang + LCS
Lésions multiples
Pronostic péjoratif

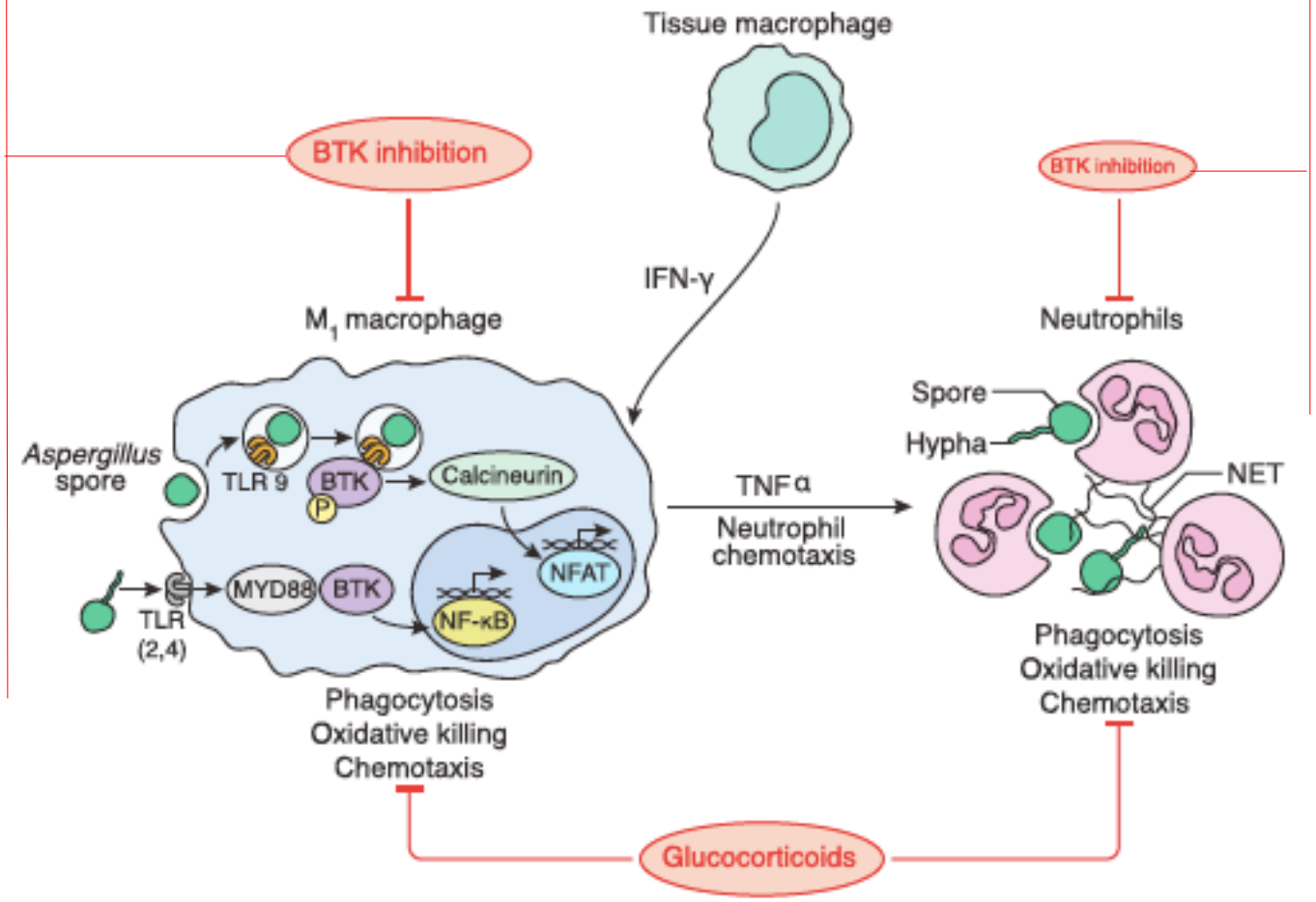
Porte d'entrée rhino-sino-orbitale
Patients plus âgés
Moins d'ID
Ag GM et PCR *Aspergillus* souvent négatifs sang mais positifs LCS
Lésion monofocale extensive
Pronostic relatif

Focus on BTK-dependent fungal immunity

Herbst S et *al.* Phagocytosis-dependent activation of a TLR9-BTKcalcineurin- NFAT pathway co-ordinates innate immunity to *Aspergillus fumigatus*. EMBO Mol Med. 2015;7(3):240-258.

Shah A et *al.* Calcineurin orchestrates lateral transfer of *Aspergillus fumigatus* during macrophage cell death. Am J Respir Crit Care Med. 2016;194(9):1127-1139.

Lougaris V et *al.* Bruton tyrosine kinase mediates TLR9-dependent human dendritic cell activation. J Allergy Clin Immunol. 2014;133(6) 1644-1650.e1644.



Fiedler K, et *al.* Neutrophil development and function critically depend on Bruton tyrosine kinase in a mouse model of X-linked agammaglobulinemia. Blood. 2011;117(4):1329-1339.

Mueller H et *al.* Tyrosine kinase Btk regulates E-selectin-mediated integrin activation and neutrophil recruitment by controlling phospholipase C (PLC) gamma2 and PI3Kgamma pathways. Blood. 2010;115(15):3118-3127.

Lionakis et al., 2017, Cancer Cell 31, 833–843
Bercusson A et al. Blood 2018; 132(18): 1985-1988

Fractions de diffusion du VORICONAZOLE

Message 2: *Aspergillus* SNC = préférer Voriconazole toujours

Message 3: bithérapie sur avis

Ex:

- Vorico + Caspo haute dose
- AmphoB + Vorico (doute mucor ou double infection)

Abcès cérébral : x1-2.3

LCS : x0.22-1

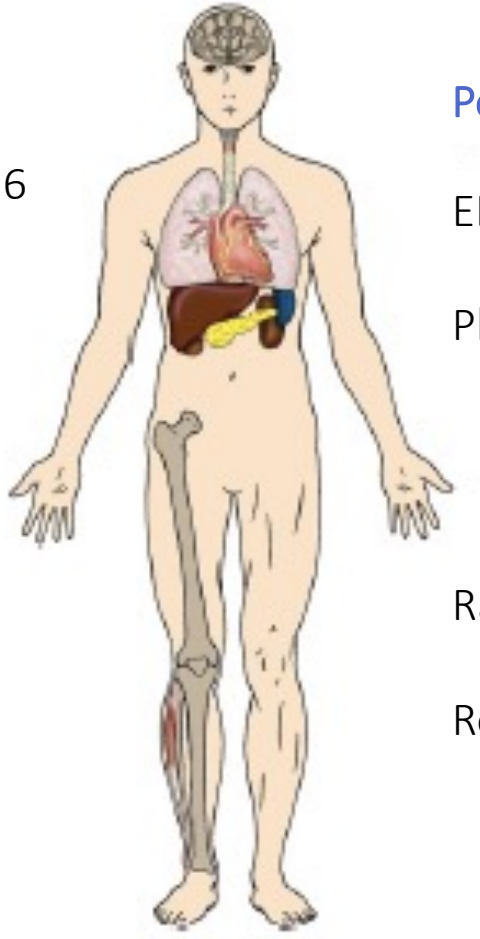
Poumons : x0,3-3,2

Myocarde : x0,4 – 4,6

ELF : x0,2 – 1,1

Foie : x1,1 – 7,4

Plèvre : x0,7 – 1



Os : x5

Rate : x0,4 – 3,5

Synoviale : x0,25

Rein : x0,6 – 2,7

Adapté de Felton T, Troke PF, Hope WW. Clin Microbiol Rev 2014

TDM, Therapeutic Drug Monitoring VCZ

Dose de charge 6 mg/kg/12h (400/400-70 kgs)
Entretien 4 mg/kg/12H (300/300-70 kgs)

Résiduel
Zone thérapeutique : **1.0 – 5.5** mg/L
4ème jour après initiation

< 1 mg/L = risque échec clinique
≥ 2 mg/L = succès clinique > 90%
Idéalement 2-4 mg/L

≥ 5 mg/L = effets secondaires
(signes d'imprégnation, toxicité)

Park WB et al., Clin Infect Dis 2012

Paramètres PK/PD Amphotéricine B liposomale (AmB-L)

	Dose (mg/kg/j)	BD (%)	C_{max} (µg/mL)	AUC (mgxh/L)	Liaison protéines (%)	**LCR (%)**	Vitré (%)	Urine (%)	$t_{1/2}$ (h)	Profil PD	Elimination
AmB Lip	3 à 10	< 5	83	131±126	**95-99**	**< 5**	0-38	< 5	**6-23**	[C]-dpdt	Bile 20% U 20%
	Liposomes < 0.08µm	IV exclusif			NON dialysable					C_{max}/CMI > 40 AUC/CMI > 100	

Fongicide in vitro sur levures et filaments

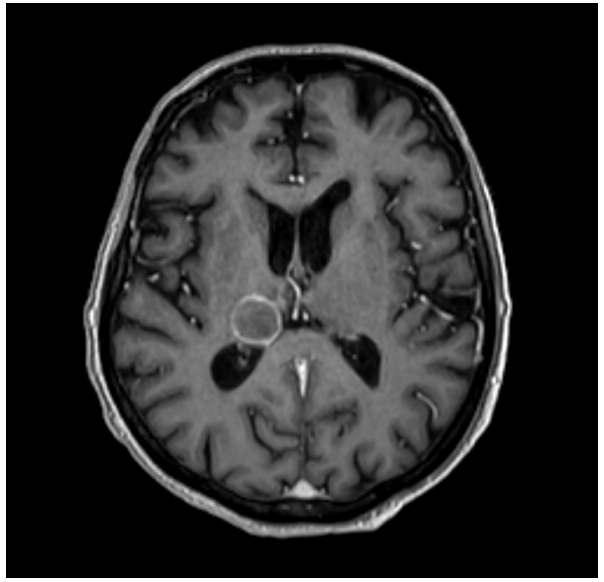
CMI:

- Sb < 2 µg/mL (0,1 – 1)
- R ≥ 2

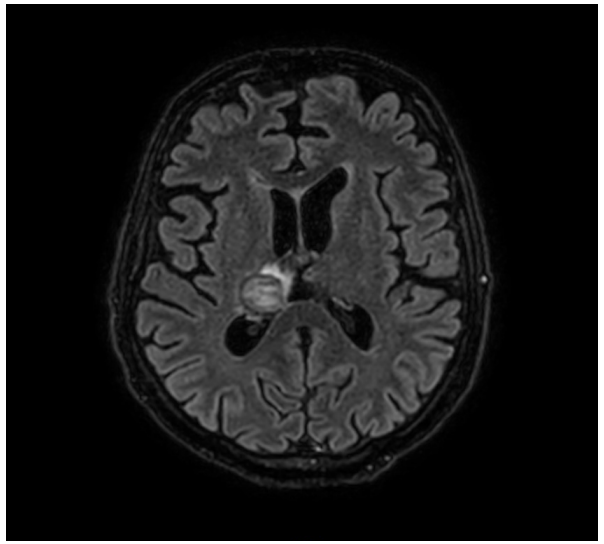
Dosages taux sériques sans intérêt

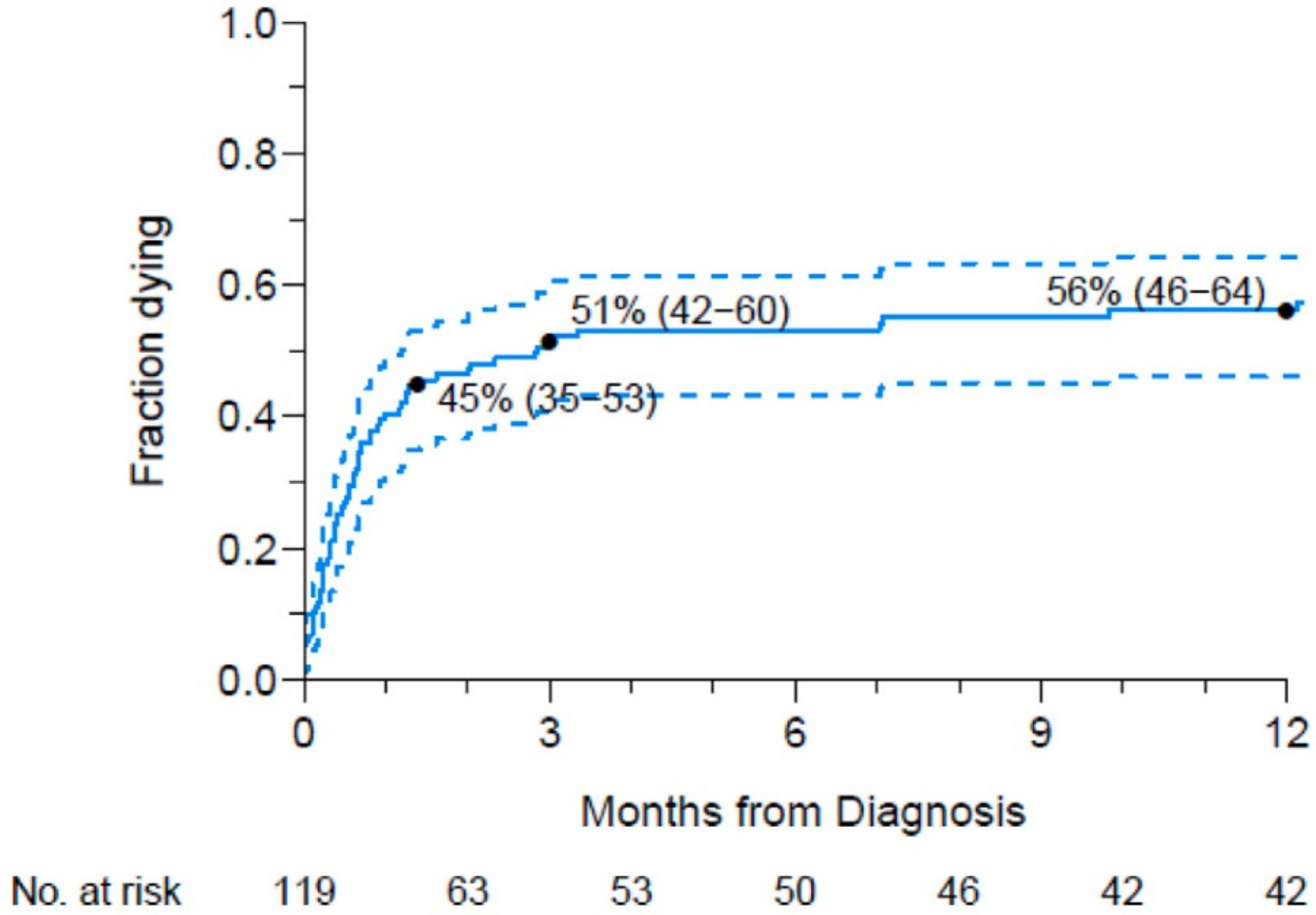
M+6

T1 gado



T2 FLAIR





Serris A et al. J Infection 2022

Merci tous…