Diplôme Inter Universitaire

Traitements des infections à bactéries intracellulaires

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Mise au point définition

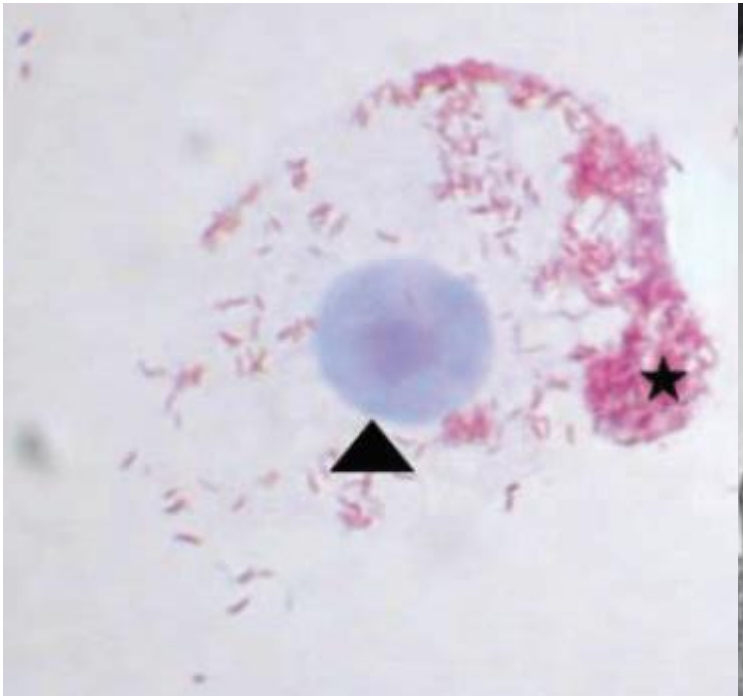
Germe: Élément microscopique qui, en se développant, produit un **organisme** (ferment, bactérie, spore, œuf).

Microbe : Un micro-organisme ou microorganisme ou microbe est un **organisme vivant** qui, **invisible à l'œil nu**, ne peut être observé qu'à l'aide d'un **microscope**.

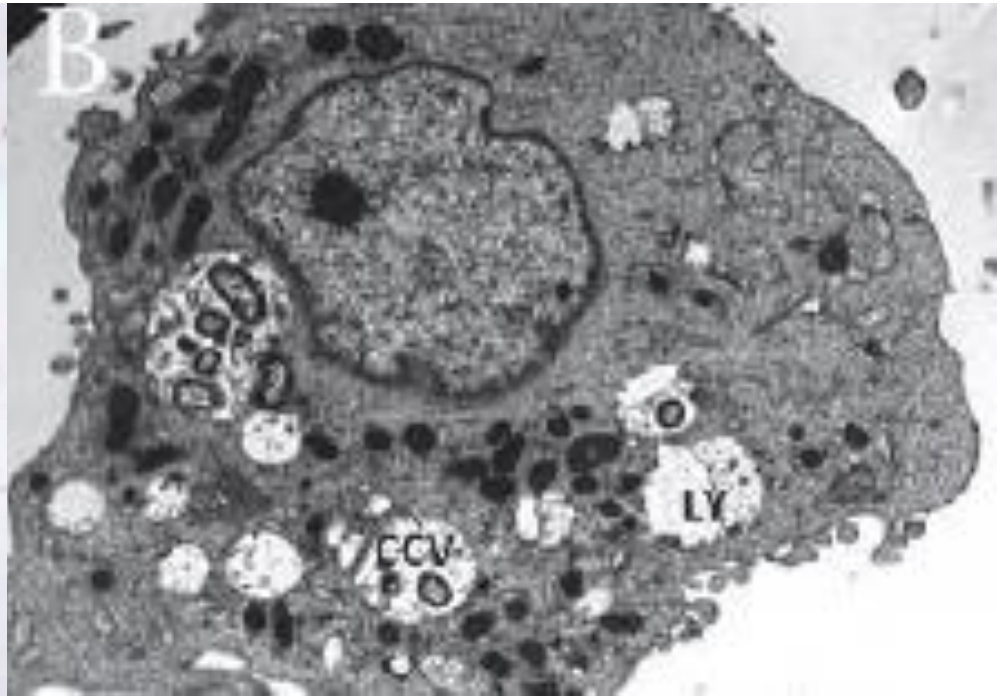
Nous allons parler des bactéries intracellulaires

Qu’est-ce qu’une bactérie intracellulaire?

Bactéries qui se développent préférentiellement
DANS LA CELLULE

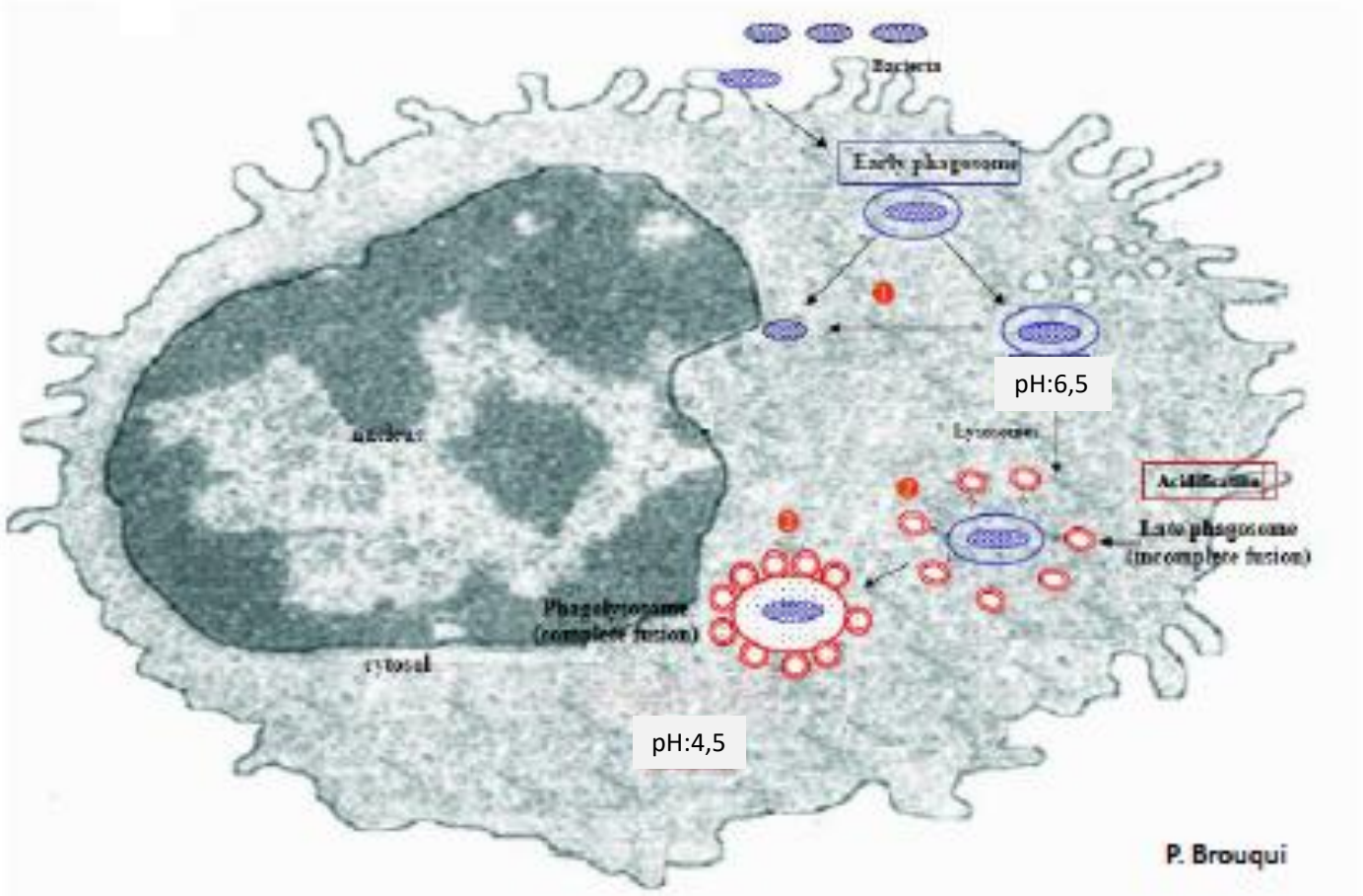


Hematoxilin eosin



Electronic microscopy

Qu’est ce qu’une bactérie intracellulaire?



Parmi les bactéries suivantes lesquelles sont intracellulaires strictes

A. *Staphylococcus aureus*
B. *Listeria monocytogenes*
C. *Coxiella burnetii*
D. *Rickettsia* spp
E. *Mycoplasma* spp

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E. *Mycoplasma* sp

Les bactéries intracellulaires

Bactéries intracellulaires strictes	**Bactéries intracellulaires facultatives (classiques)**	**Bactéries intracellulaires facultatives occasionnelles**
Coxiella burnetii *Rickettsia* spp *Chlamydia* spp *Tropheryma whipplei* *Anaplasma* spp *Ehrlichia* spp	*Legionella* spp *Mycoplasma* spp *Bartonella* spp *Francisella tularensis* *Listeria monocytogenes* *Salmonella* spp *Yersinia* spp *Brucella* *Mycobacterium* sp	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Escherichia coli*
Survie et multiplication possible qu'à l'intérieur des cellules eucaryotes	Plus ou moins dépendantes d'une cellule-hôte pour leur survie et leur propagation	

Les bactéries intracellulaires

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Rickettsia spp *Coxiella burnetii* *Chlamydia spp* *Tropheryma whipplei* *Anaplasma spp* *Ehrlichia spp*	*Legionella spp* *Mycoplasma spp* *Bartonella spp* *Francisella tularensis* *Listeria monocytogenes* *Salmonella spp* *Yersinia spp* *Brucella*	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Escherichia coli*
Survie et multiplication possible qu'à l'intérieur des cellules eucaryotes	Plus ou moins dépendantes d'une cellule-hôte pour leur survie et leur propagation	

McClure, *Nature Review Microbiol*, 2017

Quelle est la principale cellule hôte d'une bactérie intracellulaire ?

A. Polynucléaire neutrophile
B. Macrophage
C. Lymphocyte
D. Polynucléaire éosinophile
E. Cellule dendritique plasmacytoide

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C. Lymphocyte

D. Polynucléaire éosinophile

E. Cellule dendritique plasmacytoïde

Quelles cellules principalement ?

Cellules cibles

Souvent des macrophages… mais pas que

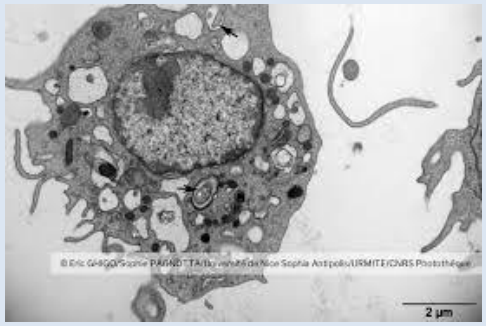
Main disease-causing intracellular bacteria and their preferential target cells.

Bacterial pathogen	Associated disease(s)	Target cells	Reference(s)
Mycobacterium tuberculosis	Tuberculosis	Macrophages, hepatocytes	[13,14]
Mycobacterium avium complex	Pulmonary infections	Alveolar macrophages	[15]
Mycobacterium leprae	Leprosy	Macrophages, epithelial cells	[16]
Listeria monocytogenes	Listeriosis, meningitis, septicaemia	Macrophages, hepatocytes, enterocytes	[17,18]
Staphylococcus aureus	Pneumonia, mastitis, phlebitis, endocarditis, nosocomial infections, urinary tract infections, osteomyelitis	Macrophages, polymor-phonuclear neutrophils	[19]
Salmonella spp.	Salmonellosis, typhoid fever	Macrophages, enterocytes	[20,21]
Brucella spp.	Brucellosis	Macrophages	[22]
Yesinia pestis	Plague	Macrophages	[23]
Escherichia coli	Diarrhoeal illness, urinary tract infections, meningitis in neonates	Epithelial cells, macrophages	[24,25]
Pseudomonas aeruginosa	Pneumonia, endocarditis, meningitis, nosocomial infection	Macrophages, epithelial cells	[26,27]
Legionella pneumophila	Pneumonia	Macrophages	[28]

N Abed et al., IJAA 2014; 43: 485–496

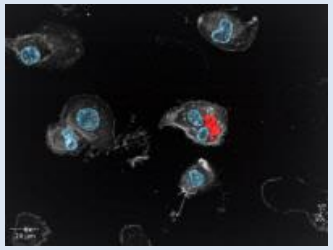
Quelles cellules principalement ?

Macrophage



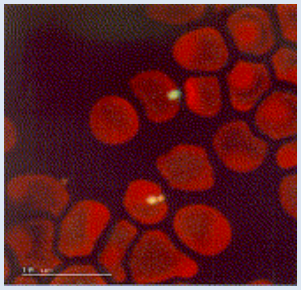
Coxiella burnetii
Rickettsia spp
Chlamydia spp
Mycobacterium spp
Tropheryma whipplei

Listeria spp
Legionella spp
Brucella spp
F. tularensis
Salmonella



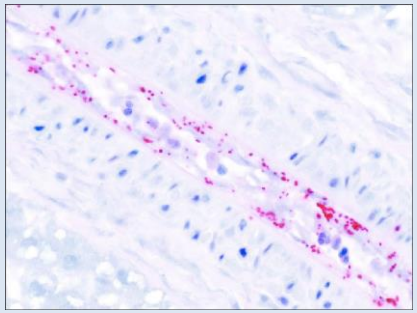
Globule Rouge

Bartonella

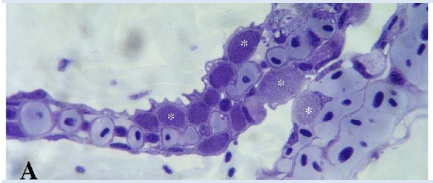


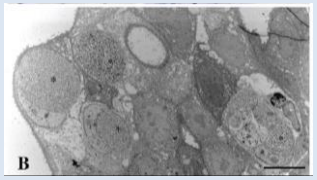
Cellules endothéliales

Rickettsia, Bartonella



Cellule épithéliale : *Chlamydia*





Non Exclusif

Dans quel(s) compartiment(s) cellulaire(s)?

A. Reticulum endoplasmique
B. Paroi cellulaire
C. Mitochondrie
D. Phagosome
E. Cytosol

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E. Cytosol

La localisation cellulaire

Table 1. Main intracellular bacteria that survive within phagocytic cells

Organism	Type of parasite	Subcellular localization	pH	Ref.
Shigella spp.	Facultative	Cytosol	~6.5	(6)
Listeria monocytogenes	Facultative	Cytosol	~6.5	(7)
Legionella pneumophila	Facultative	Phagolysosomes, endoplasmic reticulum	5.6	(8)
Clamydia spp.	Strict	Inclusions (nonacidified vacuoles)	>6.0	(9)
Mycobacterium tuberculosis	Facultative	Early endosomes	[1]ND	(10)
Mycobacterium bovis	Facultative	Early endosomes	5.5	(11)
Mycobacterium avium	Facultative	Early endosomes	(5.6-6.3)	(12)
Salmonella spp.	Facultative	Modified phagosome (Salmonella-containing vacuole)	<4.5	(13)
Ehrlichia chaffeensis	Strict	Early endosome	ND	(14)
Brucella spp.	Facultative	Endoplamic reticulum		(15)
Bartonella hesenlae	Facultative	Specialized nonendocytic membrane-bound vacuole	ND	(16)
Afipia felis	Facultative	Unfused vacuoles	ND	(17)
Coxiella burnetii	Strict	Phagolysosome	~5	(18)
Yersinia pestis	Facultative	Phagolysosomes	ND	(19)
Yersinia pseudotuberculosis	Facultative	Phagosomes	6.0	(20)
Francisella tularensis	Facultative	Phagosomes	6.7	(21)
Staphylococcus. aureus	Facultative	Phagolysosome	ND	(22)

Abbreviations: [1]ND = Not determined.

Imbuluzqueta, *Frontiers Bioscience*, 2010

Les bactéries intracellulaires
Mécanisme d'évasion au système immunitaire

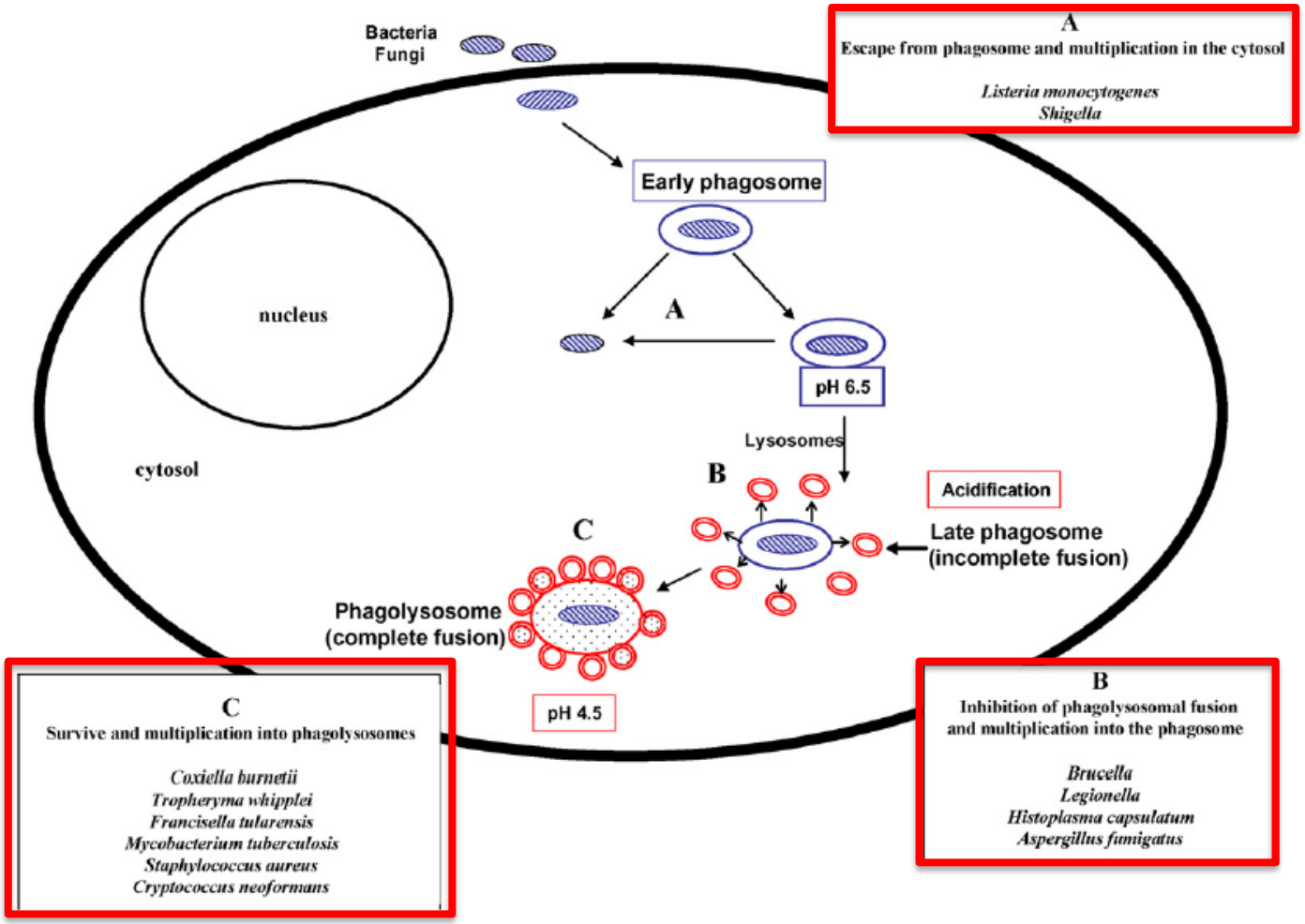
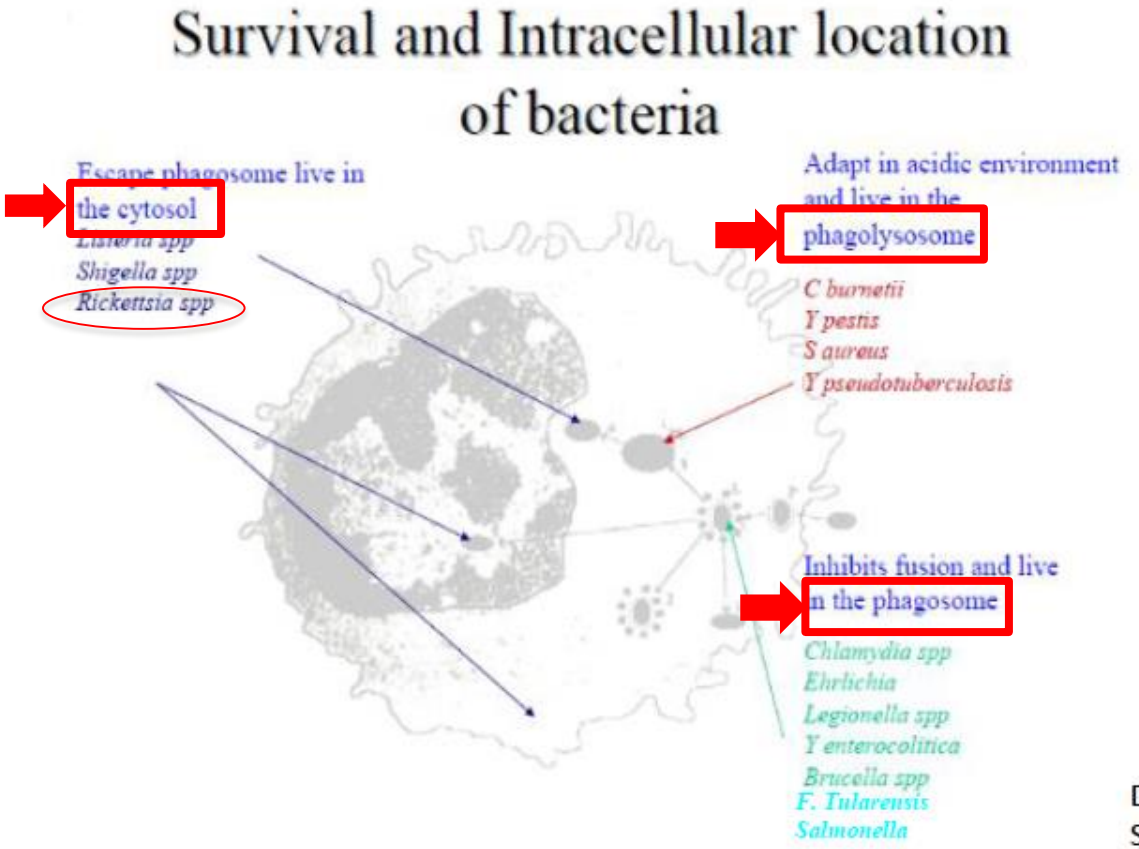


Fig. 2. Strategy for replication of intracellular bacteria and fungi known to be inhibited by chloroquine and/or hydroxychloroquine.

Rolain, *Int J Antimicrob Agent*, 2007

Cibles cellulaires



Les bactéries vont se localiser dans des compartiments cellulaires différents

D'après P. Brouqui,
S. Carryn et al / Infect Dis Clin N Am 17 (2003) 615–634

Les bactéries intracellulaires

« Immune escape »

Non « vues » par les cellules de l'immunité

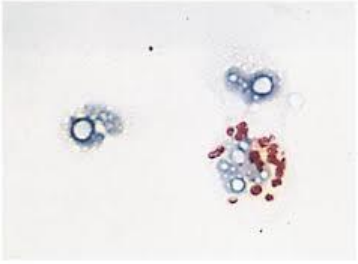
Réservoir

Responsables **d'infection persistantes**

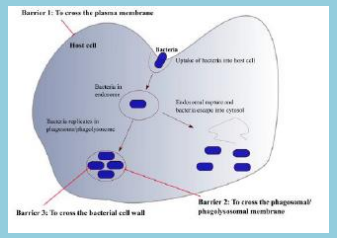
Rechutes

Dissémination

Dans d'autres tissus à distance

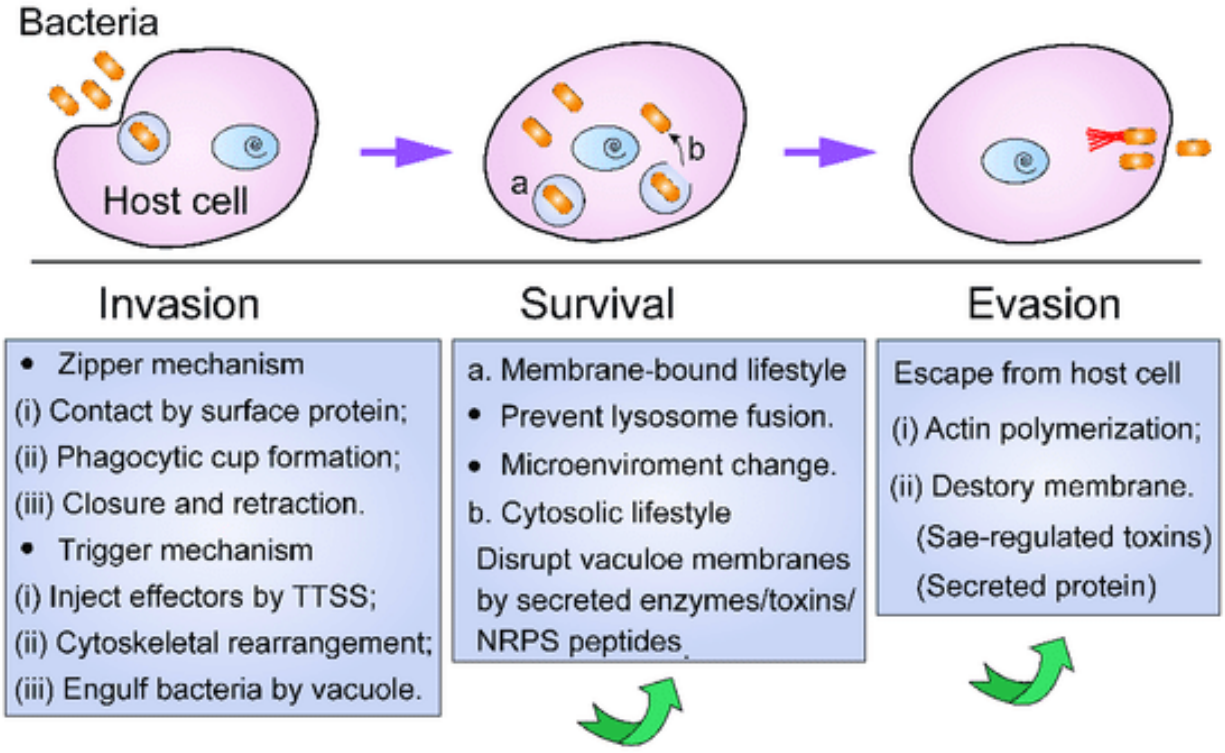


Echappement aux antibiotiques



Liu, *Frontiers Microbiol*, 2020

Les bactéries intracellulaires



Liu, *Frontiers Microbiol*, 2020

Les bactéries intracellulaires
Trois « challenges » pour le clinicien

1-Diagnostic

2- Le traitement

Choix de l'antibiotique

Selon le site intracellulaire de la bactérie

Sans antibiogramme

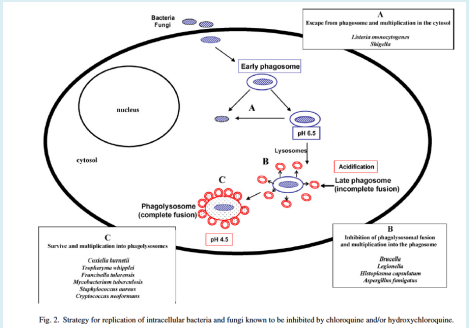
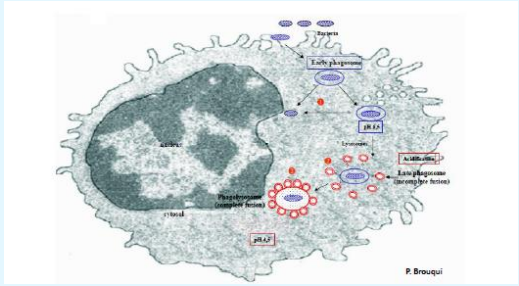


Fig. 2. Strategy for replication of intracellular bacteria and fungi known to be inhibited by chloroquine and/or hydroxychloroquine.

3- Suivi-rechute

Réservoir



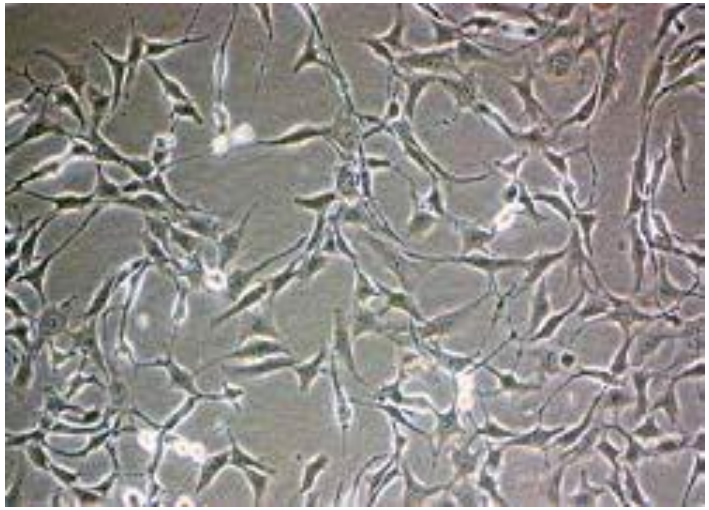
Le diagnostic

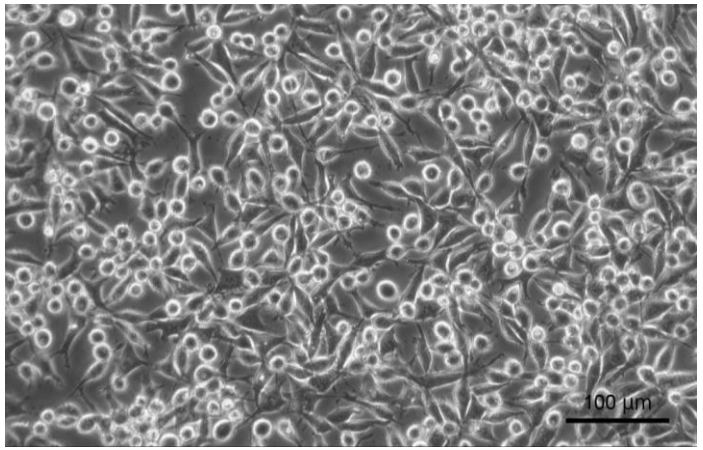
Pourquoi les bactéries intracellulaires sont dite « fastidieuses » ?

Croissance fastidieuse ou de leur absence de croissance sur les milieux de cultures conventionnels

-besoins nutritionnels spécifiques

-dépendante d'une cellule hôte (strictes)





Milieux de culture cellulaires pour les intracellulaires strictes

Croissance lente....semaines... Des mois...

Antibiogramme non systématique !

Ce qui implique....

Bactérie	Culture	Sérologie	PCR	Autres
Chlamydia pneumoniae	Non effectuée de routine	Peu utile en raison du délai pour le diagnostic	Test de choix (rapide et sensible)	–
Mycoplasma pneumoniae	Non effectuée de routine	Peu utile en raison du délai pour le diagnostic	Test de choix (rapide et sensible)	–
Coxiella burnetii	Non effectuée de routine	• Recommandée (à répéter à un intervalle de 14 jours si négatif)[1] • Aussi utile pour le suivi	Utile, en complément de la sérologie	–
Bartonella spp.	• Test de référence pour la bactériémie chronique *(B. quintana)* • Peu utile dans les autres cas (peu sensible, incubation prolongée)	Test de référence. Bonne sensibilité pour la maladie des griffes du chat et l'endocardite	Utile, en complément de la sérologie (endocardite notamment)	–
Tropheryma whipplei	Non effectuée de routine	Non disponible (taux d'anticorps faibles ou absents)	Recommandée. Sur échantillons de selles et salive (± biopsie cutanée et autres sites selon la présentation clinique)	• Histopathologie (coloration PAS) : pour la forme digestive classique • Immunohistochimie : sur échantillons ciblés

=> Antibiogramme non systématique

- Long délai
- Centre de référence et d'expertise
- Cout élevé

=> Traitement le plus souvent sans disposer de l'antibiogramme

Quelles sont les difficultés rencontrées par le clinicien pour le choix du traitement des infections liées aux bactéries intracellulaires

A. Pénétration de l'antibiotique dans les compartiments sub-cellulaires
B. Sensibilité de la bactérie à l'antibiotique (sans antibiogramme systématique)
C. pH des différents compartiments intracellulaires
D. Pénétration de l'antibiotique dans la cellule
E. Coût de l'antibiotique

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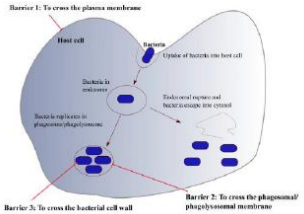


Le « challenge » du traitement antibiotique

- Pénétration intracellulaire de l'antibiotique
- Localisation sub-cellulaire de l'antibiotique /microorganisme
- Sensibilité du microorganisme à l'antibiotique
- Influence du milieu intracellulaire sur le couple antibiotique/microorganisme
  - pH, enzymes, fixation protéique...

Le « challenge » du traitement antibiotique

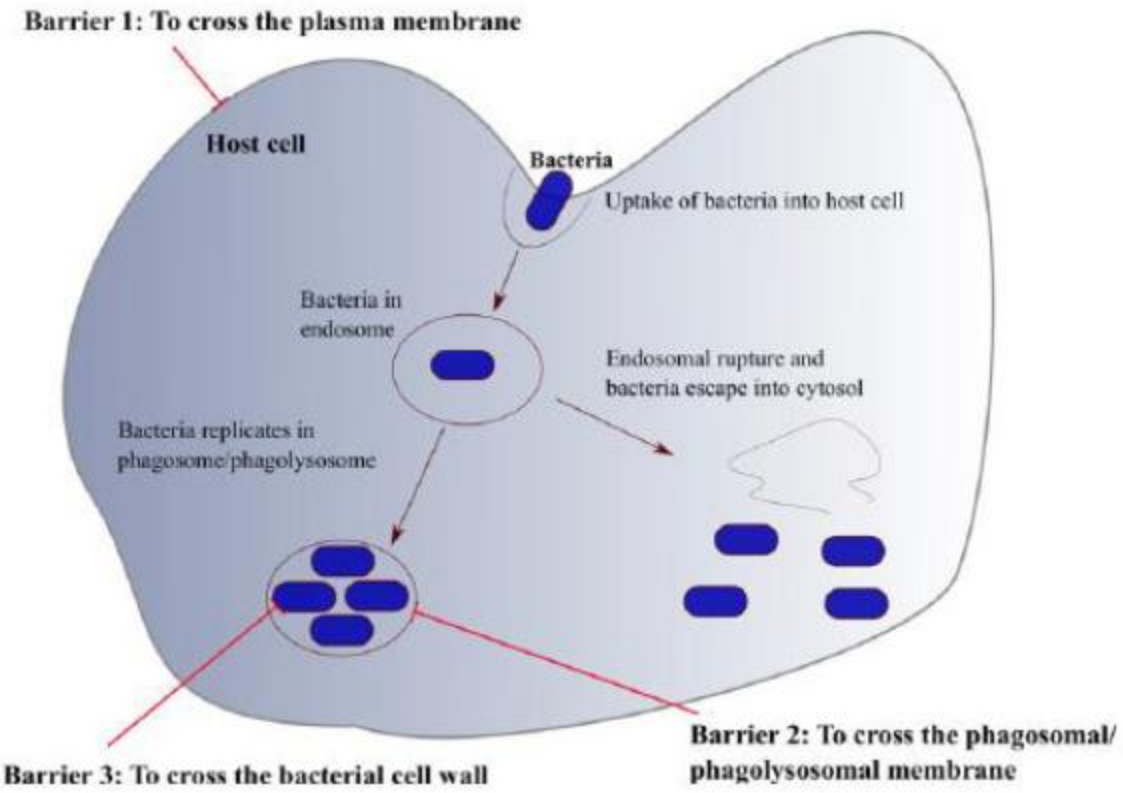


Figure 1

Illustration of bacterial localization inside the host cells and cellular barriers to antibacterial access intracellular targets. Following host cell entry, bacteria are typically enclosed inside endosomes. Bacteria can continue to survive and replicate inside endosomes as they mature into phagosomes or phagolysosomes. Certain bacteria can also induce endosome rupture and enter the cytosol. Red arrows depict three major barriers that limit antibacterial access to intracellular bacteria: (1) the plasma membrane of host cells, (2) the phagosomal/phagolysosomal membrane and (3) the bacterial cell wall. For a more detailed description of the composition of the mammalian and bacterial plasma membranes, see Silhavy *et al.* (2010), Marquardt *et al.* (2015) and Simons and Sampaio (2016).

Le « challenge » du traitement antibiotique
Pour les bactéries intracellulaires facultatives

Survie intra et extra-cellulaire

Les antibiotiques doivent avoir une activité intra et extra cellulaire

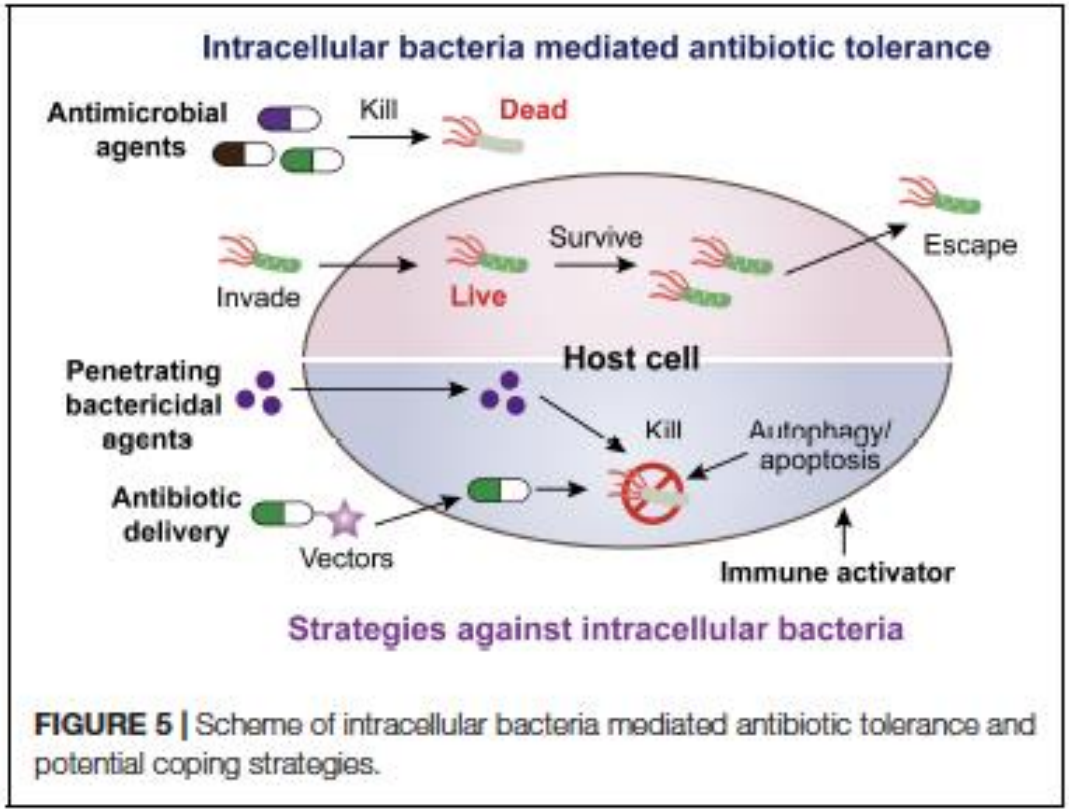


FIGURE 5 | Scheme of intracellular bacteria mediated antibiotic tolerance and potential coping strategies.

Butts, *Clin Pharmacokinet*, 1994

Le « challenge » du traitement antibiotique

- Le Ratio intracellulaire/extracellulaire
  - **Variable selon les antibiotiques**
  - **Variable selon le compartiment cellulaire**
  - **Variable selon le pH**
  - Variable selon la température
  - Variable selon que la cellule soit infectée ou non

Butts, *Clin Pharmacokinet*, 1994

Table III. Intracellular to extracellular concentration ratio (I/E ratio) for various antibacterial agents, including actual intracellular or extracellular concentrations (when available) for polymorphonuclear leucocytes and macrophages

Antibacterial agent	Assay type	Intracellular concentration (mg/L)	Extracellular concentration (mg/L)	I/E ratio	Reference
Polymorphonuclear leucocytes (PMNs)					
Human-PMNs					
Clindamycin	Radiolabelled		10	11.08	18
Erythromycin	Radiolabelled		18.4	13.32	
Ethambutol	Radiolabelled		6.9	4.83	
Rifampicin (rifampin)	Radiolabelled		20	2.33	
Chloramphenicol	Radiolabelled		10	2.23	
Lincomycin	Radiolabelled		10	1.78	
Isoniazid	Radiolabelled		3.3	1.04	
Gentamicin	Radiolabelled		18	0.84	
Cefalexin	Radiolabelled		10	0.55	
Benzylpenicillin (penicillin G)	Radiolabelled		10	0.16	
Cefamandole	Radiolabelled		10	<0.01	
Cefazolin	Radiolabelled		10	<0.01	
Sparfloxacin	Radiolabelled		0.5 to 25	>4	19
Lomefloxacin	Fluorometric		2, 5	7.9	20
Ofloxacin	Fluorometric		2, 5	7.1	
Ciprofloxacin	Fluorometric		2, 5	6.2	
Norfloxacin	Fluorometric		2, 5	5.1	
Lomefloxacin	Fluorometric		2-25	avg = 6.9	21
Ofloxacin	Fluorometric		2-25	avg = 6.1	
Ciprofloxacin	Fluorometric		2-25	avg = 5.5	
Norfloxacin	Fluorometric		2-25	avg = 4.5	
Temafloxacin	Fluorometric		2-25	avg = 3.6	

Antibacterial agent	Assay type	Intracellular concentration (mg/L)	Extracellular concentration (mg/L)	I/E ratio	Reference
Rabbit-AMs					
Benzylpenicillin	Radiolabelled		10	0.013	24
Cefazolin	Radiolabelled		10	0.07	
Cefamandole	Radiolabelled		10	0.39	
Cefalexin	Radiolabelled		10	0.44	
Rifampicin	Radiolabelled		20	1.78	
Ethambutol	Radiolabelled		6.9	6.83	
Chloramphenicol	Radiolabelled		10	2.07	
Gentamicin	Radiolabelled		18	0.56	
Isoniazid	Radiolabelled		3.3	0.55	
Tetracycline	Radiolabelled		10	0.86	
Lincomycin	Radiolabelled		10	1.64	
Erythromycin	Radiolabelled		18.4	20.64	
Clindamycin	Radiolabelled		10	42.18	
Human-AMs					
Rifabutin (ansamycin)		0.30	0.050-0.065	4.62-6.00	Unpublished data on file, Adria Laboratories
Infected Human-AMs					
Amoxicillin	Ultrasonification	ND	0.46	0	25
Amoxicillin	Ultrasonification	ND	0.94	0	
Amoxicillin	Ultrasonification	0.03	1.88	0.02	
Azithromycin	Ultrasonification	0.42	ND	?	
Azithromycin	Ultrasonification	0.88	0.08	11.00	
Azithromycin	Ultrasonification	1.78	0.23	7.74	

Butts JD, Clin . Pharmocokinet. 27 (1): 63-84.1994

Pharmacochemical class	Antibiotic	Accumulation level at equilibrium (C_C/C_E)[a]	Cellular concentration at equilibrium (mg/l)[b]	Time to equilibrium	Predominant subcellular localization
β-Lactams *	All	< 1	~ 20 to 50	Fast	Cytosol
Macrolides	Erythromycin	4 to 10	~ 40 to 150	Moderate (a few hours)	2/3 Lysosomes 1/3 Cytosol
	Clarithromycin Roxithromycin Telithromycin	10 to 50	~ 20 to 400		
	Azithromycin	40 to 300	~ 16 to 120		
Fluoroquinolones	Ciprofloxacin Levofloxacin Grepafloxacin	4 to 10	~ 16 to 40	Fast (< 1 h) to very fast (< 5 min)	Cytosol
	Moxifloxacin Garenoxacin Gemifloxacin	10 to 20	~ 40 to 80		
Aminoglycosides	All	2 to 4 (after several days)	~ 40 to 80	Slow (several days)	Lysosomes
Lincosamides	Clindamycin	5 to 20	~ 50 to 200	Fast	Unknown
	Lincomycin	1 to 4	~ 15 to 60		
Tetracyclines	Probably all	1 to 4	~ 2 to 12	Unknown	Unknown
Ansamycins (rifamycins)	Rifampin	2 to 10	~ 36 to 180	Unknown	Unknown
	Rifapentine	60 to 80	~ 1200 to 1600	Unknown	
Glycopeptides	Vancomycin	8 (after 24 h)	~ 400	Slow (several hours)	Lysosomes (in kidney)
	Teicoplanin	60	~ 6000		Unknown
	Oritavancin	150 to 300 (after 24 h)	~ 3750 to 7500		Lysosomes
	Telavancin	50 (after 24 h)	~ 4500		Lysosomes
Oxazolidinones	Linezolid	~ 1	~ 20	Unknown	Unknown

Daptomycine <1

* Sauf oxacilline *S. aureus* modèle macrophage

Tulkens, adapted from Van Bambeke *et al.*, Curr Opin Drug Discov Devel 2006;9:218-230

Le « challenge » du traitement antibiotique

Rôle du pH sur l'activité des ATB

	pH<4	pH = 6-7	pH > 7
β-lactamines	-	++	+++
Aminosides	-	+	+++
Phenicolés	-	+	+++
Tétracyclines	-	+++	++
Macrolides	-	+	+++
Rifampicine	+++	++	+++
Fluoroquinolones	-	+	+++
Cotrimoxazole	-	+	+++
Glycopeptides	-	+	+++

Rôle du pH: pH intracellulaire varie de 7,4 dans le phagosome, à 6,8 dans le cytoplasme et 5,0 dans le lysosome

Le « challenge » du traitement antibiotique

Table 3
Mode of entry within eucaryotic cells and subcellular localization of antibiotics

Antibiotics	Mode of entry	Localization within the		Antibiotic activity at pH		
		Cytosol	Lysosomes	Basic	Neutral	Acidic
Betalactams	Diffusion	+		+ + +	+ +	+
Aminoglycosides	Pinocytosis		+ + +	+ + +	+	-
Tetracyclines	Diffusion	+ +	?	+ +	+ + +	+
Chloramphenicol	Diffusion	+ +	?	+ + +	+	-
Rifampin	Diffusion	+ +	+ +	+ +	+ +	+ + +
Erythromycin	Transport	+	+ + +	+ + +	+	-
Clindamycin	Transport	+	+ + +	+ + +	+	-
Fluoroquinolones	Unknown	+ +	+ +	+ + +	+	-

Influence of the pH on antibiotic activity.

Maurin, *Int J Antimicrob Agent*, 1997

Le « challenge » du traitement antibiotique

Table 4
Antibiotic susceptibility of obligate intracellular bacteria, as determined in in vitro infected cell systems

	R. Conorii R. rickettsii	*R. Prowazekii*	*E. chaffeensis*	*C. burnetii*	*Chlamydia spp.*
Betalactams	−	−	−	−	−
Aminoglycosides	−	−	−	−	−
Chloramphenicol	+	+	−	−	−
Tetracyclines	++	++	++	++	++
Erythromycin	−	+	−	±	+
Azithromycin	−	NA	NA	−	++
Clarithromycin	++	NA	NA	++	++
Roxithromycin	++	NA	NA	++	++
Pefloxacin	++	++	−	++	++
Ofloxacin	++	++	−	++	++
Ciprofloxacin	++	++	−	++	++
Cotrimoxazole	−	−	−	+	−
Rifampin	++	++	++	+	+

−, not active; +, poorly active; ++, active; +++, bactericidal; ±, variable susceptibility among different strains; NA, not available.

Maurin, *Int J Antimicrob Agent*, 1997

Le « challenge » du traitement antibiotique

- Macrophages #Polynucléaires
  - Pénètrent bien : (C/E>4)
    - Azythromycine,Roxithromycine,Erythromycine
    - Clindamycine
    - Quinolones
  - Pénètrent : (C/E 1-4)
    - Rifampicine, Doxycycline, Chloramphénicol, Bactrim
    - Aminoglycosides ++
  - Pénètrent pas :(C/E<1)
    - Bétalactamines et glycopeptides

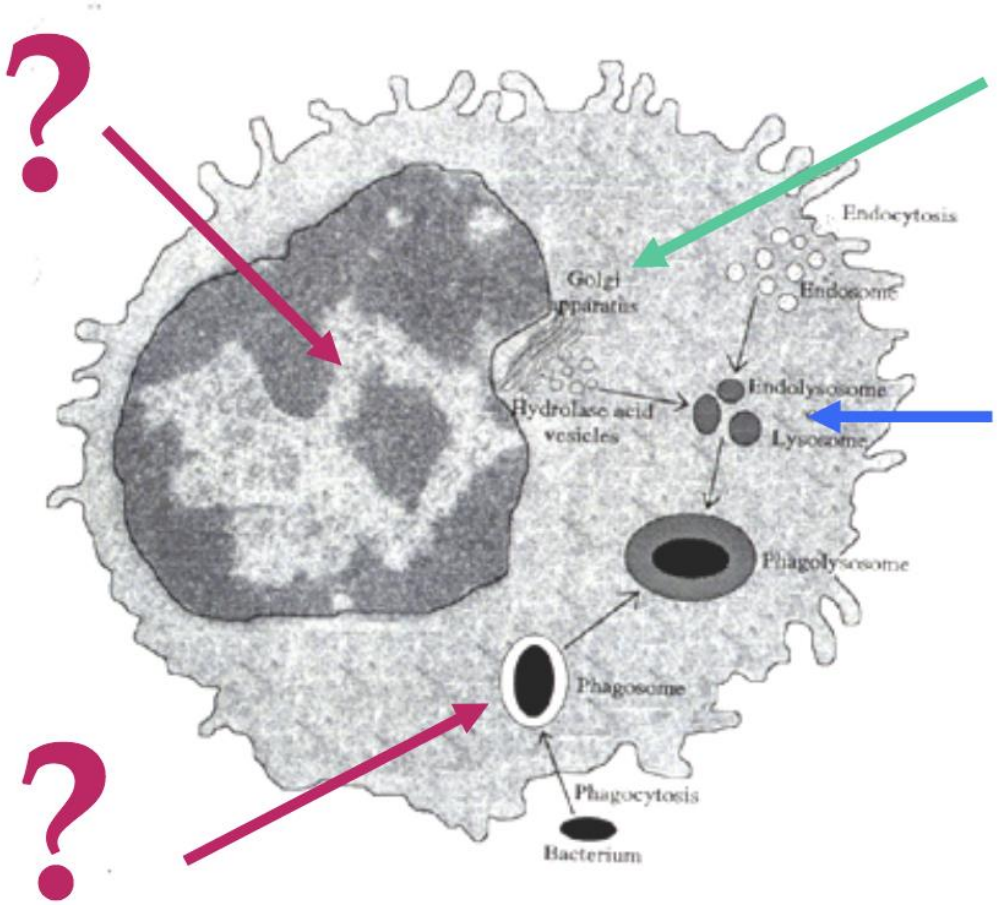
Le « challenge » du traitement antibiotique

Antibiotic uptake, subcellular localisation and pH of optimum activity of antibiotics

Antibiotic	Mode of entry	Cytosol	Lysosomes	PH optimal
Aminoglycosides	Pinocytosis		+++	7
Betalactams	Diffusion	+		7
Chloramphenicol	Diffusion	++	Unknow	7
Erythromycin	Transport	+	+++	7.8
Fluoroquinolones	Unknow	++	++	8
Rifampin	Diffusion	++	++	<5
Tetracyclines	Diffusion	++	++	6.6

Symbols : + = low concentration ; ++ = medium concentration ; +++ = high concentration

Localisation subcellulaire des antibiotiques



- Cytosol
  - Cyclines
  - Chloramphenicol
  - Rifampicine
  - Quinolones
- Lysosomes
  - Aminosides
  - Erythromycine
  - Clindamycine
  - Quinolones
  - Rifampicine
  - Cyclines et chloramphénicol

Cycline

1948: Tétracycline

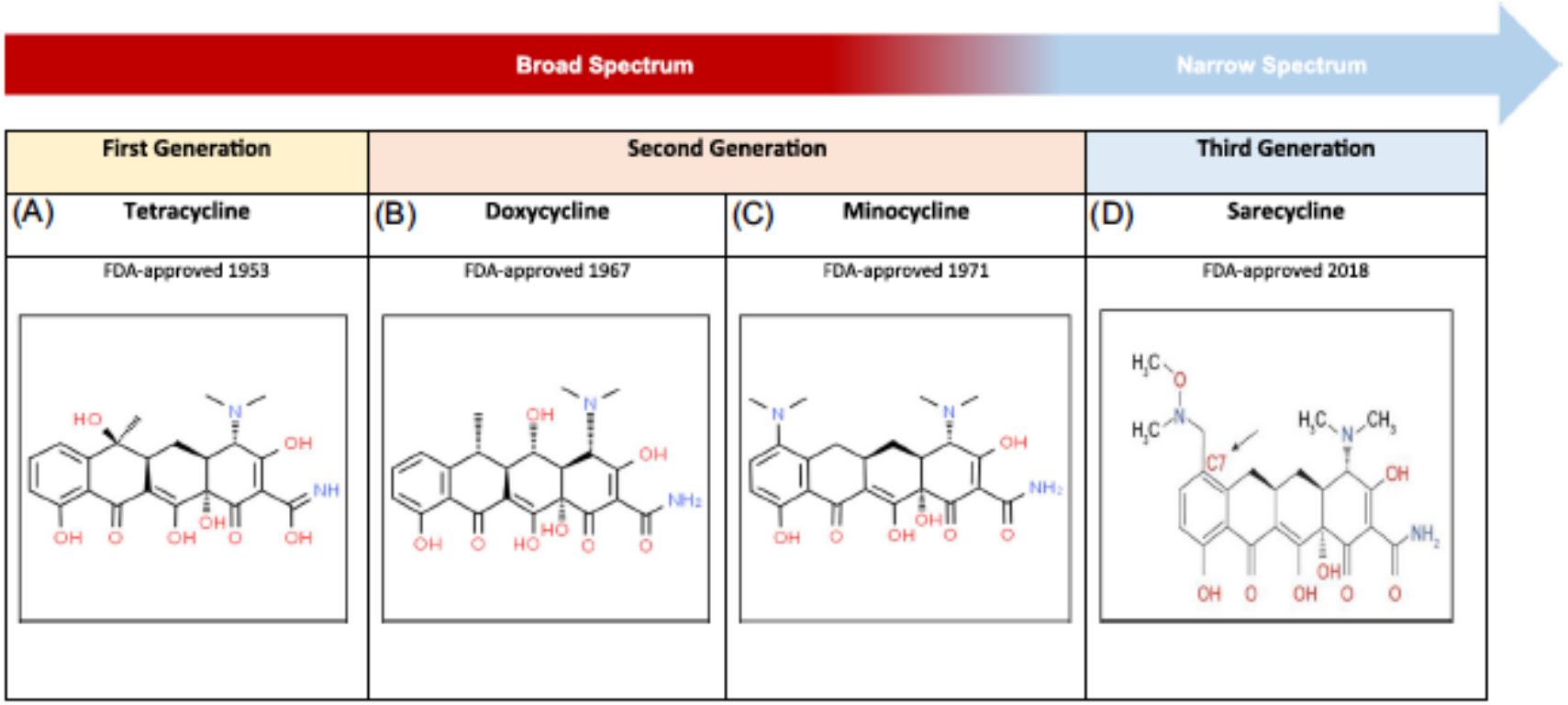


FIGURE 1 Chemical structures of the different tetracycline-class drugs use for the treatment of acne vulgaris. (A) Tetracycline. (B) Doxycycline. (C) Minocycline. (D) Sarecycline. The incorporation of a longer C7 moiety allows sarecycline to overcome tetracycline-resistant mechanisms mainly the efflux pump. *Structure image source*: http://www.chemspider.com/Chemical-Structure.28540486.html

Graber, *Dermatol Rev*, 2021

Cycline, mécanisme d'action

Fixation réversible à la sous unité 30S du ribosome
Effet bactériostatique

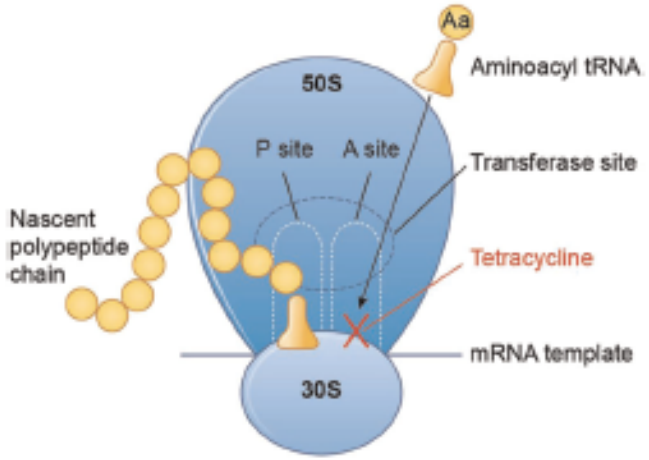


FIGURE 2 Mechanism of action of the tetracycline class of antibiotics. The tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome, which prevents acyl-transfer RNA (tRNA) from binding to the ribosome.[5] Thus, protein synthesis is ceased which halts growth and replication of the bacterial organism, producing a bacteriostatic effect. A recent study demonstrates that although sarecycline binds to the same part of the 30S ribosomal subunit as the other tetracycline members, sarecycline is unique in that it has a long C7 moiety that protrudes more toward the messenger RNA (mRNA)-binding channel and establishes a direct interaction with mRNA

Graber, *Dermatol Rev*, 2021

Surveillance de l'efficacité et de la tolérance du traitement

Contre-indications aux traitements

Doxycycline (Vibramycine®)

- en cas d'allergie aux antibiotiques de la famille des tétracyclines ou à l'un des excipients
- en association avec les rétinoïdes par voie générale (voir rubrique 4.5),
- en cas d'apport en vitamine A de 10 000 UI/j et plus : risque d'hypertension intracrânienne,
- chez la femme enceinte : l'utilisation de la doxycycline est contre-indiquée pendant la grossesse. Il apparait que le risque associé à l'utilisation des tétracyclines pendant la grossesse est principalement dû aux effets sur le développement des dents et du squelette. (voir rubrique 4.4 concernant l'utilisation pendant le développement dentaire),
- chez la femme allaitante : les tétracyclines sont excrétées dans le lait maternel et sont pour cette raison contre-indiquées pendant l'allaitement. (voir rubrique 4.4 concernant l'utilisation pendant le développement dentaire.

Précautions d'emploi avec certains traitements :

Anticonvulsivants inducteurs enzymatiques qui diminuent les concentrations plasmatiques de cyclines par augmentation du métabolisme hépatique.

Didanosine qui diminue l'absorption digestive des cyclines en raison d'une augmentation du pH gastrique.

Sels de fer, les sels de zinc et les topiques gastro-intestinaux qui diminuent l'absorption intestinale des cyclines.

Anticoagulants oraux (augmentation de l'effet anticoagulant)

Base-données-publique-médicaments.gouv

Cycline, mécanisme de résistance

Pompe à efflux

Gene de résistance=> protection ribosomale à la fixation des tétracycline

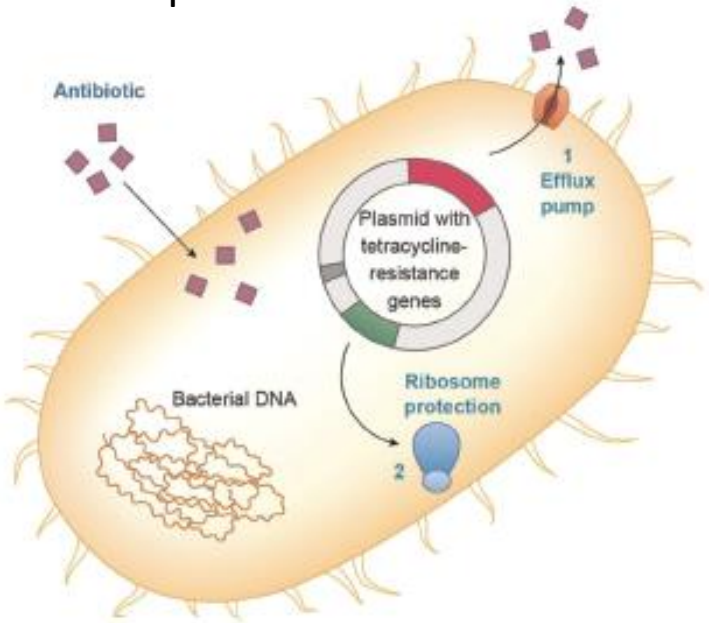


FIGURE 3 Bacterial mechanisms of resistance. Bacteria may develop resistance to the tetracycline class of antibiotics in two ways. (1) The bacteria may facilitate the removal of the antibiotic via the transmembrane efflux pump. (2) The bacteria may develop ribosomal protection mechanisms to prevent the tetracycline antibiotic from binding to the 30S ribosomal unit and exerting its effect

Graber, *Dermatol Rev*, 2021

Activity of Telithromycin against Thirteen New Isolates of *C. burnetii* Including Three Resistant to Doxycycline

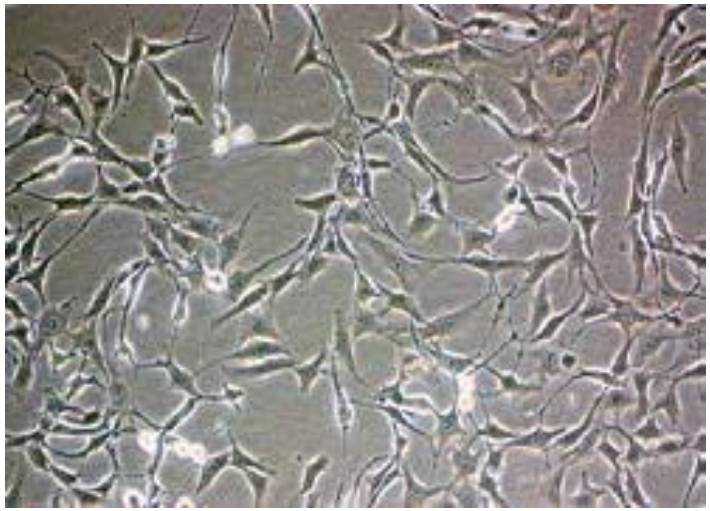
JEAN-MARC ROLAIN, FRÉDÉRIC LAMBERT, AND DIDIER RAOULT

Unité des rickettsies, IFR 48, CNRS UMR 6020, Université de la Méditerranée, Faculté de medicine, 13385 Marseille cedex 5, France

ABSTRACT: In this study we have evaluated the *in vitro* activity of antibiotics against 13 new isolates of *Coxiella burnetii* using a real-time quantitative PCR assay. MICs against doxycycline ranged from 1 to 8 μg/mL, telithromycin from 0.5 to 2 μg/mL , and all strains had MICs ≥ 8 μg/mL for erythromycin. We report that strains resistant to doxycycline exist either in humans or animals.

KEYWORDS: *Coxiella burnetii*; Q fever; telithromycin; doxycycline

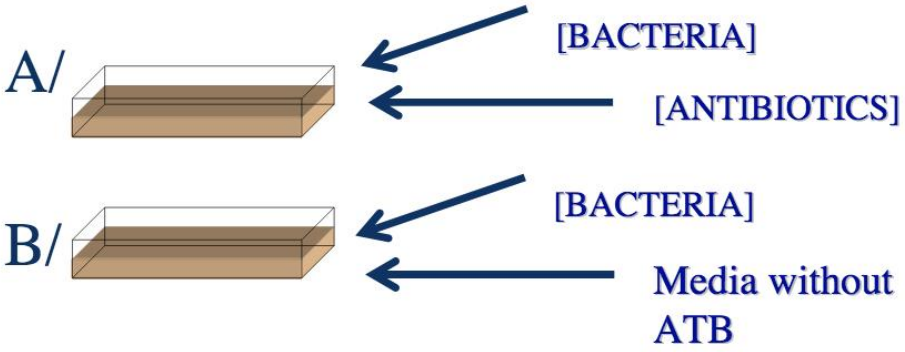
Evaluation de la résistance aux antibiotiques

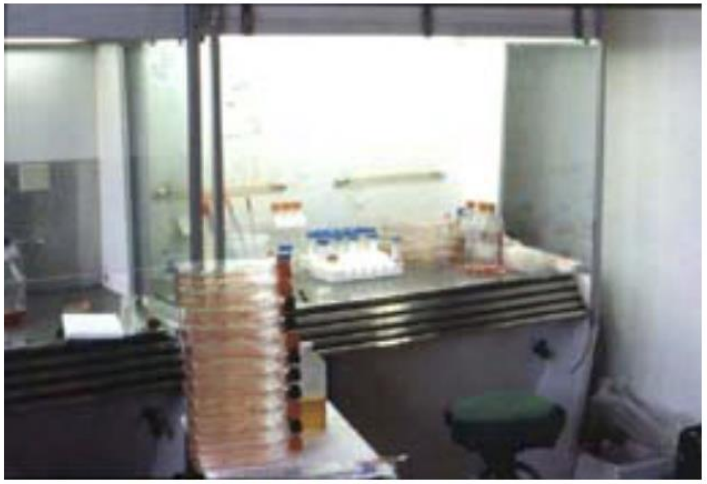


Evaluation de la résistance aux antibiotiques

Tissue-Cell culture system

- Methods

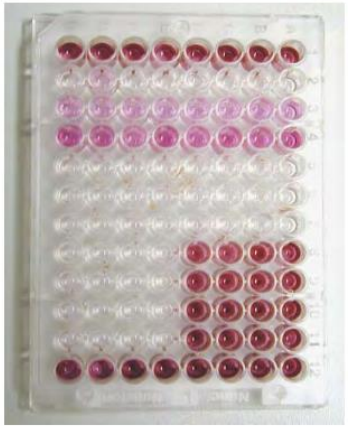




P3 laboratory

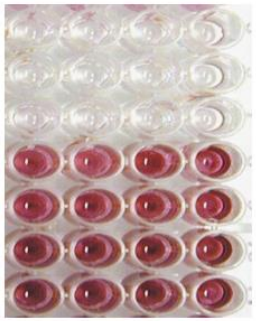
Incubation at 37°C for several days

Evaluation de la résistance aux antibiotiques



Uninfected cells OD = 1
Infected cells 2000 PFU OD = 0
Infected cells 200 PFU OD = 0.150
Infected cells 20 PFU OD = 0.700

•The optical density at 492 nm of each well is determined using a spectrophotometer



Doxycycline 0.015 µg/ml OD =0
Doxycycline 0.03 µg/ml OD = 0
Doxycycline 0.06 µg/ml OD = 0
Doxycycline 0.125 µg/ml OD =0.89 MIC
Doxycycline 0.25 µg/ml OD = 0.95
Doxycycline 0.5 µg/ml OD =1
Doxycycline 1 µg/ml OD = 1

The MIC corresponds to the lowest antibiotic concentration for which the mean OD at 492 nm is higher than that of the 20 PFU controls

Parmi les propositions suivantes lesquelles sont exactes

L'activité des antibiotiques dépend :

A. Du pH
B. De la pénétration dans le compartiment intracellulaire
C. De la pénétration dans le sous compartiment cellulaire
D. De la température
E. De la luminosité

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Clinique

Quelles sont les infections à germes intracellulaires les plus fréquemment rencontrées en pratique clinique en France?

A. Infection à *Mycoplasma pneumoniae*
B. Infection à Bartonella henselae
C. Infection à *Coxiella burnetii*
D. Infection à *Rickettsia conorii*
E. Infection à *B. bacilliformis*

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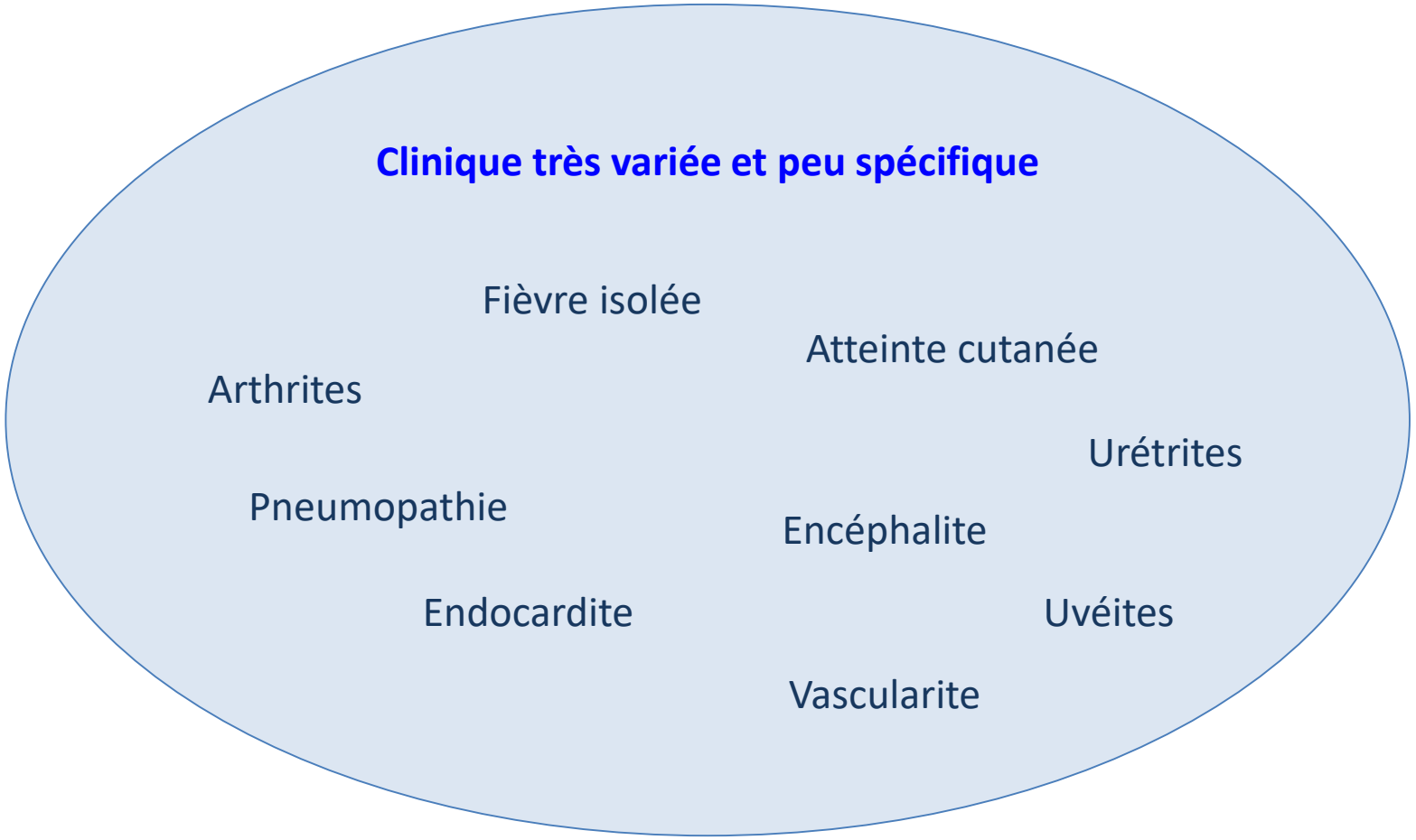
Problématique des bactéries intracellulaires



Infections à germes intracellulaires dans un service de médecine interne : à propos de 82 cas Tunisie

Introduction

Les infections à germes intracellulaires constituent un motif fréquent de consultation et d'hospitalisation des adultes. Elles sont souvent sous estimées et sous diagnostiquées vue la grande variabilité et la pauvreté des tableaux cliniques. Le but de notre étude est de décrire les caractéristiques épidémiologiques, cliniques, biologiques, microbiologiques, thérapeutiques et évolutives des infections à germes atypiques dans un service de médecine interne.

Patients et méthodes

Il s'agissait d'une étude rétrospective, descriptive, incluant 82 patients qui étaient hospitalisés dans notre service de Médecine Interne pour des infections à germes intracellulaires.

Résultats

Notre série comportait 82 patients dont 42 hommes et 40 femmes (*genre ratio* = 1,05). L'âge moyen de nos patients était de 40,8 ans. Le délai moyen de consultation était estimé à 8 jours. La notion de contact avec les chiens était présente chez 54,9 % des patients alors que la notion de piqûre d'insecte n'était rapportée que dans 2 cas. Les motifs d'hospitalisation étaient dominés par une fièvre isolée dans 56,2 % des cas, une fièvre éruptive (39 %), et des signes respiratoires (4,9 %). Sur le plan clinique, un syndrome pseudo grippal et des signes généraux étaient rencontrés respectivement chez 45,1 % et 31,7 % des patients. La tâche noire n'était retrouvée que chez 14,6 % des patients. Sur le plan respiratoire, une toux était présente dans 42,6 % des cas et une dyspnée avec hypoxie chez 3 malades. Une atteinte interstitielle était objectivée chez 34,1 % des malades. Sur le plan digestif, des vomissements étaient présents chez 31,7 % des malades, des douleurs abdominales (20,7 %) et des diarrhées (8,5 %). Des adénopathies et une viscéromégalie étaient retrouvées respectivement chez 6 et 2 patients. Sur le plan neurologique, un seul patient avait un syndrome méningé. Une rétinite était objectivée chez un seul patient. À la biologie, un syndrome inflammatoire biologique était présent dans 98,8 % des cas, une cytolyse hépatique (70,7 %), une hyponatrémie (62,2 %) et une cholestase (17,1 %). À la numération et formule sanguine (NFS), une thrombopénie était retrouvée chez 42,6 %, une hyperleucocytose (31,7 %) et une leucopénie (4,9 %). La NFS était normale chez 29,3 % des patients. Les sérologies étaient positives à *Rickettsia Conorii* dans 37,8 % des cas, à *Mycoplasme pneumoniae* (6,1 %), à *Chlamydia* (4,9 %), à *Coxiella Burnetti* (3,6 %) et à *Légionnelle* (1,2 %). Le traitement était basé sur les cyclines chez 46,3 % des patients, des fluoroquinolones (39 %) et des macrolides (14,7 %). L'évolution était favorable chez 98,8 % des patients. Une méningite lymphocytaire compliquait l'infection à germes intracellulaires dans un cas.

Conclusion

Les infections à germes intracellulaires constituent une affection aiguë fréquente dans notre pratique quotidienne. Le tableau typique fait d'une fièvre éruptive, tâche noire, un léger syndrome inflammatoire biologique, une cytolyse hépatique, une hyponatrémie et une thrombopénie est exceptionnel. Il s'agit souvent d'un tableau atypique, d'où l'importance des sérologies qui servent à conforter le diagnostic.

Mzabi, *Revue de Médecine interne*, 2022

Rickettsioses

Quels sont les principaux vecteurs de rickettsioses?

A. Tique

B. Poux

C. Punaise

D. Phlébotomes

E. Puces

Quels sont les principaux vecteurs de rickettsioses?

A. Tique

B. Poux

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D. Phlébotomes

E. Puces

Rickettsies

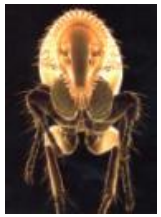
Groupe boutonneux
(20 espèces, 14 pathogènes chez l'homme)

Groupe typhus

Fièvre boutonneuse

Tiques

Typhus murin

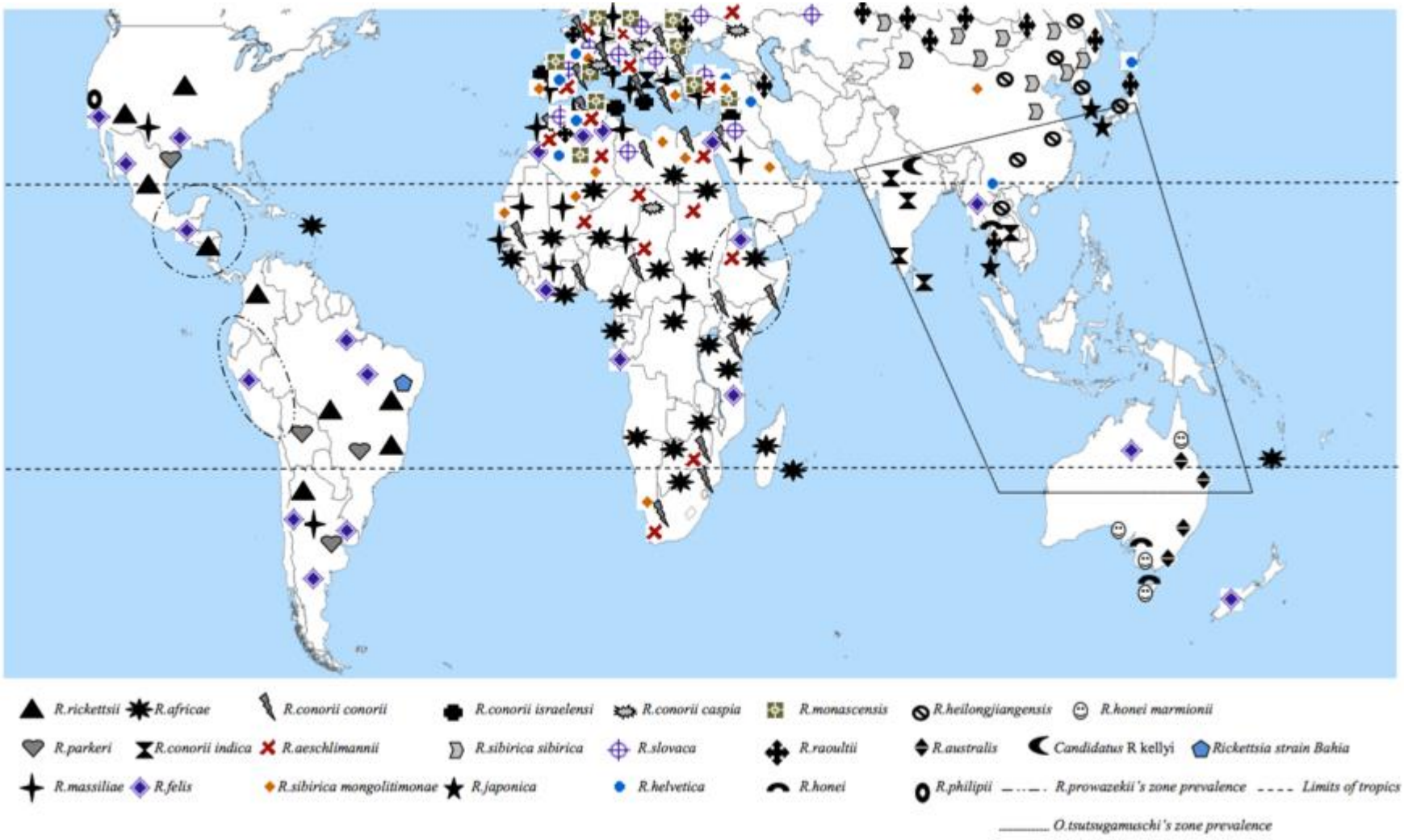


Puces

Typhus épidémique

Poux

Rickettsioses dans le monde



Les Rickettsioses du groupe boutonneux

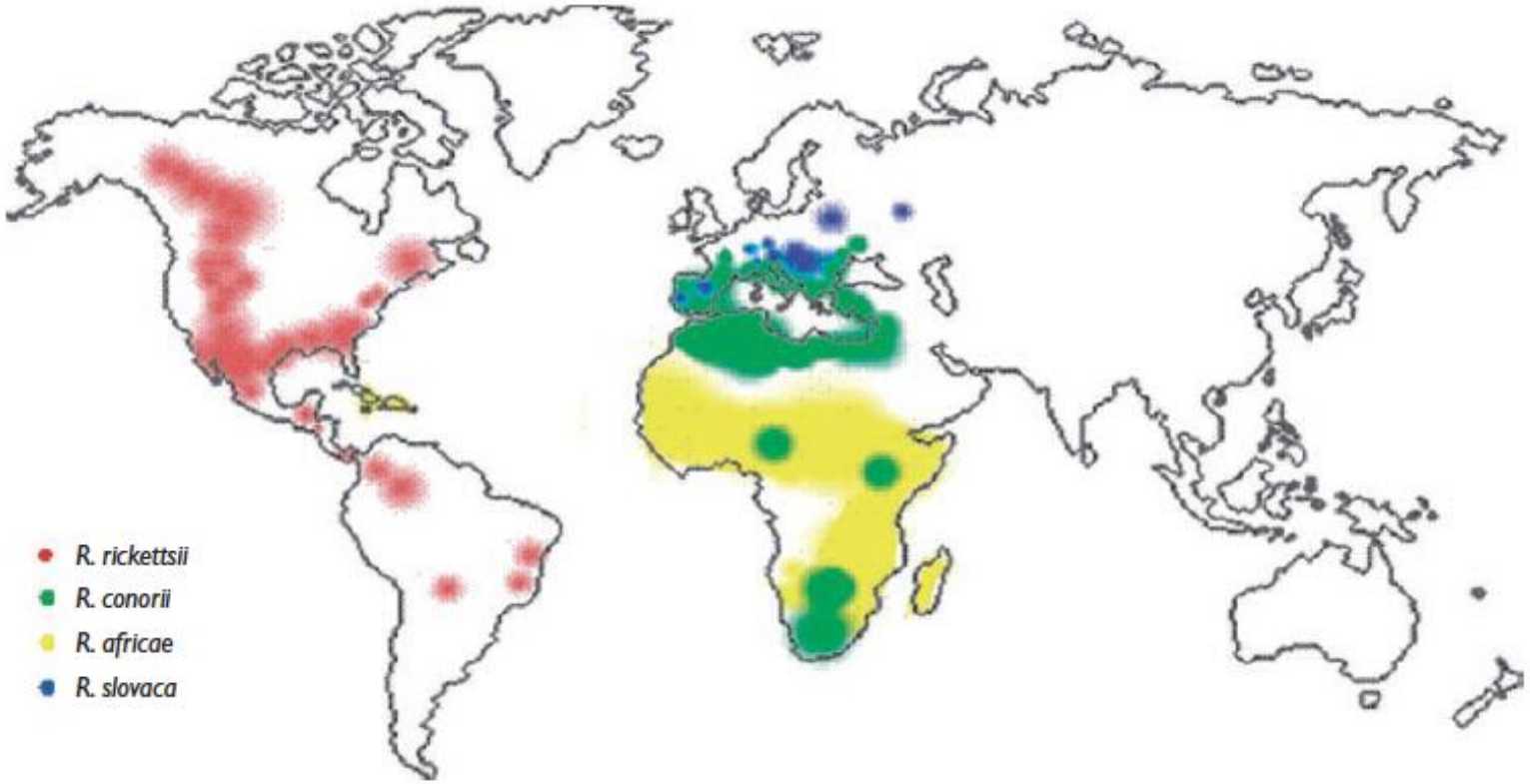


Figure 1. Distribution géographique de quelques rickettsioses du groupe boutonneux
(Adapté des réf.[2,3]).

Boillat, *Revue Med Suisse*, 2007

Rickettsioses

Tableau I. Espèces du genre *Rickettsia* pathogènes pour l'homme

Groupe typhus		
R. prowazekii	Typhus épidémique	 Pou du corps
R. typhi	Typhus murin	 Puce
Groupe boutonneux		
R. rickettsii	Fièvre pourprée des montagnes rocheuses	
R. conorii	Fièvre boutonneuse méditerranéenne	
R. akari	Rickettsiose vésiculaire	
R. sibirica	Typhus à tique de Sibérie ou typhus Nord-asiatique	
R. australis	Typhus du Queensland	
R. honei	Fièvre boutonneuse des îles Flinders	
R. africae	Fièvre à tique africaine	 Tique ***
R. japonica	Fièvre boutonneuse orientale ou fièvre boutonneuse du Japon	
R. felis	Fièvre boutonneuse à puces ou pseudotyphus californien	
R. mongolotimonae	Rickettsiose avec lymphangite	
R. slovaca	TIck-bOrne lymphAdenitis (TIBOLA)	
R. helvetica	Autre rickettsiose*	
R. aeschlimannii	Autre rickettsiose	
R. heilongjiangensis	Autre rickettsiose**	

Fièvre

Céphalée

Rash

Boillat, *Revue Med Suisse*, 2007

Quelles sont les caractéristiques cliniques de l'infection à *R. conorii* ?

A. Endemique sur le pourtour méditérranéen
B. Vecteur *Rhipicephalus sanguineus*
C. Triade: escarre, fièvre et rash
D. Jamais compliquée d'atteinte d'organe
E. Pas de traitement antibiotique disponible

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E. Pas de traitement antibiotique disponible

Rickettsia conorii

Fièvre boutonneuse méditerranéenne

Rhipicephalus sanguineus

Escarre d’inoculation, Rash, Fièvre

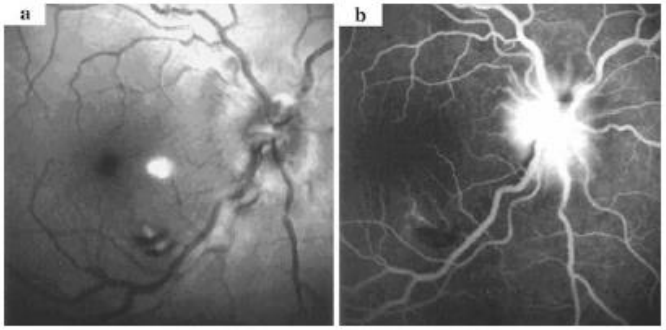
Rickettsia conorii
Fièvre boutonneuse méditerranéenne
Complications rares : vascularites

Meningoencephalitis caused by Rickettsia conorii in a young infant.

Bougtega, *Rev Neurol*, 2010

Retinopathy in *Rickettsia conorii* Infection: Case Report in an Immunocompetent Host

Figure 1. a) Red-free fundus photograph of the right eye shows optic disc edema, retinal venous dilation and tortuosity, superficial retinal hemorrhages, cotton-wool spots, and increase in retinal reflectivity. b) Late-phase fluorescein angiogram of the same eye shows optic disc hyperfluorescence, hypofluorescence from retinal hemorrhages and cotton-wool spots, and retinal vascular leakage.



Leone, *Infection*, 2008

Cerebral infarction: An unusual complication of Mediterranean spotted fever

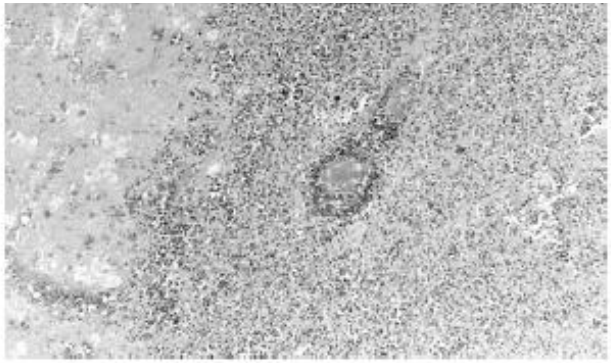
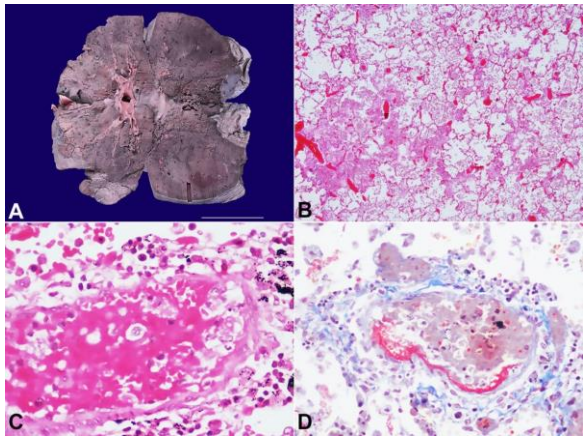


Fig. 1. Histological examination of the brain. Thrombotic vasculitis with intramural and perivascular infiltrates composed of mainly mononuclear cells and coagulative necrosis of the cerebral white matter (hematoxylin–eosin–saffron, original magnification = ×100).

Botelho-Nevers, *Eur J Intern Med*, 2005



Chugh, *Autops Case report*, 2022

Rickettsia africae
Fièvre à tique africaine

Retour
Safari
++++

Rickettsia slovaca
SENLAT: Scalp Escar and lymphadenopathy

Escarre du cuir chevelu dans 66-100% des cas

Lymphadénopathie du territoire de drainage

Rickettsia rickettsie
Fièvre pourpre des montagnes rocheuses

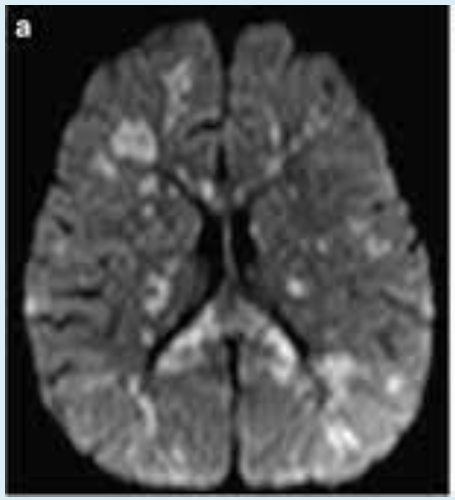
Incubation 2-14 jours

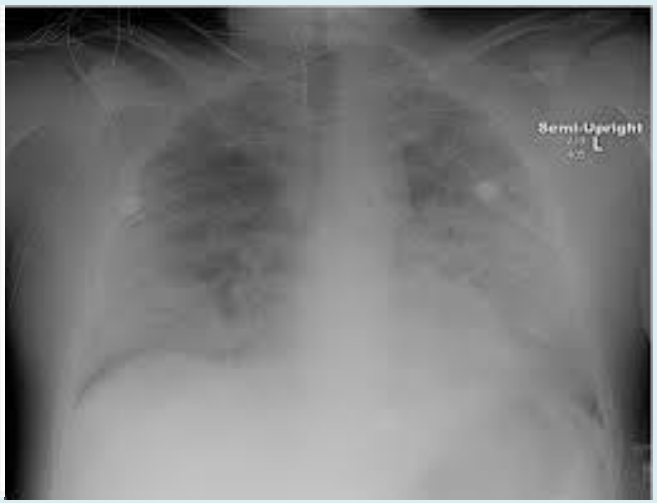
Triade: Fièvre-Céphalée-Rash

!! Retard au traitement : favorise les formes sévères !!

Encéphalites	Oedème pulmonaire non cardiogénique , SDRA	Arythmie cardiaque	Coagulopathies	Nécroses cutanée

Autres symptômes non spécifiques: : douleurs abdominales, toux, saignements, confusion, signes neurologiques focaux, crise d'épilepsie





Rickettsioses

Tableau 2. Présentation clinique et complications de différentes rickettsioses
(Adapté des réf.[7-16, 21-22]).
En gras : les caractéristiques cliniques le plus souvent retrouvées.
* La tache noire est présente au niveau du cuir chevelu et passe donc souvent inaperçue.
** Aucun décès décrit, mais la casuistique est encore limitée.

	Fièvre	Céphalées	Rash cutané	Tache noire	Taches noires multiples	Adénopathie locale	Mortalité
Typhus épidémique	**100%**	**100%**	**25-38%**	–	–	–	**15%**
Typhus murin	**98-100%**	**75-88%**	**50-80%**	–	–	–	**4%**
Fièvre pourprée des montagnes rocheuses	**99-100%**	**79-91%**	**82-90%**	**< 1%**	–	**27%**	**4-25%**
Fièvre boutonneuse méditerranéenne	**100%**	**56%**	**> 95%**	**70-85%**	**Rare**	**Rare**	**2,5%**
Fièvre à tique africaine	**59-100%**	**62-83%**	**15-46%**	**53-100%**	**21-54%**	**43-100%**	–**
TIBOLA	**12%**	–	**6%**	**82-100%***	**Rare**	**100%**	–**

Boillat, *Revue Med Suisse*, 2007

Histologie biopsie cutanée

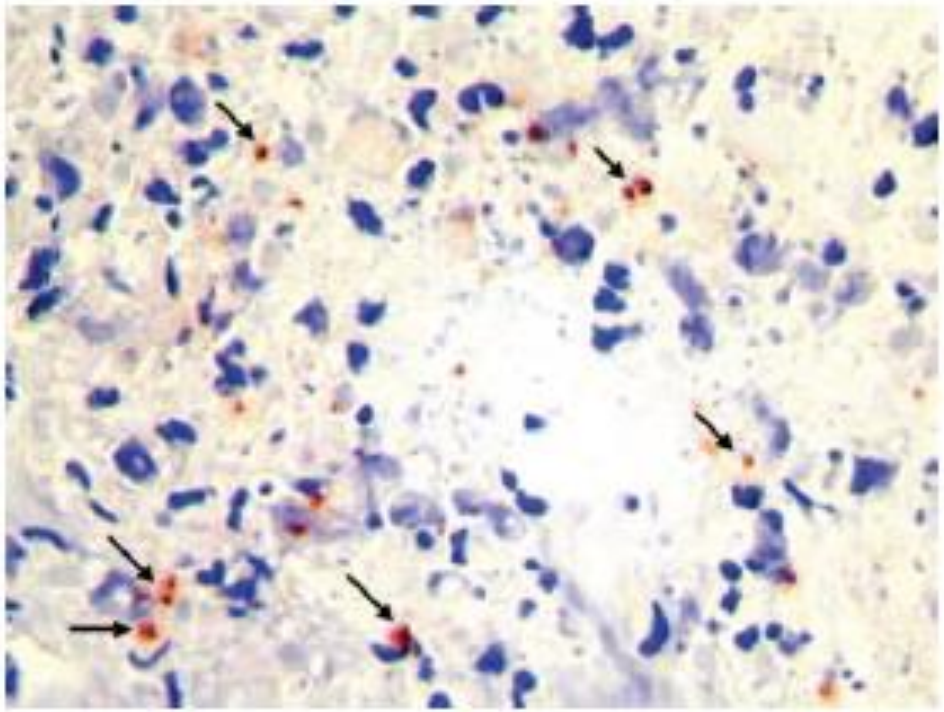


FIG. 12. Immunohistochemical detection of *Rickettsia sibirica* subsp. *mongolotimonae* (arrows, rickettsiae staining red) in a skin biopsy specimen of an eschar of the patient presented in Fig. 5. Note the abundant inflammatory infiltrate with necrotic features and vascular injury in the dermis (polyclonal rabbit anti-*R. sibirica* subsp. *mongolitimonae* antibody used at a dilution of 1/2,000 with hemalin counterstain; original magnification, ×400).

Comment faire le diagnostic d'infection à *Rickettsia* sp

A. Sérologie
B. Hémocultures
C. PCR sur la croute de l'escarre
D. PCR dans les urines
E. Ag galactomannan

Comment faire le diagnostic d'infection à *Rickettsia* sp

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Rickettsioses

Méthodes diagnostiques	Avantages	Inconvénients
Sérologie	• Méthode la plus répandue, disponible dans de nombreux laboratoires	• Diagnostic rétrospectif • Réactions croisées entre les espèces de rickettsies**
PCR : sang ou biopsie tissulaire (tache noire ou rash)	• Diagnostic phase aiguë • Peut être positive malgré antibiothérapie préalable • Résultat dans les 24 heures* • Distinction possible entre espèces	
Culture : sang ou biopsie tissulaire	• Diagnostic phase aiguë • Distinction possible entre espèces	• Dans laboratoires de référence (niveau de sécurité biologique 3) • Négative si antibiothérapie préalable
Immuno-histochimie : biopsie tissulaire	• Diagnostic phase aiguë • Peut être positive malgré antibiothérapie préalable	• Réactions croisées entre les espèces de rickettsies**

Boillat, *Revue Med Suisse*, 2007

Diagnostic des Rickettsies

PCR sur escarre

Culture

+

Sérologie

Population cible	Traitement
Adultes	• Doxycycline 100 mg 2 x/j p.o.[a] pour 7-10 jours en cas de FPMR pour 3-7 jours en cas de FBM pour 3-7 jours en cas de FTA ou de TIBOLA pour 7-15 jours en cas de typhus murin ou épidémique • Ciprofloxacine 750 mg 2 x/j p.o. pour 7 jours[b] lors de FBM
Enfants	• Doxycycline 2,5 mg/kg 2 x/j p.o. si < 45 kg ; dose adulte p.o. si > 45 kg pour 5-10 jours[a,c] lors de FPMR ou de FBM • Clarithromycine, 7,5 mg/kg 2 x/j p.o. pour 7 jours alternative lors de FBM • Azithromycine, 10 mg/kg 1 x/j p.o. pour 3 jours alternative lors de FBM

a : Traitement intraveineux en cas de vomissements ou de sévérité clinique. Un minimum de 48 heures d'apyrexie doit être obtenu avant l'arrêt du traitement.
b : Alternative pour le traitement de la FBM chez l'adulte en cas d'allergie aux tétracyclines.
c : En raison de la haute mortalité associée à la fièvre pourprée des montagnes rocheuses et de la supériorité de la doxycycline dans cette infection, la doxycycline représente le traitement de choix chez l'enfant, malgré le faible risque de coloration des dents. Pour traiter les femmes enceintes, il est préférable de demander un avis spécialisé.
FPMR : fièvre pourprée des montagnes rocheuses.
FBM : fièvre boutonneuse méditerranéenne.
FTA : fièvre à tique africaine.
TIBOLA : TIck-BOrne LymphAdenitis.

Boillat, *Revue Med Suisse*, 2007

R. prowasekii: Typhus épidémique

Pediculus humanis corporis & capitis

- Fever – 100 percent
- Headache – 91 to 100 percent
- Tachypnea – 97 percent
- Chills – 82 percent
- Muscle tenderness – 70 percent
- Rash – 64 percent
- Abdominal tenderness – 60 percent
- Arthralgias – 50 percent
- Cough – 38 percent
- Nausea – 32 percent

Complications: atteintes du système nerveux central
Myocardite
Thrombopénie

Maladie de Brill-Zinsser : récurrence des années après l'infection(réservoir+++)
Fièvre-céphalée-malaise-rash

Rickettsia typhi: Typhus Murin

Vecteur: *Xenopsylla cheopis* (puce du rat)

Réservoirs: Rats

Incubation: 7 – 14 jours

Fièvre + éruption + céphalées = CLASSIQUE mais < 15% des cas !!!

Fréquents: nausées – vomissements – douleurs abdominales

ictère – confusion ……

< 50%: contacts avec des puces ou des rats

Fréquent cause de “fièvre indeterminée” au retour des tropiques

Coxiella burnetii

L'infection à *C. burnetii*

A. Zoonose de répartition mondiale
B. Transmission par aérosol
C. Transmission par consommation de lait cru
D. Maladie asymptomatique dans 60% des cas
E. Atteinte cardio vasculaire dans 5%

L'infection à *C. burnetii*

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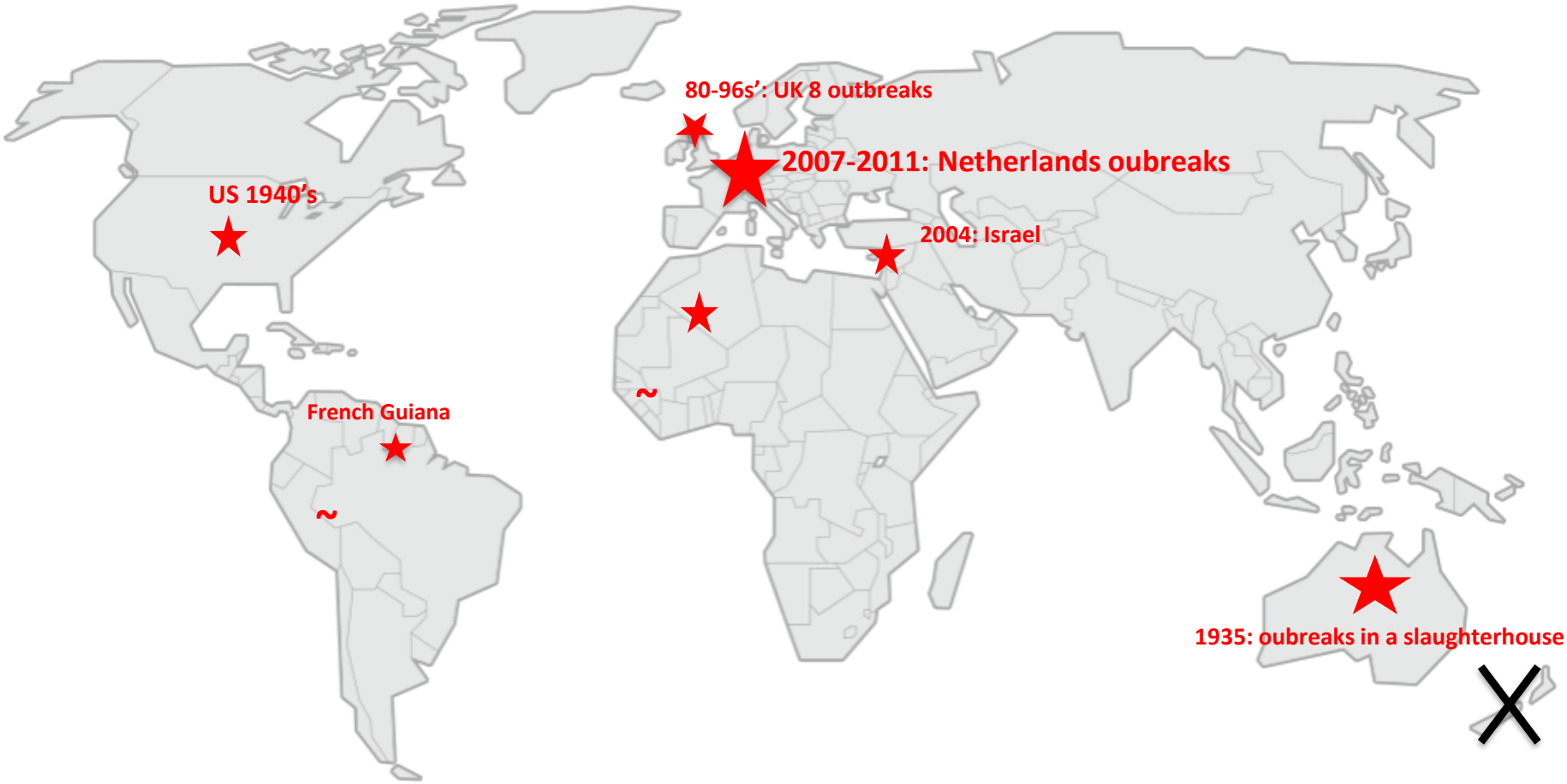
Épidémiologie



Underdiagnosed : 5% of pneumonia in Tanzania

Angelakis, *Iran J Public Health*, 2011
Eldin, *CMR*, 2015
Van der Hoeck, *Eurosurv*, 2012

Épidémiologie

In France : incidence : 2,5/ 100 000 habitants
French Guiana : 37-150 / 100 000 habitants
Netherlands in 2009: 69/ 100 000 habitants

Angelakis, *Iran J Public Health*, 2011
Eldin, *CMR*, 2015
Van der Hoeck, *Eurosurv*, 2012

Transmission







Aerosols, morsure de tique, lait non pasteurisé, transfusion

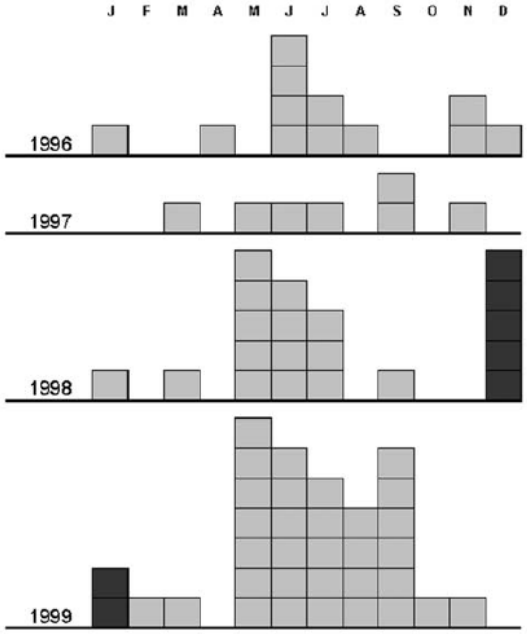
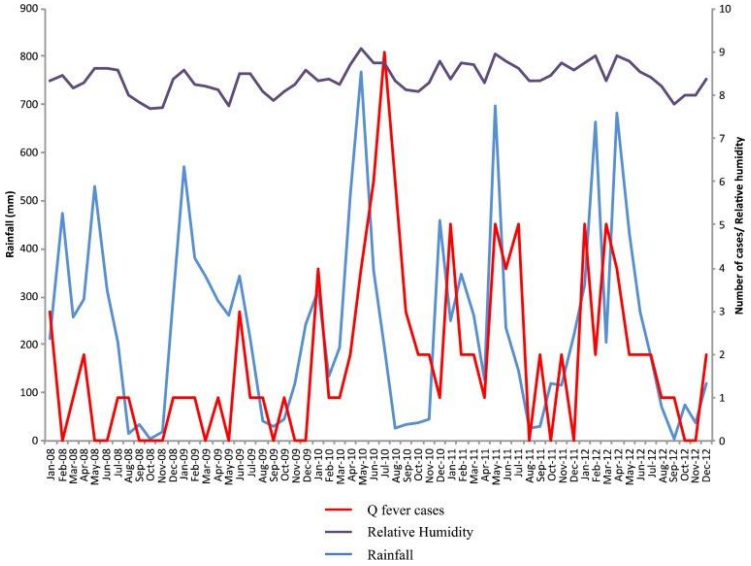


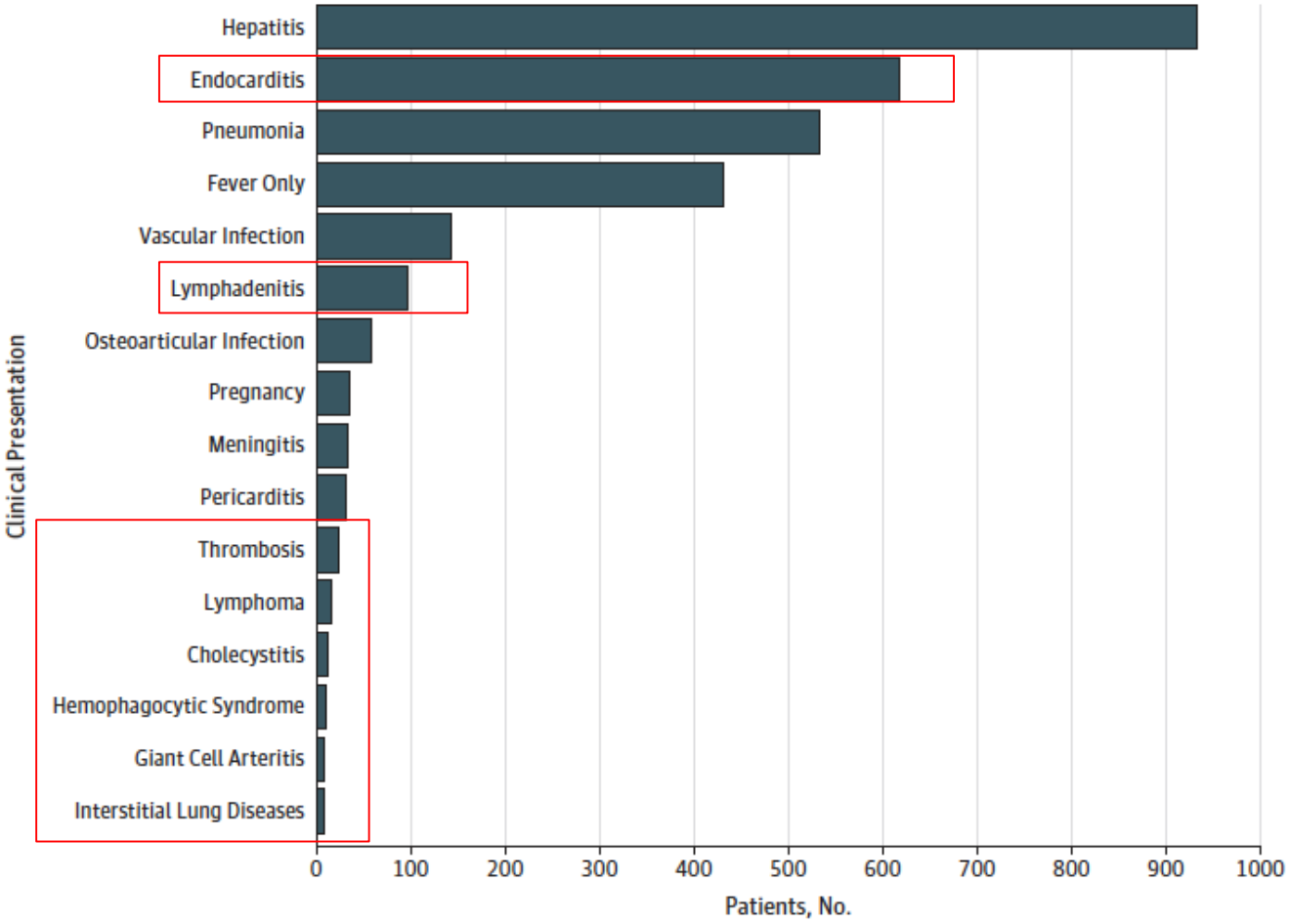
Figure 3. Monthly distribution of Q fever cases in the Etang de Berre area of France: comparison between the years 1996–1999, showing an unusual peak in December 1998 and January 1999.



Tissot Dupont, *Emergin infect Dis*, 2004
Eldin, *J Trop Med Hyg*, 2014

Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

51 ± 17.4 years old, Sex Ratio (Men/women): 2.2



Melenotte, *Jama Network Open*, 2018

Quelles sont les propositions exactes concernant la fièvre Q aigüe ?

A. Responsable d'hépatite
B. Responsable de pneumopathie aigue communautaire
C. Se complique toujours d'endocardite infectieuse en l'absence de traitement
D. Est fatale en l'absence de traitement
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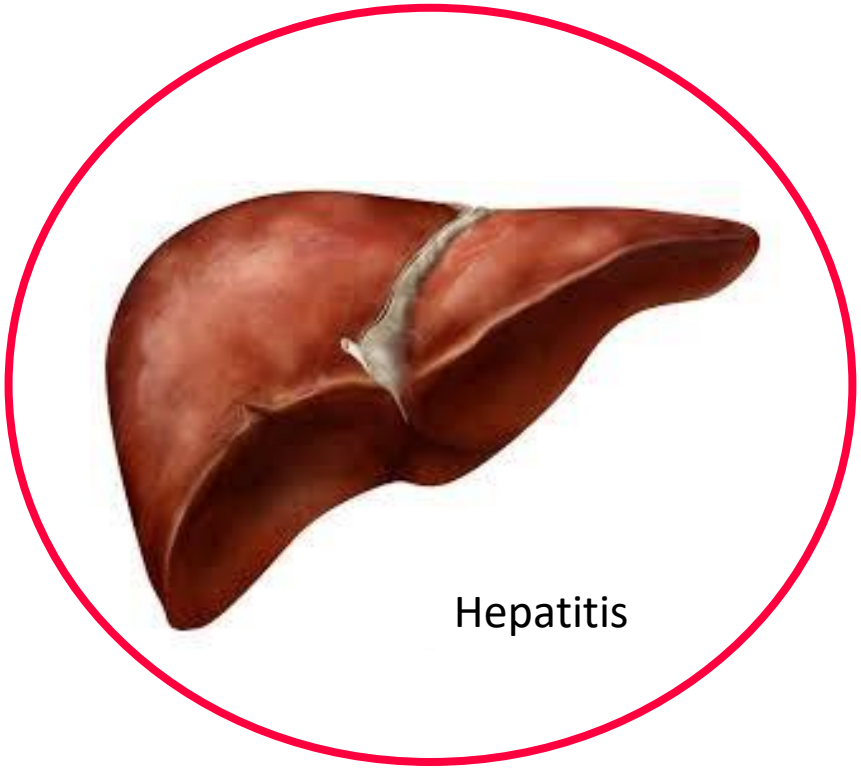
Acute Q fever



Hepatitis

Pneumonia

Q Fever Pneumonia in French Guiana: Prevalence, Risk Factors, and Prognostic Score

Loïc Epelboin,[1,3,a] Cédric Chesnais,[1,4,a] Charlotte Boullé,[4] Anne-Sophie Drogoul,[2] Didier Raoult,[5] Félix Djossou,[1] and Aba Mahamat[1]

[1]Department of Infectious and Tropical Diseases, Centre Hospitalier Andrée Rosemon; [2]Institut Pasteur de Guyane, Cayenne, French Guiana; [3]Department of Infectious and Tropical Diseases, Centre Hospitalier Pitié-Salpêtrière, Paris; [4]UMI 233, Institut de Recherche pour le Développement (IRD)/Université Montpellier 1 (UM1), Montpellier; and [5]URMITE UMR CNRS IRD 6236 IFR 48, Faculté de Médecine, Université de la Méditerranée, Marseille, France

Background. Community-acquired pneumonia (CAP) is the major manifestation of Q fever, an emerging disease in French Guiana. Consequently, the empirical antibiotherapy used for the treatment of CAP combines doxycycline and the recommended amoxicillin. Our objectives were to estimate the prevalence of Q fever pneumonia and to build a prediction rule to identify patients with Q fever pneumonia for empirical antibiotic guidance.

Methods. A retrospective case-control study was conducted on inpatients admitted with CAP in the Department of Infectious Diseases of Cayenne Hospital from 2004 to 2007. Serodiagnosis for *Coxiella burnetii* was performed for all patients. Risk factor analysis was performed using multivariate logistic regression, and a prognostic score was computed using bootstrap procedures. The score performance characteristics were used to choose the best prediction rule to identify patients with Q fever pneumonia.

Results. One hundred thirty-one patients with CAP were included and the Q fever pneumonia prevalence was 24.4% (95% confidence interval [CI], 17.1–31.9). In multivariate analysis, male sex, middle age (age, 30–60 years), headache, leukocyte count $<10 \times 10^9$/L and C-reactive protein level >185 mg/L were independently associated with Q fever pneumonia. Patients with a predictive score ≤3 had a low risk of Q fever pneumonia with a negative predictive value of 0.97 (95% CI, .90–1) and a sensitivity of 0.97 (95% CI, .89–1).

Conclusions. The prediction rule described here accurately identifies patients with low risk of Q fever pneumonia and may help physicians to make more rational decisions about the empirical use of antibiotherapy. Further prospective studies should be performed to validate this score.

Epelboin, *Clin Infect Dis*, 2015

Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

eTable 13. ROC Analysis of IgG Anticardiolipin Antibodies and Acute Q Fever Complications

Variable	AUC	95%CI		*P*
Acute Q fever endocarditis	.67	.58	.76	.0001
Hemophagocytic syndrome	.78	.67	.89	.003
Meningitis	.68	.56	.79	.01
Thrombosis	.72	.6	.85	.002
Alithiasic cholecystitis	.75	.6	.9	.05

AUC: area under curve, CI: confidence interval

Melenotte, *Jama Network Open*, 2018

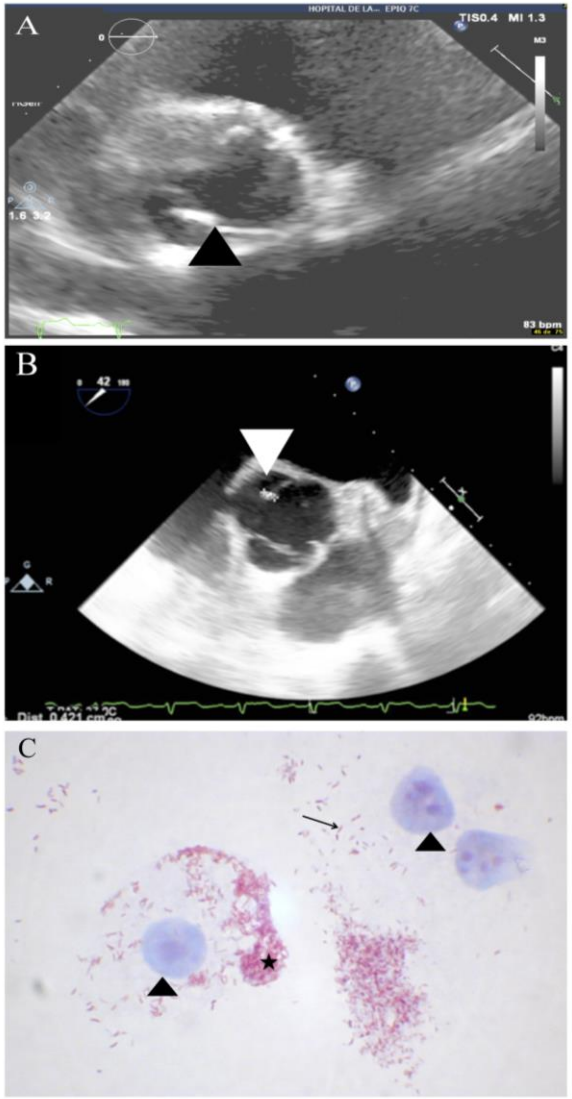
Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

Table 2. Positive aCL Antibodies Associated With Clinical Complications of *Coxiella burnetii* Infection in 1328 Patients With Available IgG aCL Titers

Acute Q Fever Manifestation	No. (%) of Patients		Univariate Analysis *P* Value[a]	Multivariate Logistic Regression[b]	
	IgG aCL ≤22 GPLU (n = 830)	IgG aCL >22 GPLU (n = 498)		OR or IRR (95% CI)	*P* Value
Pneumonia (n = 319)	236 (28.4)	83 (16.7)	<.001	0.5 (0.4-0.6)[c]	<.001
Hepatitis (n = 503)	217 (26.1)	286 (57.4)	<.001	3.7 (2.9-4.7)[c]	<.001
Cholecystitis (n = 5)	1 (0.1)	4 (0.8)	.07	6.9 (0.7-62.8)[d]	.09
Hemophagocytic syndrome (n = 9)	0	9 (1.8)	<.001	NR	NR
Acute endocarditis (n = 42)	13 (1.6)	28 (5.6)	<.001	3.9 (2.0-7.5)[d]	<.001
Thrombosis (n = 21)	10 (1.2)	11 (2.2)	.18	2.1 (0.9-5.2)[d]	.09

Melenotte, *Jama Network Open*, 2018

Acute Q fever endocarditis : a paradigm shift following the systematic use of transthoracic echocardiography during acute Q fever



50 cases of acute Q fever endocarditis

28 % had a preexisting valvulopathy

Clinical paradigm change

70% had positive IgG aCL (>22GPLU)
OR=2.4; 95 confidence interval [1.2-4.9]; p=0.011

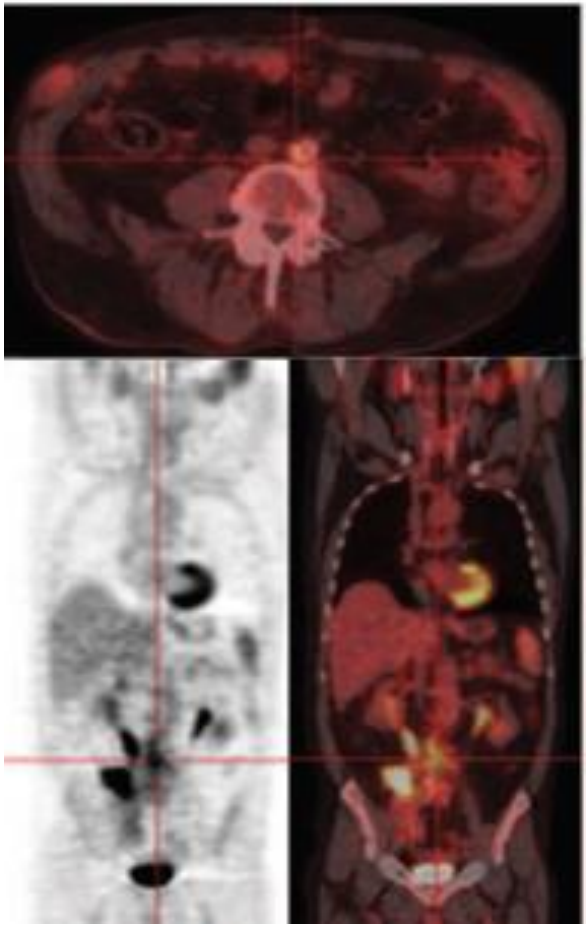
3 positive culture from blood

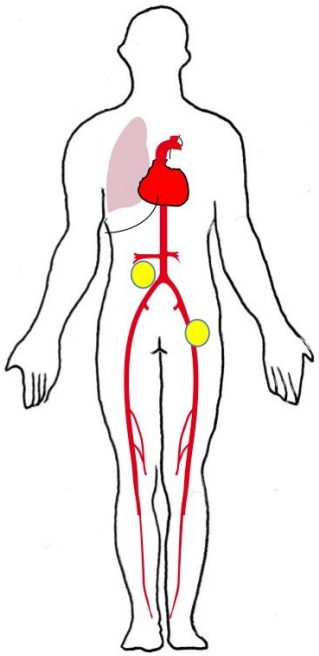
Positive aCL & thrombosis
were independantly associated
with acute Q fever endocarditis

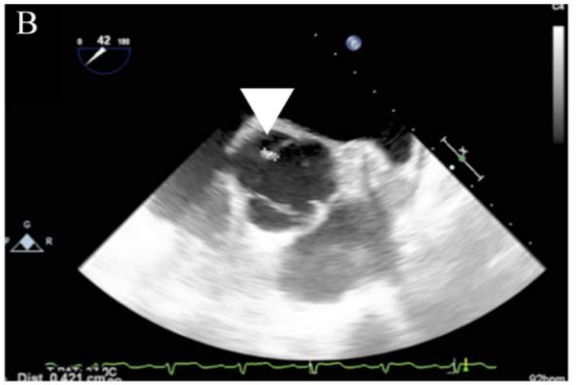
TTE at the acute phase of the disease !

Melenotte et al., *Clinical infectious Diseases, 2018*

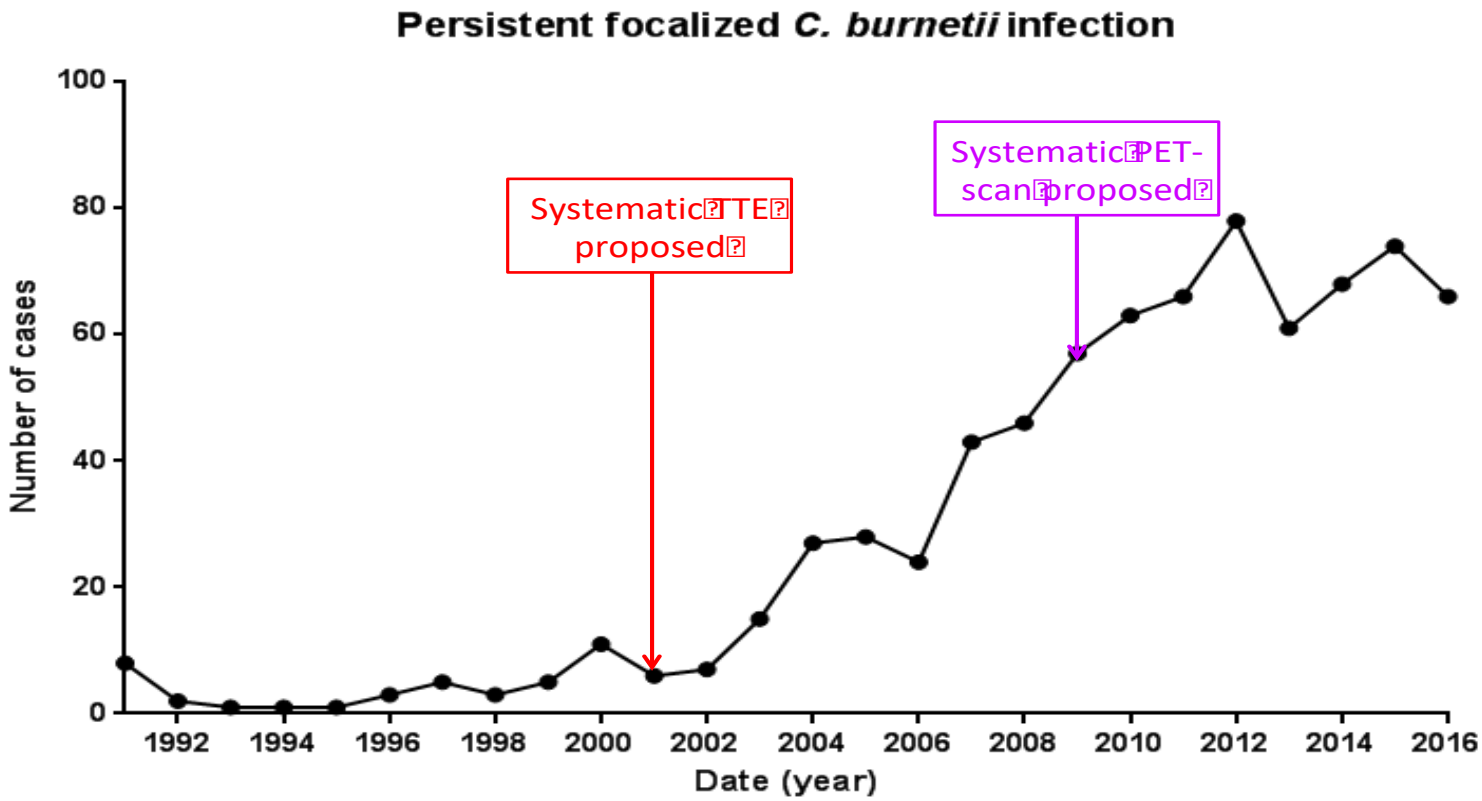
Persistent focalized *C. burnetii* infection







Clinical features and complications of *Coxiella burnetii* infections from the French National Reference Center for Q fever



Melenotte, *Jama Network Open*, 2018, Supplementary data

PET scan and *C. burnetii* infection

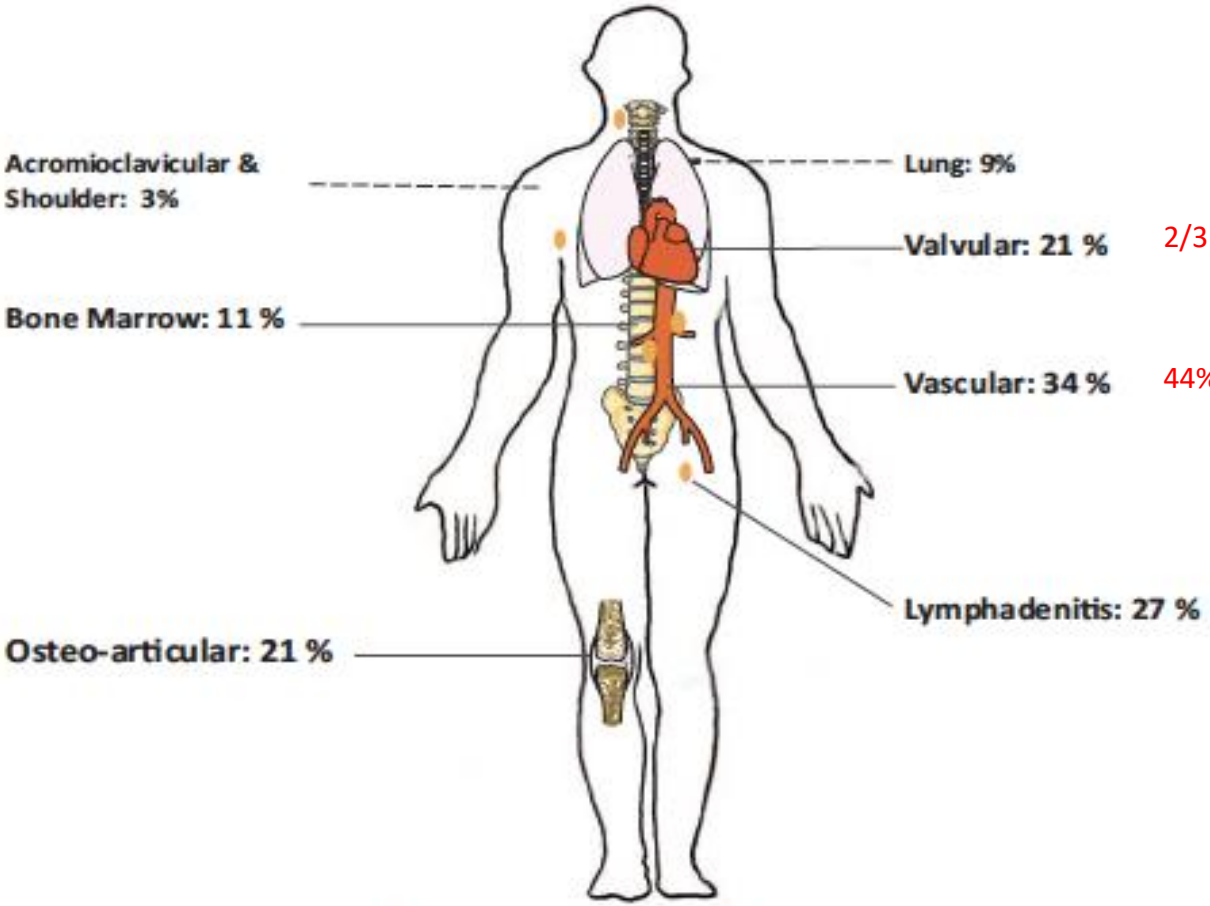


Figure 3. Distribution of Q fever foci identified by ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT=^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

Eldin & Melenotte, *Medicine*, 2016
Ghellab, Melenotte, *Eur J Clin Microb*, 2018

Définition de l’endocardite à *C. burnetii*

Diagnostic Sérologique

Q fever

Diagnosis is serologic

« Acute and chronic Q fever clinical entities may be recognized by serological »

Peacock, *Infect Imm*, 1983

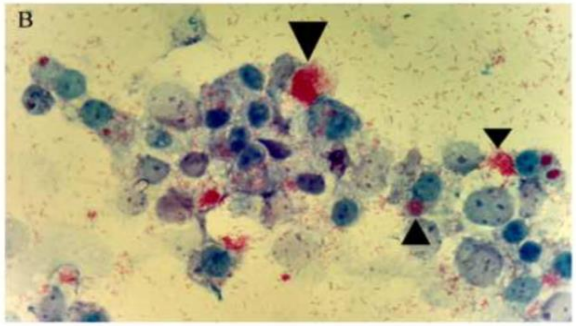
TABLE 2. Results for various cutoff titers of antibodies against phase I and phase II *C. burnetii* in the diagnosis of chronic Q fever

Cutoff titer(s)	Phase	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IgG ≥ 800	I	100.0	99.6	98.1	100.0
	II	100.0	93.4	53.5	100.0
IgG ≥ 1,600	I	80.4	99.8	100.0	99.6
	II	88.5	96.4	71.4	99.9
IgA ≥ 25	I	96.6	96.2	48.6	100.0
	II	96.6	87.0	23.8	100.0
IgA ≥ 50	I	94.6	98.0	63.9	100.0
	II	93.2	91.9	34.0	100.0
IgA ≥ 100	I	85.8	98.9	77.8	99.8
	II	83.1	95.8	52.1	99.9
IgA ≥ 200	I	71.6	99.4	83.3	99.6
	II	72.3	97.9	66.2	99.8
IgA ≥ 400	I	56.8	99.9	97.4	99.3
	II	59.5	99.0	80.0	99.4
IgG ≥ 800 and IgA ≥ 25	I	96.6	100.0	98.1	100.0
	II	96.6	95.3	57.6	100.0
IgG ≥ 800 and IgA ≥ 100	I	85.8	100.0	98.0	99.8
	II	83.1	97.8	74.6	99.9
IgG ≥ 800 and IgA ≥ 400	I	56.8	100.0	97.4	99.3
	II	59.5	99.3	87.0	99.4
IgG ≥ 1,600 and IgA ≥ 400	I	52.7	100.0	100.0	99.3
	II	56.8	99.5	95.0	99.3

Tissot-Dupont, *Infect Imm*, 1994
Fournier, *J Clin Microbiol*, 1998

Isolation of Coxiella burnetii from an acromioclavicular infection with low serological titres

Phase I : IgG, 100, IgM, 0, IgA 0
Phase II : IgG, 200, IgM, 0, IgA, 0



Melenotte, *Int J infect dis*, 2018

Bayesian analysis of Q fever serology to diagnose persistent *C. burnetii* infection, the inconsistence of the serological cutoff

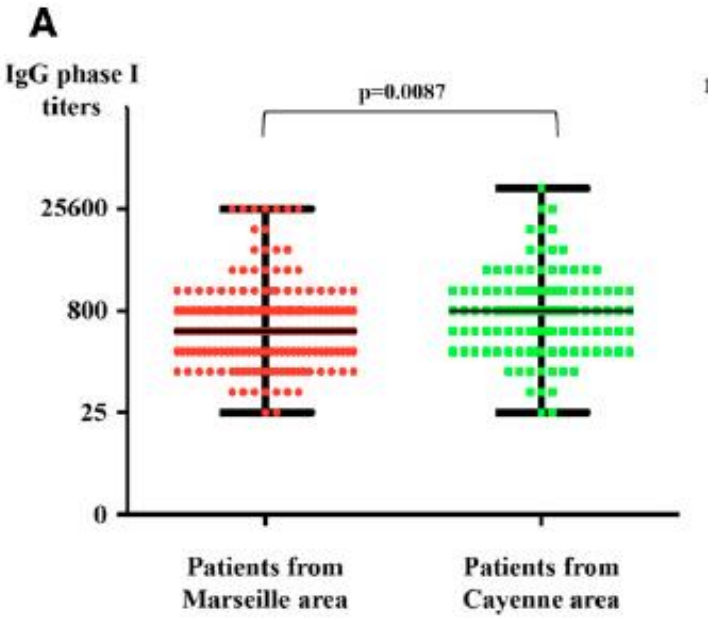
12.9% of persistent *C. burnetii* infection with low serological titers

	Endocarditis N=64	Vascular infection N=18	Osteoarticular infection N=11
Age (Mean ±SD)	62±15	68±14,5	54±31
Sex (Men/female)	47/18	19/0	7/4
Severe immunosuppression	0	1	0
Acute Q fever	14	7	0
Acute Q fever endocartidis	1	0	0
Pneumonia	5	4	0
Hepatitis	7	1	1
Other persistent infectious focus			
Lymphadenitis	2	0	0
Vascular infection	8	-	0
Osteo articular infection	2	0	-
Endocarditis	-	8	2
Serology			
First Phase I IgG (Median [IQR 25-75])	200 [100-400]	300 [125-400]	200 [125-400]
Max Phase I IgG (Median [IQR])	400 [100-400]	400 [200-400]	200 [125-400]
Last Phase I IgG (Median [IQR])	100 [75-400]	200 [100-400]	200 [100-400]
Outcome			
Death	5	3	0

Melenotte, *Exp Rev of anti infect therapy*, 2020

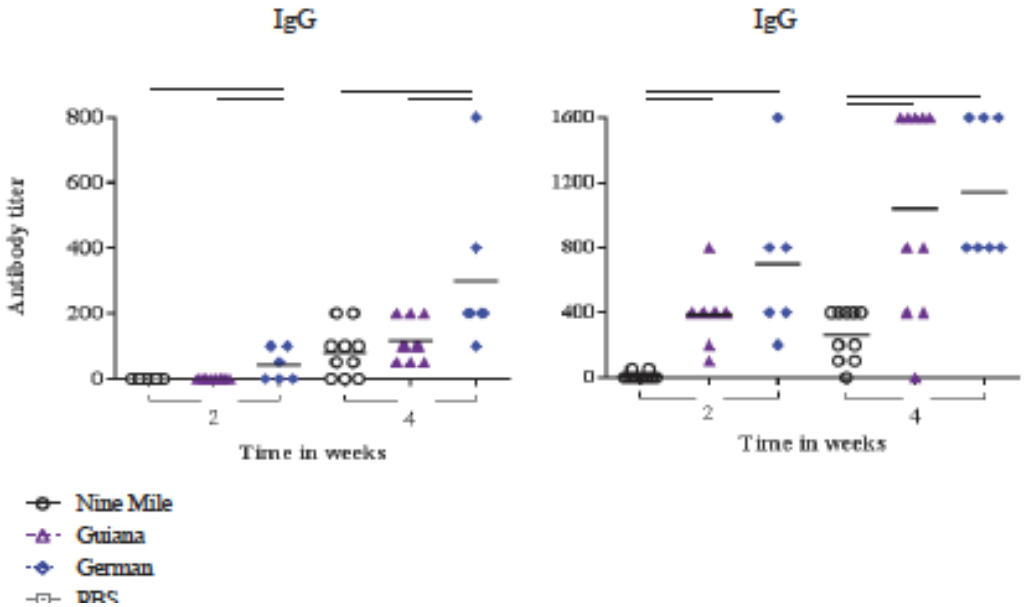
Réponse sérologique selon la zone géographique

In human



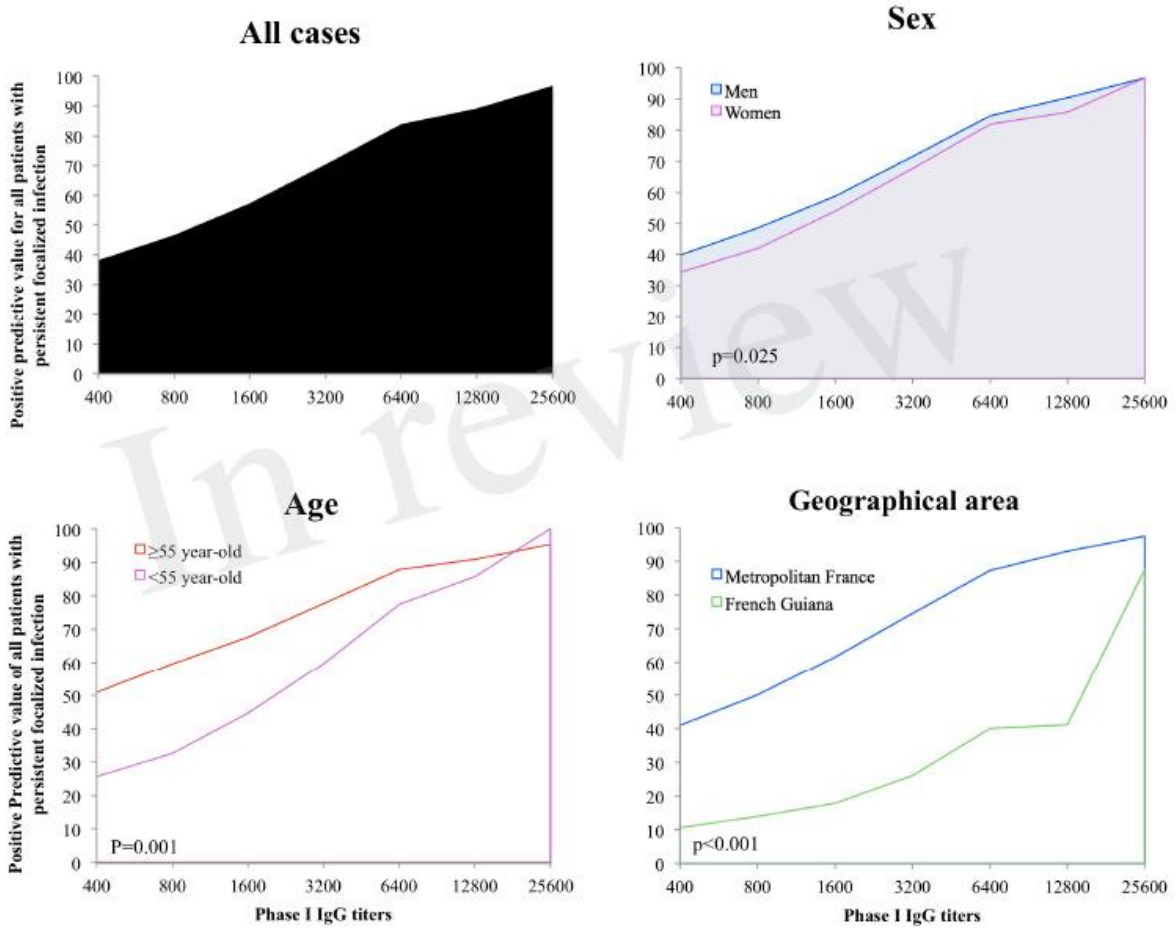
Edouard, *Trop Med hyg*, 2013

In mouse



Melenotte, *Clinical Microbiol Infect*, 2020

Bayesian analysis of Q fever serology to diagnose persistent *C. burnetii* infection, the inconsistence of the serological cutoff



Melenotte, *Unpublished* ,2019

From Q fever to *C. burnetii* persistent infection: a changing paradigm

Organic lesion

+

Microbiological evidence

(serology, PCR, culture)

Raoult, *Clin infect Dis*, 2017
Eldin, *CMR*, 2017
Melenotte, *JAMA Open Network*, 2018

TABLE 3 Definition criteria for *C. burnetii* persistent focalized infections

Criterion or diagnosis type	Definition for *C. burnetii*: Endocarditis	Vascular infection	Prosthetic joint arthritis	Osteoarticular infection (without prosthesis)	Lymphadenitis
Criteria					
Definite	Positive culture, PCR, or immunochemistry of a cardiac valve	Positive culture, PCR, or immunochemistry of an arterial sample (prosthesis or aneurysm) or a periarterial abscess or a spondylodiscitis linked to aorta	Positive culture, PCR, or immunochemistry of a periprosthetic biopsy specimen or joint aspirate	Positive culture, PCR, or immunochemistry of bone or synovial biopsy specimen or joint aspirate	Positive culture, PCR, immunohistochemistry, or fluorescence *in situ* hybridization of lymphadenitis
Major	Microbiology—positive culture or PCR of the blood, an embolus or serology with IgG1 antibody titer of ≥6,400 mg/dl. Evidence of endocardial involvement—(i) Echocardiogram positive for infective endocarditis: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; new partial dehiscence of a prosthetic valve; or new valvular regurgitation (worsening or changing of preexisting murmur is not sufficient). (ii) PET scan displaying a specific valve fixation and mycotic aneurism.	Microbiology—positive culture, PCR of the blood or emboli, or serology with IgG1 antibody titer of ≥6,400 mg/dl. Evidence of vascular involvement—(i) CT scan: aneurysm or vascular prosthesis + periarterial abscess, fistula, or spondylodiscitis. (ii) PET scan specific fixation on an aneurism or vascular prosthesis.	Microbiology—(i) Positive culture or PCR of the blood. (ii) Positive *Coxiella burnetii* serology with IgG1 antibody titer of ≥6,400 mg/dl. Evidence of prosthetic involvement—(i) CT scan or MRI positive for prosthetic infection: collection or pseudotumor of the prosthesis. (ii) PET scan or indium leukocyte scan showing a specific prosthetic hypermetabolism consistent with infection.	Microbiology—(i) Positive culture or positive PCR of the blood. (ii) Positive serology with IgG1 antibody titer of ≥800 mg/dl. Evidence of bone or joint involvement—(i) Clinical arthritis, osteitis, or tenosynovitis. (ii) CT scan or ultrasonography (for joint) or MRI: osteo-articular destruction, joint effusion, intra-articular collection, spondylodiscitis, synovitis, acromio-clavicular localization. (iii) PET scan or indium leukocyte scan showing a specific osteo-articular uptake.	Microbiology—(i) Positive culture or positive PCR of the blood. (ii) Positive serology with IgG antibody titer of ≥800 mg/dl. Evidence of lymph node involvement—(i) Clinical lymphadenitis. (ii) CT scan or ultrasonography (for joint) or MRI: lymphadenitis of >1 cm. (iii) PET scan showing specific lymph node uptake.
Minor	Predisposing heart condition (known or found on ultrasound). Fever, temp of >38°C. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (observed during PET scan), intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, or rheumatoid factor. Serological evidence: IgG1 antibody titer of ≥800 and <6,400 mg/dl.	Serological IgG1 antibody titer of ≥800 and <6,400 mg/dl. Fever, temp of ≥38°C. Emboli. Underlying vascular predisposition (aneurysm or vascular prosthesis).	Presence of a joint prosthesis (indispensable criterion). Fever, temp of >38°C. Joint pain. Serological evidence: positive *C. burnetii* serology with IgG1 antibody titer of >800 and <6,400 mg/dl.	Serological IgG1 antibody titer of ≥400 and <800 mg/dl. Fever, temp of ≥38°C. Mono- or polyarthralgia.	Serological IgG1 antibody titer of ≥400 and <800mg/dl. Fever, temp of ≥38°C.
Diagnoses					
Definite	(i) 1 definite criterion, (ii) 2 major criteria, or (iii) 1 major criterion and 3 minor criteria (including 1 microbiological characteristic and a cardiac predisposition)	(i) 1 definite criterion, (ii) 2 major criteria, or (iii) 1 major criterion and 2 minor criteria (including 1 microbiological characteristic and a vascular predisposition)	(i) 1 definite criterion, (ii) 2 major criteria, or (iii) 1 major criterion and 3 minor criteria (including 1 piece of microbiology evidence and presence of a joint prosthesis)	(i) 1 definite criterion, (ii) 2 major criteria, or (iii) 1 major criterion and 3 minor criteria (including 1 microbiological characteristic)	(i) 1 definite criterion, (ii) 2 major criteria, or (iii) 1 major criterion and 2 minor criteria (including 1 microbiological characteristic)
Possible	(i) 1 major criterion and 2 minor criteria (including 1 microbiological characteristic and a cardiac predisposition) or (ii) 3 minor criteria (including 1 microbiological characteristic and a cardiac predisposition)	Vascular predisposition, serological evidence, and fever or emboli	(i) 1 major criterion and 2 minor criteria (including 1 piece of microbiology evidence and presence of a joint prosthesis) or (ii) 3 minor criteria (including positive serology and presence of a joint prosthesis)	(i) 1 major criterion and 2 minor criteria or (ii) 3 minor criteria	(i) 1 major criterion and minor criterion or (ii) 2 minor criteria

Eldin, *Clin Microb Rev*, 2017

Chronic Q fever in the Netherlands

TABLE 1 Dutch consensus guidelines on chronic Q fever diagnosis[a]

Diagnosis	Characteristics[b]
Proven chronic Q fever	Positive *Coxiella burnetii* PCR in blood or tissue[c] OR an IFA titer of ≥800 or 1,024 for *C. burnetii* phase I IgG[d] with either definite endocarditis according to the modified Duke criteria (19) or proven large vessel or prosthetic infection by imaging studies (FDG-PET [18], CT, MRI, or AUS)
Probable chronic Q fever	IFA titer of ≥800 or 1,024 for *C. burnetii* phase I IgG[c] AND valvulopathy not meeting the major criteria of the modified Duke criteria (19) OR known aneurysm and/or vascular or cardiac valve prosthesis without signs of infection by imaging studies (TEE/TTE, FDG-PET [18], CT, MRI, or AUS) OR suspected osteomyelitis, pericarditis, or hepatitis as manifestations of chronic Q fever OR pregnancy OR symptoms and signs of chronic infection such as fever, weight loss, night sweats, hepatosplenomegaly, and persistent raised ESR and CRP OR granulomatous tissue inflammation as proven by histological examination OR immunocompromised state
Possible chronic Q fever	IFA titer of ≥800 or 1,024 for *C. burnetii* phase I IgG[d] without manifestations meeting the criteria for proven or probable chronic Q fever

[a] See reference 15.
[b] IFA, immunofluorescence assay; FDG-PET, fluorodeoxyglucose positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; AUS, abdominal ultrasound; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
[c] In the absence of acute infection.
[d] Cutoff is dependent on the IFA technique used (developed in-house or a commercial IFA technique, respectively).

Kampschreur, *JCM*, 2014

Facteurs de risque d'endocardite infectieuses à *Coxiella burnetii*

Facteurs de risque d'Endocardite

1985-2000 -Fr

12 patients avec fièvre Q aigüe ont développé une EI

102 endocardite persistante à *C. burnetii*

200 patients avec une fièvre Q aigüe

-valvulopathie pré-existante

-valve prothétique

2007-2012-Fr

72 patients (ETT et prophylaxie), 31% de valvulopathie (inconnue auparavant 33%)

1999-2015-USA

140 endocardites, 52% valvulopathie pré-existante

CNR: ETT et si valvulopathie, chimio-prophylaxie DP 12 mois

Million, *Lancet Infect Dis*, 2010
Fenollar, *Clin Infect Dis*, 2001
Million, *Clin Infect Dis*, 2013
Straily, *Clin Infect Dis*, 2017

Table 1. Evolution to Persistent *Coxiella burnetii* Infection in 1806 Patients With Acute Q Fever

Patient Characteristic	No. (%) of Patients		Univariate Analysis P Value[a]	Logistic Regression			
	Acute Q Fever Without Persistent C burnetii Infection (n = 1668)	Acute Q Fever Progressing to Persistent C burnetii Infection (n = 138)		Univariate		Multivariate	
				OR (95% CI)	P Value	OR (95% CI)	P Value
Immunosuppression							
No	1608 (96.4)	132 (95.7)	NA	1 [Reference]	NA	NA	NA
Yes	60 (3.6)	6 (4.3)	.63	1.2 (0.5-2.9)	.65	NR	NA
Valvulopathy							
No	1498 (89.8)	53 (38.4)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	170 (10.2)	85 (61.6)	<.001	14.1 (9.7-20.6)	<.001	9.8 (6.1-15.8)	<.001
Sex							
Male	1115 (66.8)	110 (79.7)	.002	1.9 (1.3-3.0)	.002	1.9 (1.1-3.1)	.01
Female	553 (33.2)	28 (20.3)	NA	1 [Reference]	NA	1 [Reference]	NA
Age at baseline, median (IQR), y	48 (37-59)	55.5 (46-68)	<.001	1.03 (1.02-1.04)	<.001	1.01 (1.00-1.03)	.03
Year category at baseline							
Before 2009	186 (11.2)	55 (39.9)	NA	1 [Reference]	NA	1 [Reference]	NA
2009-2012	680 (40.8)	32 (23.2)	NA	4.6 (3.1-7.0)	<.001	3.2 (1.9-5.3)	<.001
After 2012	802 (48.1)	51 (37.0)	.03	0.7 (0.5-1.2)	.19	0.8 (0.5-1.4)	.42
Pneumonia							
No	1211 (72.6)	115 (83.3)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	457 (27.4)	23 (16.7)	.005	0.5 (0.3-0.8)	.007	0.6 (0.3-1.0)	.07
Lymphadenitis							
No	1616 (96.9)	124 (89.9)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	52 (3.1)	14 (10.1)	<.001	3.5 (1.9-6.5)	<.001	3.3 (1.6-7.1)	.002
Thrombosis							
No	1657 (99.3)	133 (96.4)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	11 (0.7)	5 (3.6)	.005	5.7 (1.9-16.5)	.002	6.8 (1.9-24.8)	.004
Acute endocarditis							
No	1636 (98.1)	120 (87.0)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	32 (1.9)	18 (13.0)	<.001	7.7 (4.2-14.1)	.001	3.8 (1.5-9.8)	.006
IgG titer to phase I on first serologic analysis							
≤800	1476 (88.5)	84 (60.9)	NA	1 [Reference]	NA	NA	NA
>800	192 (11.5)	54 (39.1)	<.001	4.9 (3.4-7.2)	<.001	NR	NA
Maximum IgG titer to phase I							
≤800	1313 (78.8)	48 (34.8)	NA	1 [Reference]	NA	1 [Reference]	NA
>800	354 (21.2)	90 (65.2)	<.001	7.0 (4.8-10.1)	<.001	5.2 (3.3-8.1)	<.001
IgG aCL antibody titer							
≤90 GPLU	722 (77.4)	59 (67.8)	NA	1 [Reference]	NA	NA	NA
>90 GPLU	211 (22.6)	28 (32.2)	.048	1.6 (1.0-2.6)	.046	NR	NA
Positive C burnetii PCR							
No	1481 (91.3)	105 (77.8)	NA	1 [Reference]	NA	1 [Reference]	NA
Yes	142 (8.7)	30 (22.2)	<.001	3.0 (1.9-4.6)	<.001	1.9 (1.0-3.4)	.03

Predictive factor for evolving to persistent focalized *C. burnetii* infection

Valvulopathy
Men
Lymphadenopathy
Thrombosis
Acute Q fever endocarditis
IgG phase I>800
Positive PCR in blood

Melenotte, *Jama Network Open*, 2018

Facteurs de risque

105 patients avec des infections prouvée (n=44), probables (n=28) ou possibles (n=33)

Table 3. Results of multivariate analyses of risk factors for development of chronic Q fever, the Netherlands*

	All chronic Q fever		Proven and probable chronic Q fever		Proven chronic Q fever	
Risk factor*†	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Valvular surgery†‡	31.5 (3.99–249)	0.001	47.7 (5.87–387)	0.000	43.6 (4.70–405)	0.001
Vascular prosthesis‡§	10.4 (2.17–50.0)	0.003	14.9 (2.96–75.2)	0.001	26.8 (4.88–147)	0.000
Aneurysm§¶	8.65 (1.74–42.9)	0.008	13.5 (2.60–70.4)	0.002	25.9 (4.55–147)	0.000
Renal insufficiency¶#	–	–	9.08 (1.44–57.2)	0.019	16.0 (2.06–123)	0.008
Nonhematologic malignancy	3.90 (1.33–11.5)	0.013	–	–	–	–
Age, continuous	1.03 (1.01–1.06)#	0.005	1.06 (1.03–1.09)#	0.000	1.06 (1.02–1.11)#	0.005

Kamprschreur, *Emerging Infect Dis*, 2012

Endocardite à *C. burnetii*,
Quelles lésions histologiques?
Analyse histologique des valves cardiaques de 28 patients

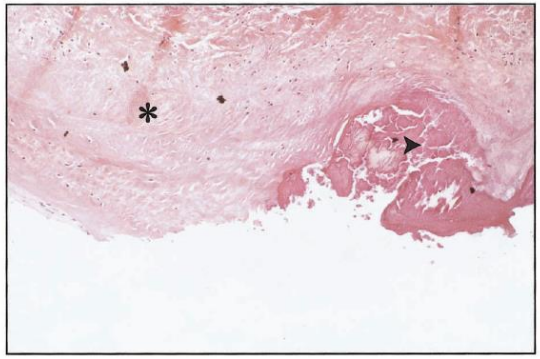


Figure 1. Aortic valve from a patient with Q fever endocarditis. Note the extensive fibrosis of the connective valve tissue (*) and focal calcifications on the valve surface *(arrow)*. (Hematoxylin-eosin-saffron stain; original magnification, ×100.)

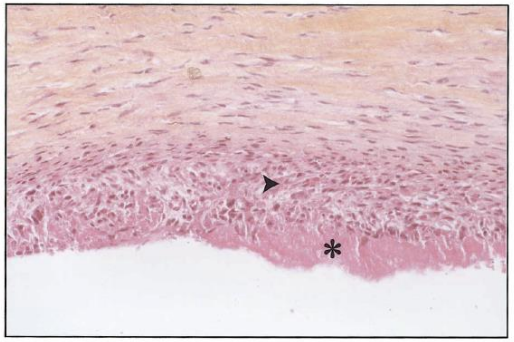


Figure 2. Mitral valve from a patient with Q fever endocarditis. Note the small vegetation on the surface of the valve tissue (*) with a mononuclear inflammatory cell infiltrate *(arrow)*. (Hematoxylin-eosin-saffron stain; original magnification, ×250.)

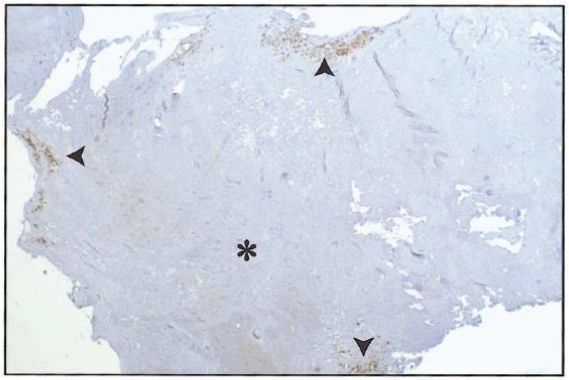
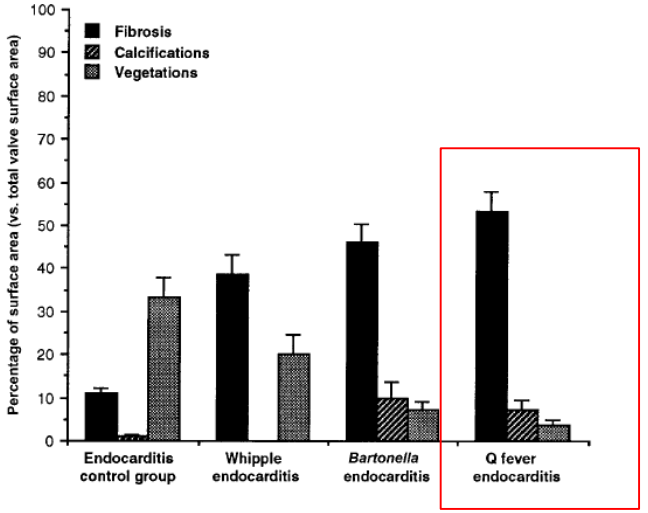


Figure 4. Focal and small inflammatory infiltrates with immunostained macrophages *(arrows)*, representing a small area in the whole valve tissue surface. The valve stroma is reorganized and fibrotic (*). (Immunoperoxidase staining with an anti-CD68 monoclonal antibody; original magnification, ×100.)



Lepidi, *J Infect Dis,* 2003
Lepidi, *J Infect Dis*, 2004

Endocardites infectieuses

1983-2006

104 endocardites infectieuses

Facteurs déterminants associées à la mortalité:

-âge, OR: 1,1; IC 95 [1,05-1,18] p=0,003

-Evènement vasculaire au moment du diagnostic OR: 7,09; IC95 [2-25] p=0,001

-EI sur valve prothétique OR: 6; IC95 [1,47-24] p=0,044

-Absence de décroissance x4 des IgGI IgAI à 1 an OR: 6; IC95 [5,69-32] p=0,049

(Hommes, taux élevés IgG phase I, retard à l'initiation du traitement)

Facteurs associés à la rechute

-EI sur valve prothétique (OR: 21 IC95 [2-221] p=0,01)

-Traitement <18 mois **(**OR: 9,69 IC95 [1-86] p=0,042)

Million, *Lancet Infect Dis*, 2010

Endocardites infectieuses à *C. burnetii*

	<1 month (n=15)	≥1–12 months (n=15)	13–24 months (n=5)	>24 months (n=11)
PCR	9/12 (75%)	6/10 (60%)	3/5 (60%)	2/8 (25%)
Immunohistochemistry	4/10 (40%)	4/7 (57%)	1/4 (25%)	1/6 (14%)
Culture	12/15 (80%)	6/13 (46%)	1/5 (20%)	0/10 (0%)
Pathology	11/13 (85%)	7/8 (87%)	1/2 (50%)	1/6 (14%)

Table 3: Results of the analysis of excised valves according to delay of surgery

Million, *Lancet Infect Dis*, 2010

Endocardites infectieuses à *C. burnetii*

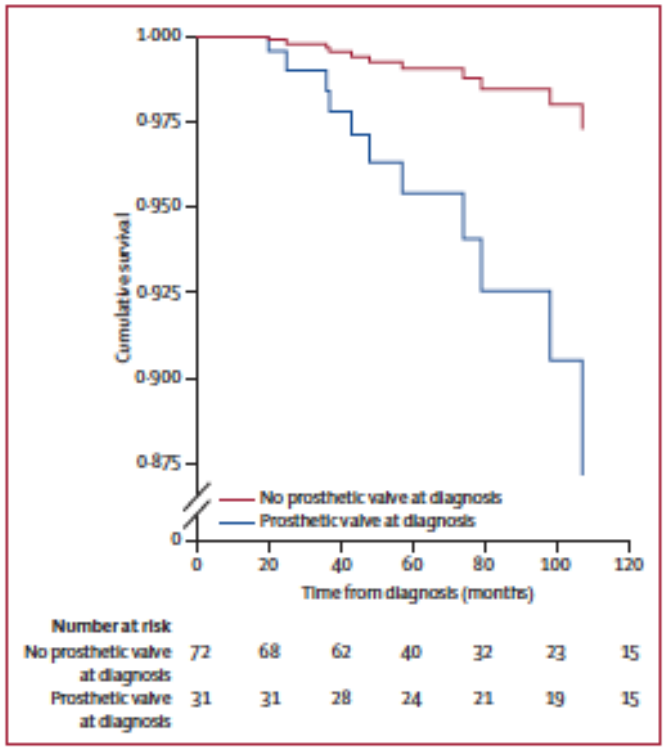


Figure 4: Cox regression analysis for prosthetic valve endocarditis

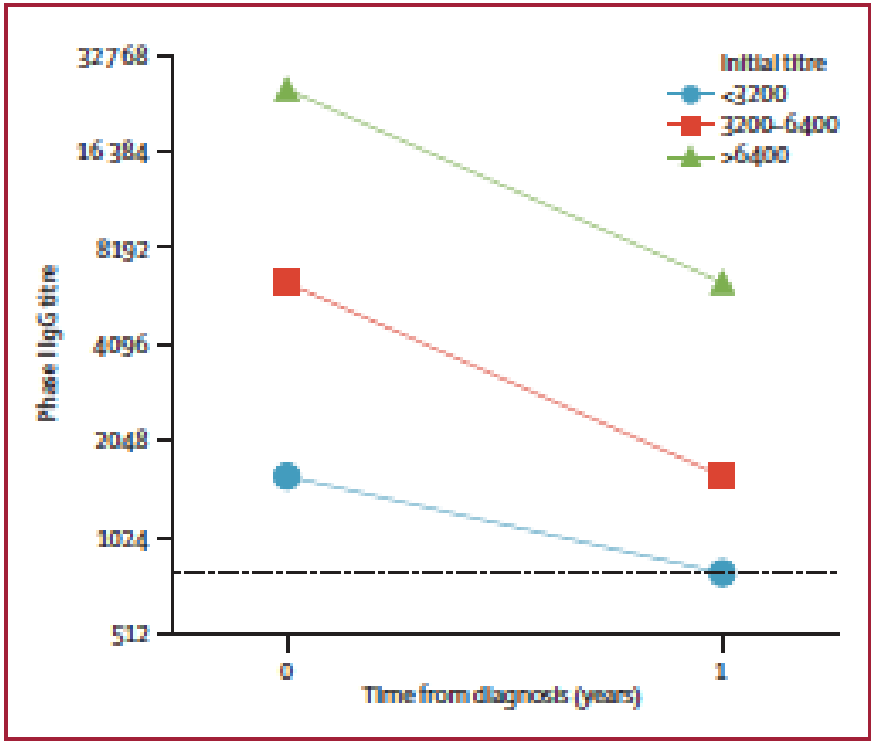


Figure 6: Phase I IgG median at 1 year according to initial titre
p<0·0001 among the three groups at 1 year. Dotted line indicates the cut-off phase I IgG of 800.

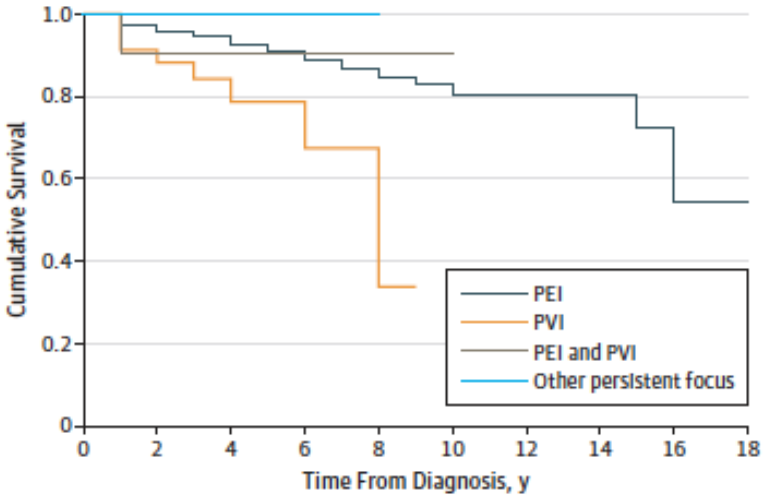
Million, *Lancet Infect Dis*, 2010

Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

58 patients died

C. burnetii persistent focal infections HR=10.9, 95% CI [3.2-37.1], p<.001
Endocarditis (HR=2.4, 95% CI [1.1-5.1], p<.01)
Vascular infection (HR=3.1, 95% CI [1.7-5.7], p<.01)

Figure 3. Kaplan-Meier Survival Analysis



No. at risk

PEI	532	245	157	105	63	35	22	16	8	0
PVI	96	24	12	6	2	0	0	0	0	0
PEI and PVI	49	18	9	5	2	2	0	0	0	0
Other persistent focus	89	18	9	2	1	0	0	0	0	0

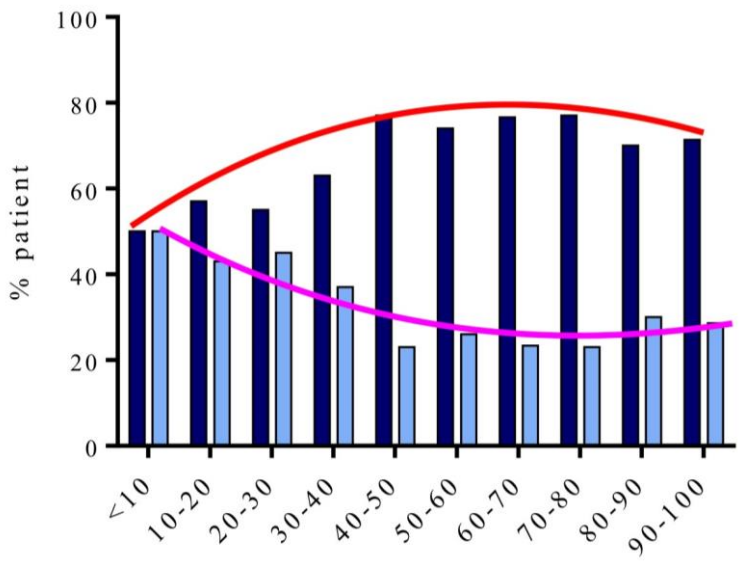
Includes patients with *Coxiella burnetii* infection. PEI indicates persistent endocarditis; PVI, persistent vascular infection.

Melenotte, *Jama Network Open*, 2018

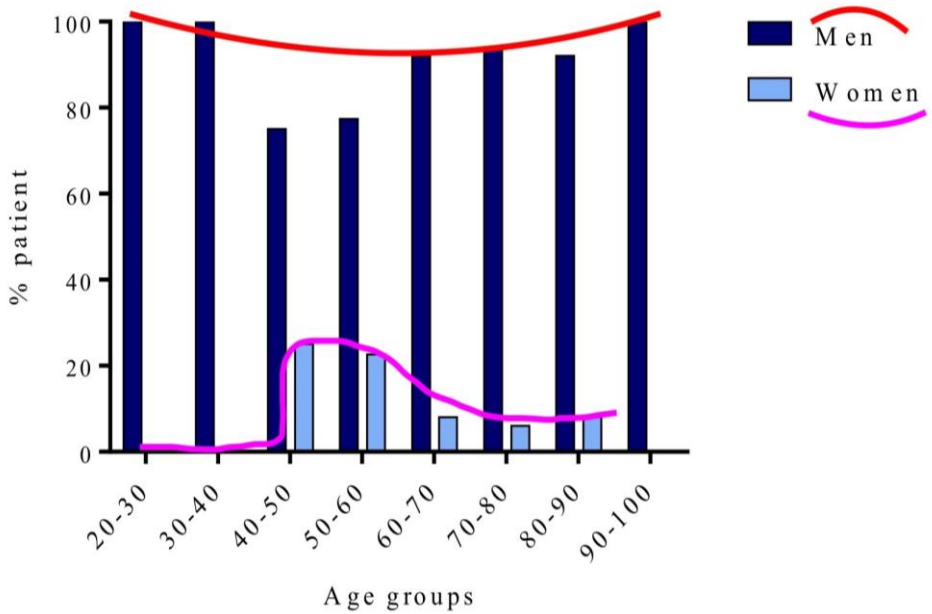
The sexual dimorphism in Q fever

Sex ratio : 2.2
Children (<16 yo) :0.9

C. burnetii persistent focalized endocarditis



C. burnetii persistent vascular infection



Being male

was associated with an increased aCL secretion in the acute phase of the disease

was associated with an increased risk of vascular infection independent of age (odds ratio [OR], 3.4; 95%CI, 2.0-5.7; P < .001).

Melenotte, *Clin Microbiol Infect*, 2018

Chronic Q fever in the Netherlands

284 « chronic Q fever », 151 (53,7%) prouvée, 64 (22,5%) probable, 69 (24,3%) possible
Parmi les prouvées et les probables, 56,7% infections vasculaires, 34,9% d'endocardites
Mortalité globale: 13%, 9,3% pour les endocardites infectieuses, 18% pour les infections vasculaires

TABLE 5 Adjusted risk factors for mortality among patients with proven and probable chronic Q fever

Multivariable model with risk factors included[a]	All-cause mortality (HR [95% CI])[b]	Mortality definitely or probably due to chronic Q fever (HR [95% CI])
Model 1		
Age in 10 yr (continuous)	1.57 (1.13–2.19)	1.68 (1.09–2.59)
Proven chronic Q fever	1.63 (0.62–4.26)	5.65 (0.71–44.82)
Vascular infection	1.48 (0.73–2.99)	1.81(0.71–4.59)
Acute presentation with chronic Q fever	1.96 (1.02–3.78)	2.75 (1.27–5.95)
Model 2		
Age in 10 yr (continuous)	1.59 (1.14–2.21)	1.71 (1.11–2.62)
Proven Q fever	1.84 (0.71–4.76)	6.66 (0.84–52.59)
Vascular infection	1.34 (0.63–2.85)	1.46 (0.53–3.99)
Surgical treatment of chronic Q fever	1.51 (0.75–3.04)	2.09 (0.89–4.89)

[a] Two multivariable models were constructed because of multicollinearity between acute presentation with chronic Q fever and surgical treatment of chronic Q fever. Model 1 includes acute presentation with chronic Q fever and model 2 surgical treatment of chronic Q fever.
[b] HR, hazard ratio; 95% CI, 95% confidence interval.

Kampschreur, *JCM*, 2014

Chronic Q fever related complications in the Netherlands

Complications chez 38% des patients (166/439),

61% prouvées (153/249), 15% probables (11/74), 2% possibles (2/116).

Table 2
Complications and mortality in all chronic Q fever patients

	All patients
N (%)	439 (100)
Follow-up duration (median) (IQR)	4.3 years (2.0–5.4)
Complications of Q fever	
Complications per patient	1.5
Patients with complications (%)	166 (38)
Time to first complication[a] (median)	0.0 years
Before initiation of treatment[a,b] (%)	101 (61)
<12 weeks after start of treatment[a,b] (%)	109 (66)
<24 weeks after start of treatment[a,b] (%)	113 (68)
Type of complication[c]	
Acute aneurysm (non-fistula)[d] (%)	63 (14)
Fistula (%)	24 (5)
Abscess (non-cardiac) (%)	45 (10)
Spondylodiscitis/osteomyelitis (%)	20 (5)
Heart failure (%)	55 (13)
Arterial embolic complications (%)	21 (5)
Mortality	
Deceased (%)	118 (27)
Definitely/probably chronic Q fever related (%)	66 (15)
Possibly Q fever-related (%)	13 (3)
Time diagnosis to death [e] (median)	0.7 years
<12 weeks after start of therapy[b,e] (%)	19 (29)
<24 weeks after start of therapy[b,e] (%)	23 (35)
Cause of death[f]	
Complications of aneurysm (%)	24 (20)
Cardiac causes[g] (%)	17 (14)
Surgical complications (%)	10 (8)
Arterial embolic complications (%)	6 (5)
Other (%)	61 (52)

-Anévrysmes (14%)
-Insuffisance cardiaque (13%)
-Abcès non cardiaque (10%)

Mortalité globale :
38% pour les infections prouvées
22% pour les probables

Van Roeden, *Clin Microbiol Infect*, 2019

C. burnetii vascular infection and complications

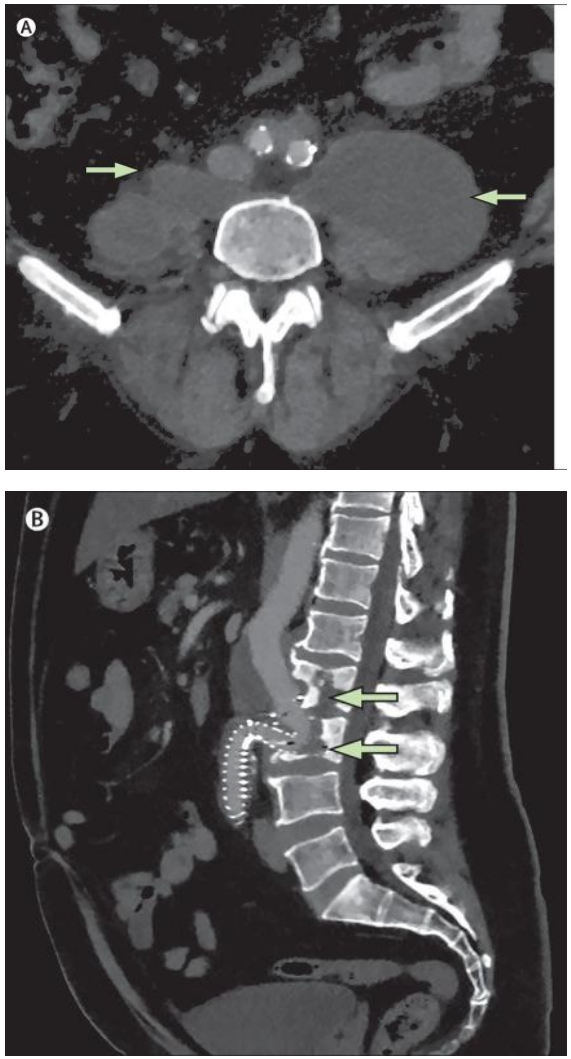


Table 5 List of major surgical complications that occurred in 11 patients[a]

Death	5 (19%)
Renal failure	2 (7%)
Pneumonia	1 (4%)
Graft thrombosis	1 (4%)
Anastomotic leak/ pseudoaneurym	3 (11%)
Graft infection	3 (11%)
Vertebral ostomyelitis	3 (11%)
Aortoduodenal fistula	2 (7%)

[a] The presence/absence of surgical complications was reported in only 27 patients.

Wegdam-Blans, *Eur J Endovasc Surg*,2011

Infections vasculaires à *C. burnetii*

1986-2015: 100 patients

Surgery to treat vascular infection

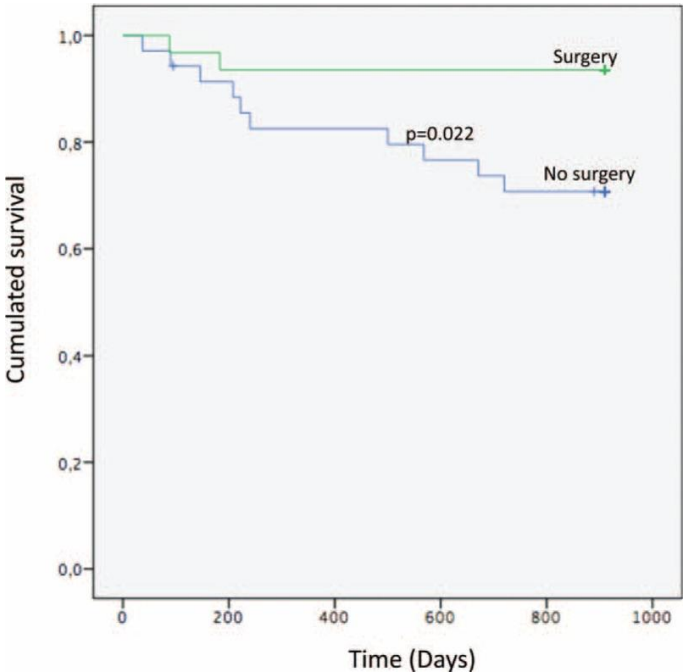
->↗survival at 2,5 years using univariate analysis [hazard ratio: 0.17 [95% CI]: [0.039–0.79]; *P* = 0.024].

->good serological outcome (74.1% vs 57.1% of patients, *P* = 0.03).

Surgery to treat vascular graft infections (n = 47)

-> positive impact on serological outcome at 2 and a half years (85.7% vs 42.9%, *P* < 0.001) [hazard ratio: 0.40 [95% CI]: [0.17–098]; *P* = 0.046]

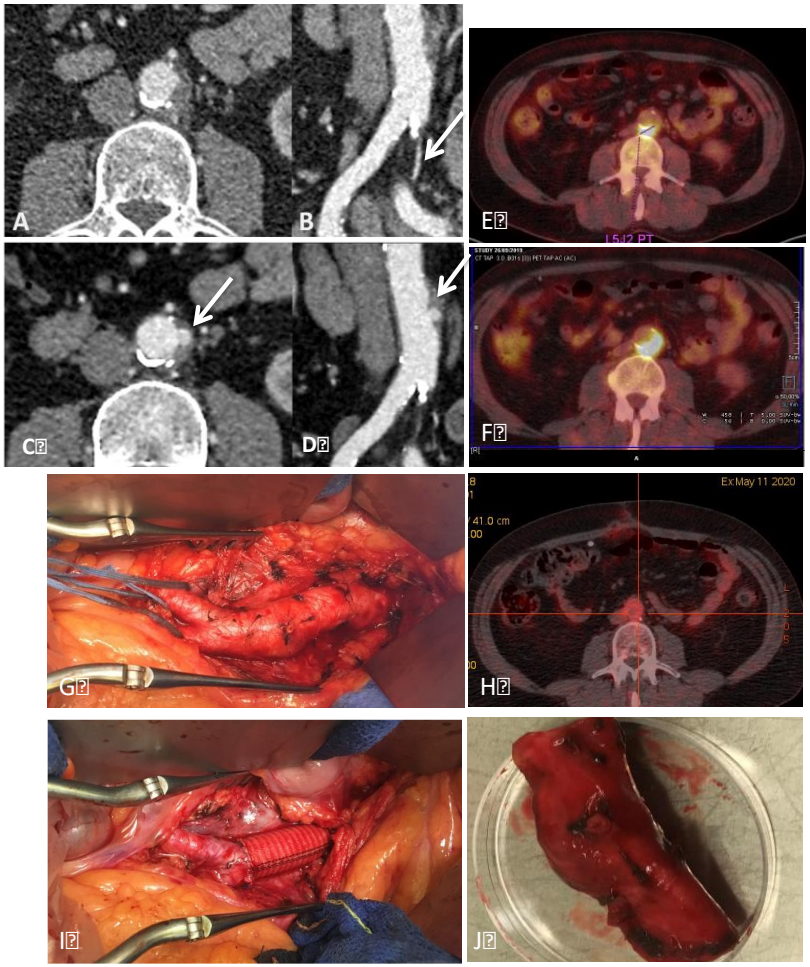
-> lower, not statistically significant, mortality (11.1% vs 27.6% of deaths, *P* = 0.19).



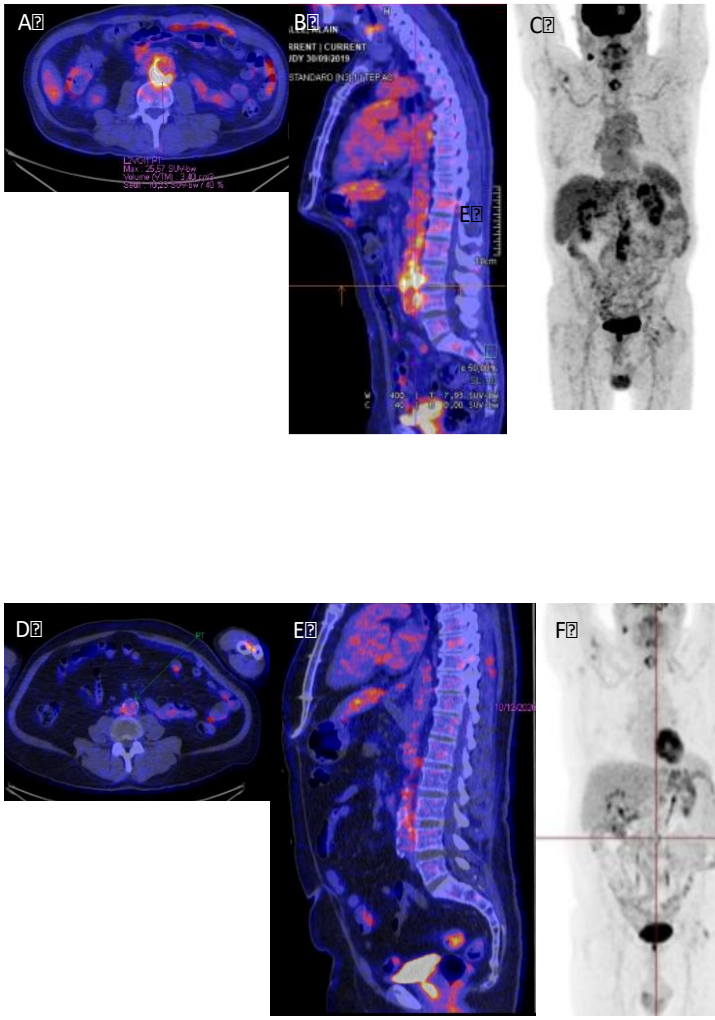
Botelho-Nevers, *Eur J Infect Dis*, 2007
Eldin, *Medicine*, 2017

C. burnetii atherosclerotic plaque vascular infection

Patient 1 case of *C. burnetii* atherosclerotic vascular plaque infection on vascular ectasia



C. burnetii atherosclerotic plaque vascular infection without vascular aneurysm.



Melenotte, *Submitted*

Concernant l'infection vasculaire à *C. burnetti*, quelles sont les propositions vraies

A. Touche plus les hommes que les femmes
B. Peuvent se compliquer de fistule et de spondylodiscite
C. Sont mortelles en l'absence de traitement
D. Doivent faire discuter un traitement chirurgical
E. Nécessitent un traitement de 3 mois

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Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

eTable 9. Clinical Presentation of Persistent *C burnetii* Infections in 766 Patients

	Endocarditis N=581		Vascular infection N=145		Osteo articular infection N=56	
Age (mean±SD)	59.4±17.3	-	63.4±14.3	-	59.6±19.9	-
Sex (men)	419	72.1%	127	88.2%	37	66.1%
Immunosuppression	22	3.8%	6	4.2%	1	1.8%
Valvular predisposition	449	77.4%	57	39.6%	7	12.5%
Prosthetic material	204	35%	62	44%	10	17.8%
Endocarditis	-	-	49	34.0%	7	12.5%
Vascular infection	49	8.4%	-	-	11	19.2%
Osteoarticular infection	8	1.3%	11	7.5%	-	-
Hepatitis	123	21.2%	28	19.4%	6	10.7%
Pneumonia	52	8.9%	10	6.9%	2	3.6%
Lymphadenitis	26	4.5%	6	4.2%	4	7.1%
Acute endocarditis	13	2.2%	1	0.7%	0	0%
Lymphoma	10	1.7%	2	1.4%	0	0%
Meningitis	7	1.2%	0	0%	1	1.8%
Hemophagocytic syndrome	1	0.2%	1	0.7%	0	0%

Melenotte, *Jama Network Open*, 2018, Supplementary data

Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever

eTable 12. *C burnetii* Infection in Children (n = 58)

	Patients (n=58)	**100%**
Age (Mean ±SD)	10±5	-
Sex (boy)	27	46%
Medical history	**1**	**1.7%**
Severe immunodeficiency	14	25%
Pre-existing valvulopathy	14	25%
Endocarditis	7	12%
Native valve	7	12%
Prosthetic valve	3	5.1%
Vascular infection	**2**	**3.4%**
Prosthetic material	1	1.7%
Native vessel	3	5.1%
Osteomyelitis	22	38%
Isolated Fever	10	17%
Hepatitis	5	8.6%
Pneumonia	3	5.1%
Primary *C. burnetii* infection	19	32%
Persistent *C. burnetii* infection	30	51.7%

Melenotte, *Jama Network Open*, 2018, Supplementary data

C. burnetii infection during pregnancy

Few symptoms
Acute and persistent infection

2 third trimester of pregnancy
- -Abortion
- - Intrauteruine growth retardation
- - Oligoamnios
- - Intrauterine fetal death
- - Premature delivery

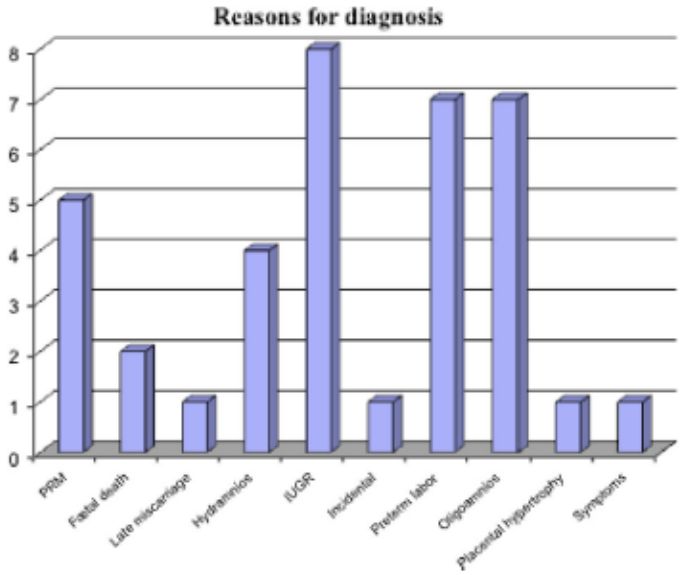

Fig. 1 Reasons for diagnosis

Q fever during pregnancy : 60% of complications

Melenotte, *JAMA Network Open*, 2018
Carcopino, *Ann NY Academy of sciences*, 2009
Coste Mazeau, *Arch Gynecol obstetric*, 2015

Q fever

Diagnosis is serologic

« Acute and chronic Q fever clinical entities may be recognized by serological »

Peacock, *Infect Imm*, 1983

TABLE 2. Results for various cutoff titers of antibodies against phase I and phase II *C. burnetii* in the diagnosis of chronic Q fever

Cutoff titer(s)	Phase	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IgG ≥ 800	I	100.0	99.6	98.1	100.0
	II	100.0	93.4	53.5	100.0
IgG ≥ 1,600	I	80.4	99.8	100.0	99.6
	II	88.5	96.4	71.4	99.9
IgA ≥ 25	I	96.6	96.2	48.6	100.0
	II	96.6	87.0	23.8	100.0
IgA ≥ 50	I	94.6	98.0	63.9	100.0
	II	93.2	91.9	34.0	100.0
IgA ≥ 100	I	85.8	98.9	77.8	99.8
	II	83.1	95.8	52.1	99.9
IgA ≥ 200	I	71.6	99.4	83.3	99.6
	II	72.3	97.9	66.2	99.8
IgA ≥ 400	I	56.8	99.9	97.4	99.3
	II	59.5	99.0	80.0	99.4
IgG ≥ 800 and IgA ≥ 25	I	96.6	100.0	98.1	100.0
	II	96.6	95.3	57.6	100.0
IgG ≥ 800 and IgA ≥ 100	I	85.8	100.0	98.0	99.8
	II	83.1	97.8	74.6	99.9
IgG ≥ 800 and IgA ≥ 400	I	56.8	100.0	97.4	99.3
	II	59.5	99.3	87.0	99.4
IgG ≥ 1,600 and IgA ≥ 400	I	52.7	100.0	100.0	99.3
	II	56.8	99.5	95.0	99.3

Tissot-Dupont, *Infect Imm*, 1994
Fournier, *J Clin Microbiol*, 1998

C. burnetii persistent infection: a changing paradigm

Organic lesion

+

Microbiological evidence

(serology, PCR, FISH, IHC, culture)

Raoult, *Clin infect Dis*, 2017
Melenotte, *Exp Rev Anti-infect ther*, 2020

Treatment

L’infection cardio-vasculaire est fatale en l’absence de traitement

Le traitement de la fièvre Q

1980-1990: Observation de nombreuses rechutes avec la doxycycline seule

Rechutes probablement liées au pH acide du phagolysosome (pH:4,5)

Le pH acide diminue l'efficacité des antibiotiques en prévenant l'activité bactéricide.

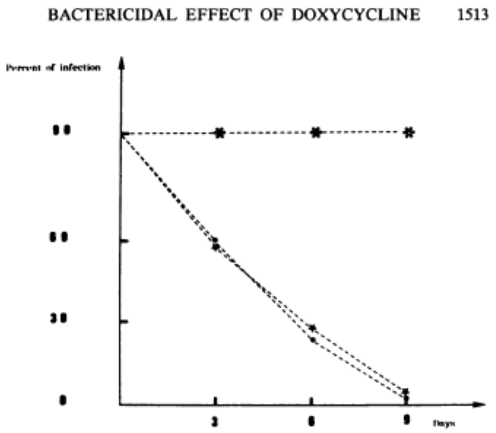

FIG. 1. Effect of doxycycline alone (4 μg/ml) (*) and in combination with chloroquine (1 μg/ml) (*) and amantadine (1 μg/ml) (●) in P388D$_1$ 90% *C. burnetii*-infected cells blocked with cycloheximide.

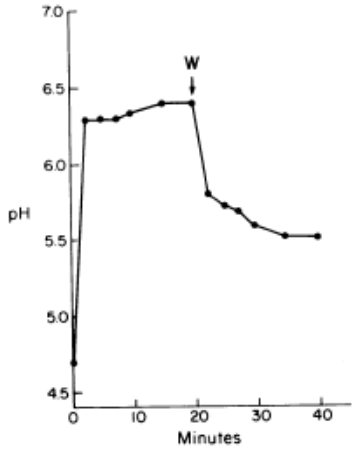

FIG. 11. Effect of chloroquine on intralysosomal pH. Procedures as in Fig. 6. The perfusion medium contained 100 μM chloroquine for the first 20 min.

Drancourt, *AAC*, 1990

Ohkuma, *PNAS*, 1978

Le rôle du plaquenil

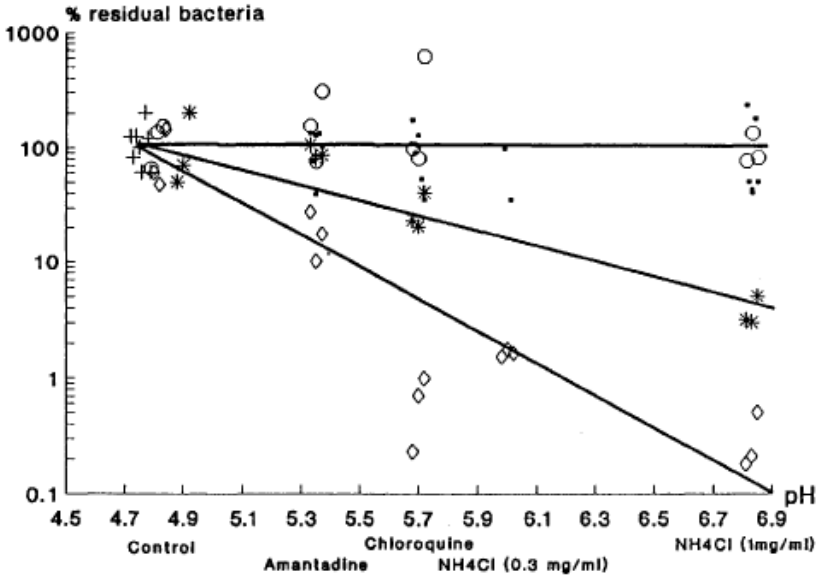

Figure 4. Bactericidal effect of drugs on intracellular *Coxiella burnetii:* percentages of residual viable bacteria in untreated controls (+), in cultures treated with lysosomotropic agents alone (·), and in cultures treated with doxycycline, 4 μg/mL (◇), pefloxacin, 1 μg/mL (•), or rifampin, 4 μg/mL (○), alone or combined with lysosomotropic agents.

Rôle du plaquenil:

- Agent alcalinisant
- Permet l'activité de la doxycycline par alcalinisation du pH du phagolysosome
- Car doxycycline inactive pour les pH bas
- Coxiella survie moins bien à pH alcalins

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2005, p. 2673–2676 Vol. 49, No. 7
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.7.2673–2676.2005

Correlation between Ratio of Serum Doxycycline Concentration to MIC and Rapid Decline of Antibody Levels during Treatment of Q Fever Endocarditis

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Received 23 February 2005/Returned for modification 8 March 2005/Accepted 18 March 2005

Endocarditis is the major clinical manifestation of chronic Q fever. Although doxycycline along with hydroxychloroquine remains the mainstay of medical therapy for Q fever endocarditis, there are wide variations in the rapidity of the patient's decline of antibody levels during such therapy. We undertook a retrospective examination of whether there was any correlation between the ratio of serum concentration to MIC of doxycycline and response to treatment in patients with Q fever endocarditis. Included herein are 16 patients from whom *Coxiella burnetii* was isolated from cardiac valve materials. Serology and measurement of doxycycline and hydroxychloroquine serum levels were performed and recorded after 1 year of treatment. The MIC of doxycycline for *C. burnetii* isolates was determined using the shell vial assay in a real-time quantitative PCR assay. At the completion of a yearlong therapy with doxycycline-hydroxychloroquine, all those that showed a low decline of antibody levels ($n = 6$) (i.e., <2-fold decrease in antibody titer to phase I *C. burnetii* antigen) had a ratio of serum doxycycline concentration to MIC between 0.5 and 1. In contrast, those having a ratio of ≥1 showed a rapid decline of phase I antibody levels ($n = 9$; $P < 0.05$). The only patient who died had a serum doxycycline-to-MIC ratio of <0.5, and the isolate of *C. burnetii* cultured from this patient was resistant to doxycycline (MIC = 8 μg/ml). The ratio of serum doxycycline concentration to MIC should be monitored

Molécule	Taux cible
Doxycycline	5-10 mg/l (= µg/ml)
Hydroxychloroquine	0.8-1.2 mg/l (= µg/ml)

Surveillance mensuelle

Si possible tester la sensibilité de la souche aux antibiotiques

Treatment

No randomized control trial

No registred randomized control trials

Stahl, *Clin Microb Infect*, 2022

In vitro

	Doxycycline + ofloxacin N = 14	Doxycycline + HCQ N = 21	*p*
Deaths	1	1	.77
Valvular surgery	10	10	.16
Relapses after completed treatment	7/15	2/23	.01
Relapses after 18 months of treatment	6/11	0/16	.001
Mean treatment duration among cured patients (month)	55 ± 18	31 ± 14	<.001
Photosensibilization	14	21	NA

Table 1 comparison of outcome between the 2 therapeutic regimens

Stahl, *Clin Microb Infect*, 2022
Raoult, *Arch Int Med*, 1999

Clinical Infectious Diseases

MAJOR ARTICLE

Treatment of Chronic Q Fever: Clinical Efficacy and Toxicity of Antibiotic Regimens

Sonja E. van Roeden,[1] Chantal P. Bleeker-Rovers,[2] Marieke J. A. de Regt,[1] Linda M. Kampschreur,[3] Andy I. M. Hoepelman,[1] Peter C. Wever,[4] and Jan Jelrik Oosterheert[1]

[1]Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, [2]Department of Internal Medicine, Division of Infectious Diseases and Radboud Expert Centre for Q Fever, Radboud University Medical Center, Nijmegen, [3]Department of Internal Medicine and Infectious Diseases, Medical Centre Leeuwarden, and [4]Department of Medical Microbiology and Infection Control, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

Background. Evidence on the effectiveness of first-line treatment for chronic Q fever, tetracyclines (TET) plus hydroxychloroquine (HCQ), and potential alternatives is scarce.

Methods. We performed a retrospective, observational cohort study to assess efficacy of treatment with TET plus quinolones (QNL), TET plus QNL plus HCQ, QNL monotherapy, or TET monotherapy compared to TET plus HCQ in chronic Q fever patients. We used a time-dependent Cox proportional hazards model to assess our primary (all-cause mortality) and secondary outcomes (first disease-related event and therapy failure).

Results. We assessed 322 chronic Q fever patients; 276 (86%) received antibiotics. Compared to TET plus HCQ (n = 254; 92%), treatment with TET plus QNL (n = 49; 17%), TET plus QNL plus HCQ (n = 29, 10%), QNL monotherapy (n = 93; 34%), or TET monotherapy (n = 54; 20%) were not associated with primary or secondary outcomes. QNL and TET monotherapies were frequently discontinued due to insufficient clinical response (n = 27, 29% and n = 32, 59%). TET plus HCQ, TET plus QNL, and TET plus QNL plus HCQ were most frequently discontinued due to side effects (n = 110, 43%; n = 13, 27%; and n = 12, 41%).

Conclusions. Treatment of chronic Q fever with TET plus QNL appears to be a safe alternative for TET plus HCQ, for example, if TET plus HCQ cannot be tolerated due to side effects. Treatment with TET plus QNL plus HCQ was not superior to treatment with TET plus HCQ, although this may be caused by confounding by indication. Treatment with TET or QNL monotherapy should be avoided; switches due to subjective, insufficient clinical response were frequently observed.

Keywords. chronic Q fever; *Coxiella burnetii*; treatment; antibiotics.

Treatment

	Infectious focus	Treatment
ACUTE Q FEVER		
Acute Q fever	Spontaneous recovery Isolated fever Hepatitis Pneumonia	No treatment D 3 we
Acute Q fever + Antiphospholipid antibodies	Isolated fever Hepatitis Pneumonia Alithiasic cholecystitis Meningitis Haemophagocytic syndrome Thrombosis Acute Q fever endocarditis	DH until normalization of antiphospholipid antibodies (IgG, IgM, Beta2 GP1) and normalization of aPTT AND cure of any antiphospholipid antibodies related complications DH (18 mo)*
Acute Q fever with underlying valvulopathy	Whatever the clinical presentation	DH (12 mo)

Pregnancy :BACTRIM twice a day during the 8th month of pregnancy
After delivery : evaluation of C. burnetii microbiological test for the mother, in developped countries contraindication of breastfeeding

Melenotte, *Exp Rev of anti infect therapy*, 2020

Treatment

PERSISTENT COXIELLA BURNETII INFECTION	
Infectious focus	**Treatment**
Endocarditis (possible or definite)	
Native valve	DH 18 mo If a surgery is necessary, wait 3 weeks of treatment
Intra-cardiac prosthetic material	DH 24 months If a surgery is necessary, wait 3 weeks of treatment
Vascular infection (possible or definite)	
Native vessel	DH 18 months Systematic remove of infected material after one month of treatment. Before surgery if possible, wait 4 weeks of treatment
Prosthetic material	DH 24 months Systematic remove of infected material after one month of treatment Before surgery if possible, wait 4 weeks of treatment
Lymphadenitis	DH till TEP cure TEP-scan every 3 months
Osteoarticular infection On native bone On bone with material (prosthesis,…)	Call National Reference Center for experts advice
For all the other cases	Call National Reference Center for experts advice

Melenotte, *Exp Rev of anti infect therapy*, 2020

Prise en charge de l'infection à *Coxiella burnetii*

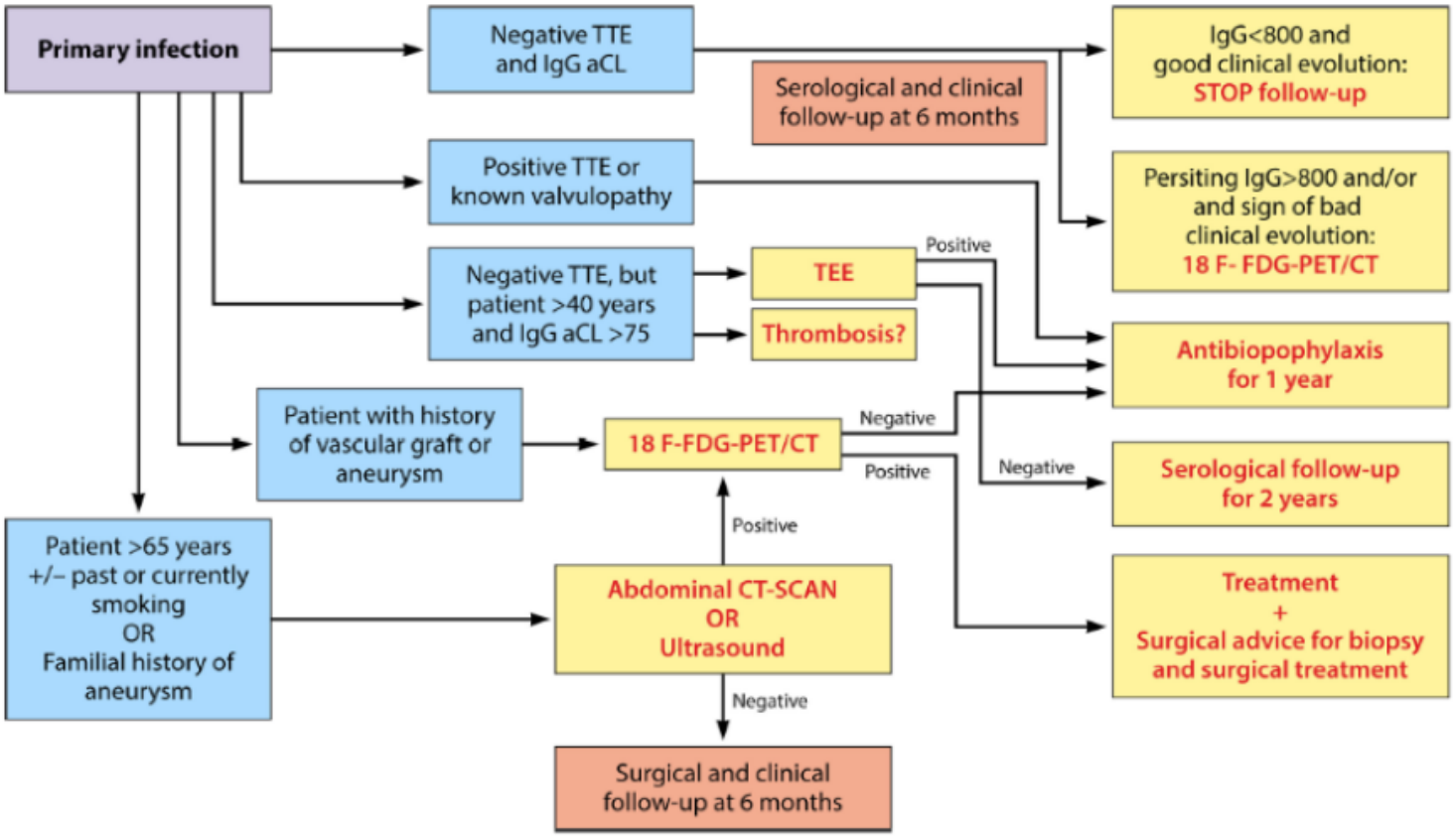

FIG 5 Management strategy for *C. burnetii* infection.

Eldin et al., CMR 2017

Prise en charge de l'infection à *Coxiella burnetii*

La surveillance des taux thérapeutiques est capitale pour obtenir une bonne efficacité et une bonne tolérance du traitement

Pour tous les patients traités par doxycycline et hydroxychloroquine, il est conseillé de surveiller mensuellement le taux sérique des antibiotiques.

Bien que la posologie initiale soit : doxycycline cp à 100mg 2 cp/j + hydroxychloroquine cp à 200mg 3 cp par jour, les posologies nécessaires pour atteindre les taux cibles (cf ci-dessous) sont très variables.

Une protection solaire est recommandée compte tenu de la photosensibilisation (à ne pas confondre avec une toxidermie) due à la doxycycline.
Une consultation ophtalmologique doit être effectuée en début de traitement et à 6 mois.

Molécule	Taux cible
Doxycycline	5-10 mg/l (= µg/ml)
Hydroxychloroquine	0.8-1.2 mg/l (= µg/ml)

CNR, Fièvre Q

Bartonella

Parmi les propositions suivantes concernant *Bartonella*, lesquelles sont vraies

A. Il existe une seule espèce de Bartonella, *Bartonella henselae* responsable de la maladie des griffes du chat

B. *Bartonella* est une bactérie intracellulaire présente dans les globules rouges et les cellules endothéliales

C. *Bartonella quintana* est responsable de bactériemie chronique et d'endocardite chez les patients SDF

D. Bartonella est responsable d'angiomatose bacillaire chez les patients immunodéprimés

E. Il n'existe pas de traitement spécifique de l'infection à BArtonella

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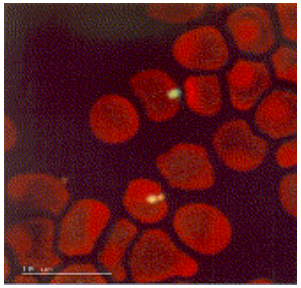
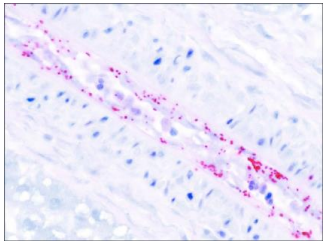


BARTONELLA



Bartonella
bactérie intracellulaire facultative
infecte les cellules endothéliales et les globules rouges.
Grâce à une protéine appelée BadA
(*Bartonella* adhesin A)
Stimule l'angiogenèse en induisant la production par les cellules endothéliales de différents facteurs pro-angiogéniques

Tableau I. Réservoirs, vecteurs et maladies causées par les douze espèces de *Bartonella* considérées comme pathogènes chez l'homme
* un seul cas décrit; ** trois cas décrits en Thaïlande.
(Adapté des réf.[3-5]).

	Réservoir	Vecteur	Maladie
B. henselae	Chats	Puces	• Maladies des griffes du chat • Bactériémie • Endocardite • Angiomatose bacillaire et péliose hépatique
B. quintana	Humains	Poux du corps	• Fièvre des tranchées • Bactériémie chronique • Endocardite • Angiomatose bacillaire
B. bacilliformis	Humains	Mouches des sables	• Maladie de Carrion (fièvre d'Oroya et verrues péruviennes)
B. elizabethae	Rats	Mouches	• Endocardite* • Neurorétinite*
B. grahamii	Rats		• Uvéite*
B. vinsonii* subsp. *arupensis	Rongeurs		• Endocardite*
B. vinsonii* subsp. *berkhoffii	Chiens	Mouches et tiques	• Endocardite*
B. washoensis	Rongeurs		• Myocardite*
B. tamiae	Rongeurs		• Fièvre, myalgies**
B. koehlerae			• Endocardite*
B. alsatica			• Endocardite*
B. rochalimaea			• Fièvre, splénomégalie*

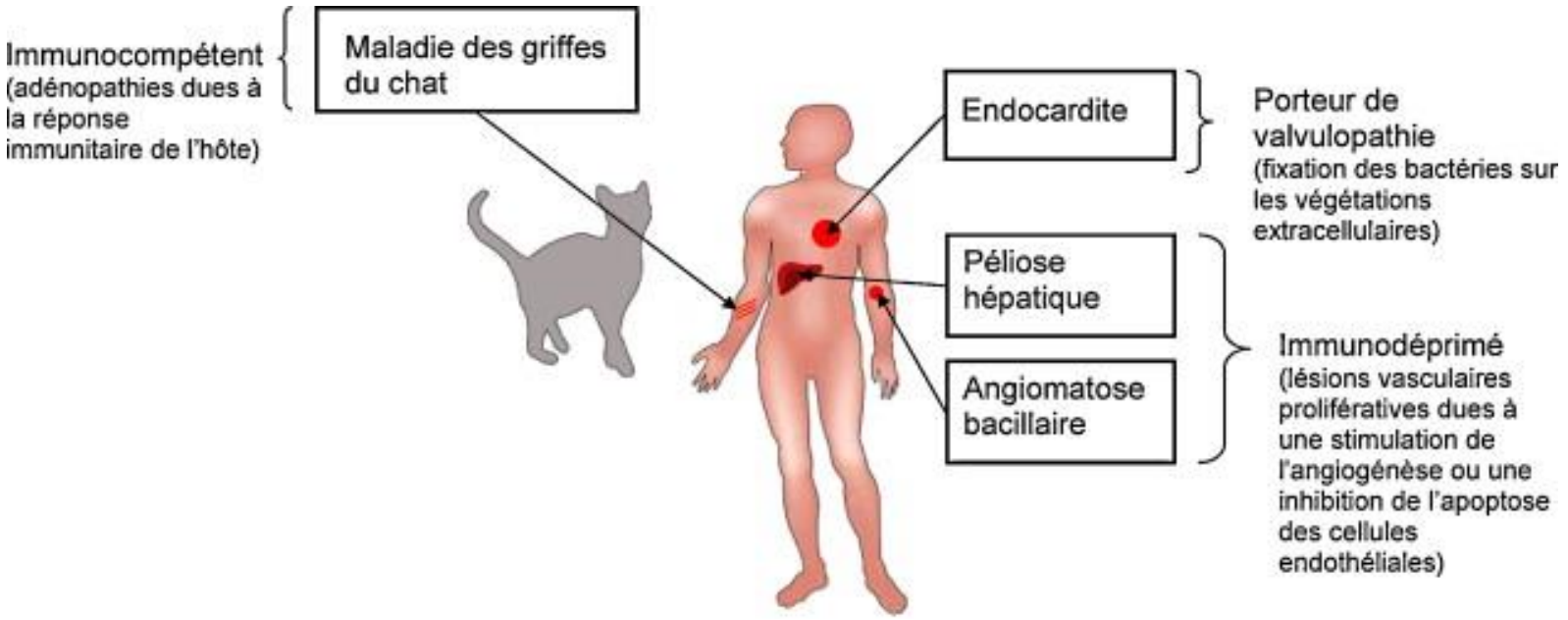
Boillat, *Rev Med Suisse*, 2007

Bartonella

B. henselae	
• Contact avec un chat	→ Maladie des griffes du chat
• Contact avec un chat + valvulopathie	→ Endocardite
• Contact avec un chat + infection VIH	→ Angiomatose bacillaire
	→ Péliose hépatique
B. quintana	
• Sans domicile fixe (SDF), alcoolisme	→ Bactériémie chronique
	→ Endocardite
• SDF, alcoolisme + infection VIH	→ Angiomatose bacillaire
B. bacilliformis	
• Touristes* au Pérou, Bolivie ou Equateur	→ Fièvre d'Oroya
• Autochtones Pérou, Bolivie ou Equateur	→ Verrues péruviennes

Boillat, *Rev Med Suisse*, 2007

Bartonella henselae



Adénopathie

Péliose hépatique

Angiomatose bacillaire

EIHN

Syndrome oculoglandulaire de Parinaud: conjonctivite et adénopathie prétragienne

Edouard, *Rev Med Int*, 2010

Bartonella quintana

Fièvre des tranchées (1er GM)

Pediculus humanus corporis

Fièvre

Angiomatose bacillaire
Bactériémie

Endocardites

Edouard, *Rev Med Int*, 2010

Boillat, *Rev Med Suisse*, 2007

Bartonella bacilliformis

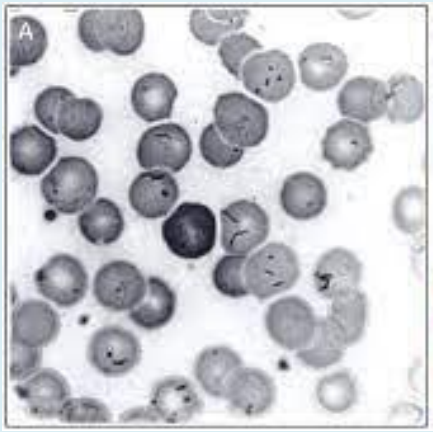
Phlébotomes

2 mois

Fièvre d'Oroya

Fièvre, asthénie, céphalée

2 à 4 semaines
Atteintes capillaires



Verrues péruviennes

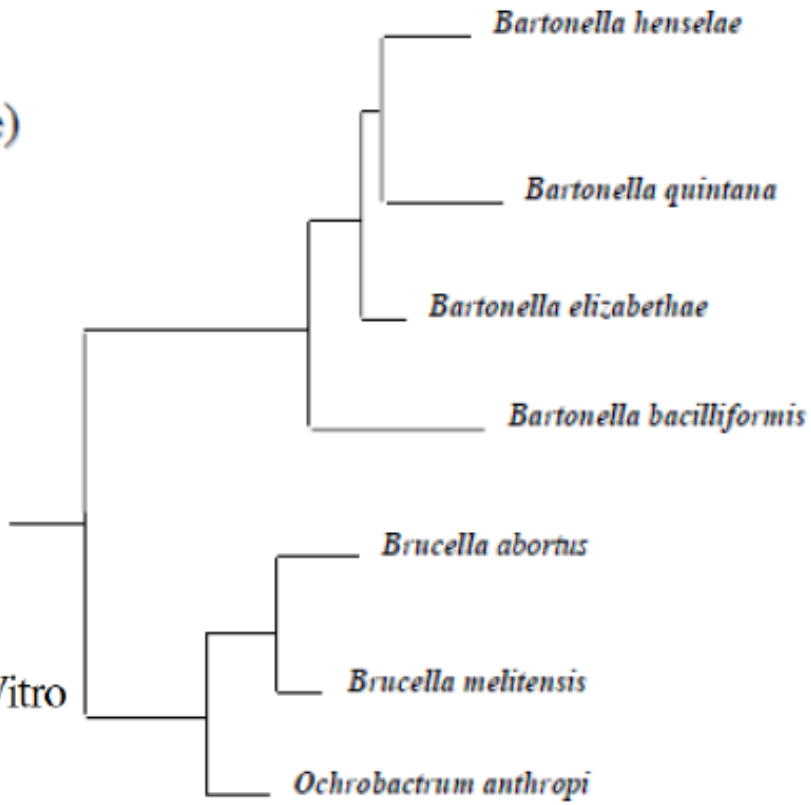
Miliary lesions (eruptive-phase bartonellosis)

Mular lesion (eruptive-phase bartonellosis)

Diagnostic

Les hémocultures avec culture sur agar et incubation prolongée sont le test diagnostique de référence.[3,20] La sérologie est beaucoup moins sensible (tableau 4).[20,35] La sensibilité de la PCR sur le sang EDTA reste à préciser.

- In cellulo sensible à:
  - Aminoglycosides (bactéricide)
  - Doxycycline
  - Quinolones
  - Rifampicine
  - Erythromycine



Antiangiogenic Effect of Erythromycin: An In Vitro Model of *Bartonella quintana* Infection

Soraya Meghari,* Jean-Marc Rolain,* Georges E. Grau, Esther Platt, Lina Barrassi, Jean-Louis Mège, and Didier Raoult

Pathogenicity	*Bartonella* agent	Clinical manifestation		Treatment	Duration	Reference
Local manifestations	*B. henselae*, *B. quintana*, *B. alsatica*, *B. clarridgeiae*	Lymphadenitis		No treatment		[31]
		Atypical CSD	Neuroretinitis	Doxycycline (200 mg/day) and rifampicin (600 mg/day)	4–6 weeks	[36,37]
			Hepatosplenic	Rifampicin (20 mg/kg/day) alone or with gentamicin (3 mg/kg/day)	4–6 weeks	[39]
Intracellular erythrocyte parasitism	*B. bacilliformis*	Oroya fever		Chloramphenicol (50 mg/kg/day for 3 days and then 25 mg/kg/day until completion of 14 days)	2 weeks	[7,48,67,70]
			Pregnancy	Chloramphenicol (50–100 mg/kg/day) and penicillin G (50 000–100 000 IU/kg/day)	2 weeks	[70]
	B. quintana	Trench fever		Gentamicin (3 mg/kg/day for 2 weeks) and doxycycline (200 mg/day for 4 weeks)	6 weeks	[62]
	B. henselae, *B. rochalimae*, *B. vinsonii* subsp. *arupensis*, *B. vinsonii*, *B. melophagi*	Bacteraemia		Gentamicin (3 mg/kg/day for 2 weeks) and doxycycline (200 mg/day for 4 weeks)	6 weeks	[62]
Endocarditis	*B. quintana*, *B. henselae*, other *Bartonella* spp.	Endocarditis		Gentamicin (3 mg/kg/day for 2 weeks) and doxycycline (200 mg/day for 6 weeks)	6 weeks	[81]
Angioproliferative lesions	*B. bacilliformis*, *B. ancashi*	Verruga peruana		Rifampicin (10 mg/kg/day) (maximum total daily dose 600 mg/day for children)	2–3 weeks	[27,70]
				Streptomycin (15–20 mg/kg/day)	2–3 weeks	[31,67]
	B. quintana, *B. henselae*	Bacillary angiomatosis, bacillary peliosis	Uncomplicated	Erythromycin (2 g/day) or doxycycline (200 mg/day)	3 months	[7,91,92]
			Complicated	Doxycycline (200 mg/day) with rifampicin (600 mg/day)	3 months	[7,91,92]
			Relapses	Erythromycin (2 g/day) or doxycycline (200 mg/day)	4–6 months	[35,96]

CSD, cat-scratch disease.

Angelakis, *Int J Antimicrob Agent*, 2014

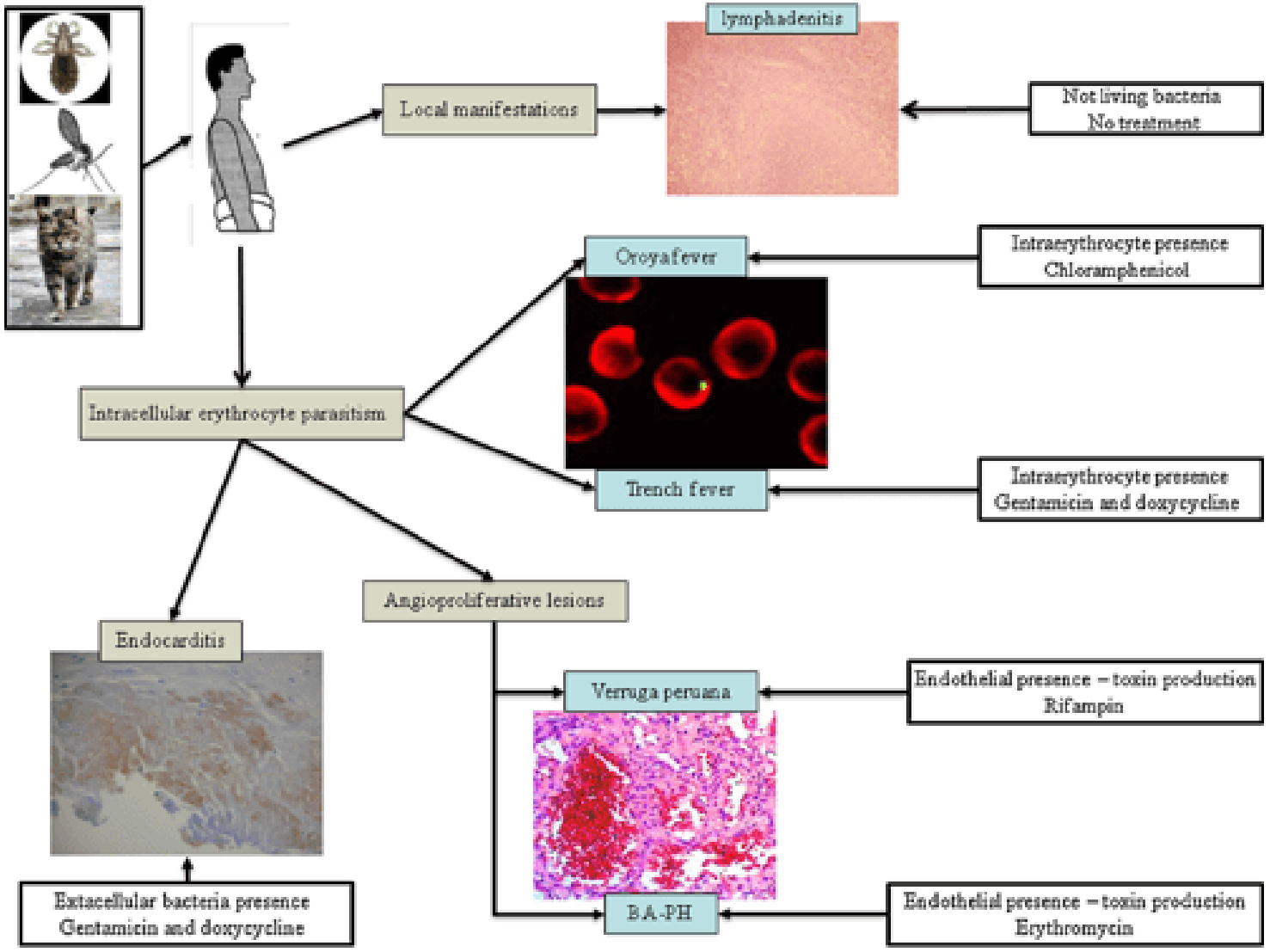


Fig. 1. Pathogenicity and treatment of *Bartonella* infections. BA, bacillary angiomatosis; PH, peliosis hepatis.

Angelakis, *Int J Antimicrob Agent*, 2014

Tropheryma whipplei

Parmi les propositions suivantes lesquelles sont vraies

A. La maladie de whipple est due à *Tropheryma whipplei*
B. Dans sa forme classique la maladie est responsable d'un syndrome de malabsorption
C. Il existe des atteintes isolées du SNC de la maladie de whipple
D. La maladie est mortelle en l'absence de traitement
E. Il existe de nombreuses études randomisées contôlée ayant démontré l'efficacité du traitement antibiotique associant une bithérapie

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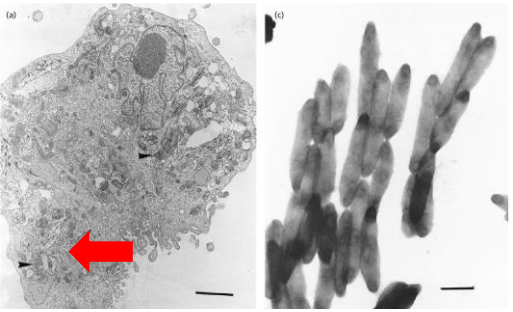
Bactérie intra et extra-cellulaire

Bactérie intracellulaire Gram positive



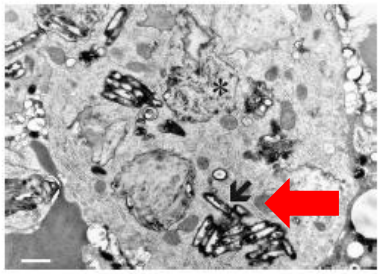
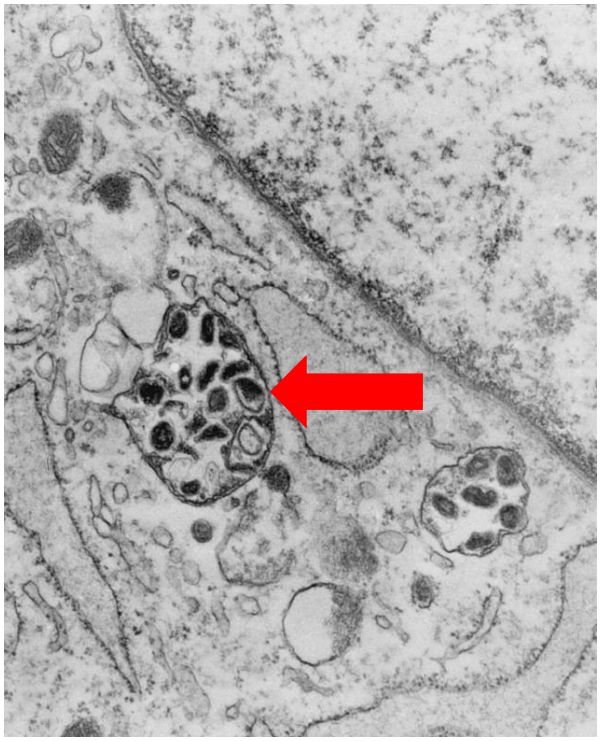
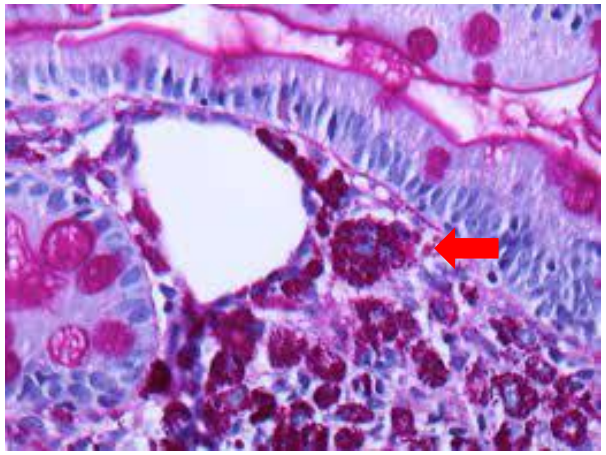
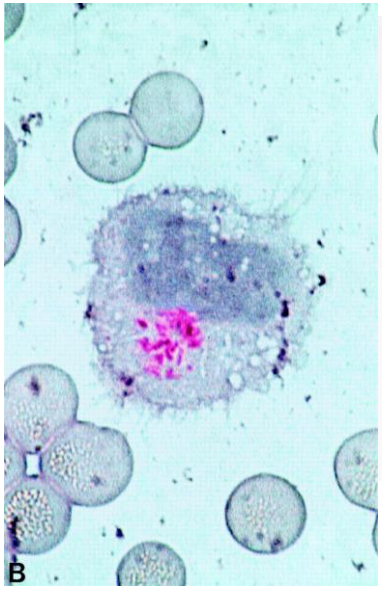
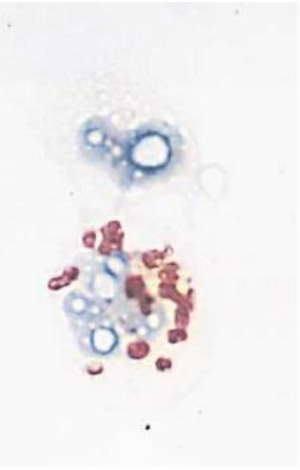


FIGURE 17: Groups of microbes (arrow) and characteristic lysosomes (asterisk) present in an intestinal histiocyte in Whipple's disease. Electron micrograph, scale = 2 μm. Courtesy of Professor Josef Špaček, MD, DSc. Reproduced with permission from Bureš and Rejchrt [42].









La Scola, *Medicine biol*, 2001
Raoult, *NEJM*, 2001
Bures, *Gastroenterology research and practice*, 2013
Unité des Rickettsies, Marseille, France

Histoire : *Tropheryma whipplei*

PCR 16S sur les biopsies duodénales de 5 patients vs 10 contrôles

Trophe: nourriture croissance/**eryma**: le rempart en référence à la malabsorption qui caractérise la maladie

Tropheryma whipplei

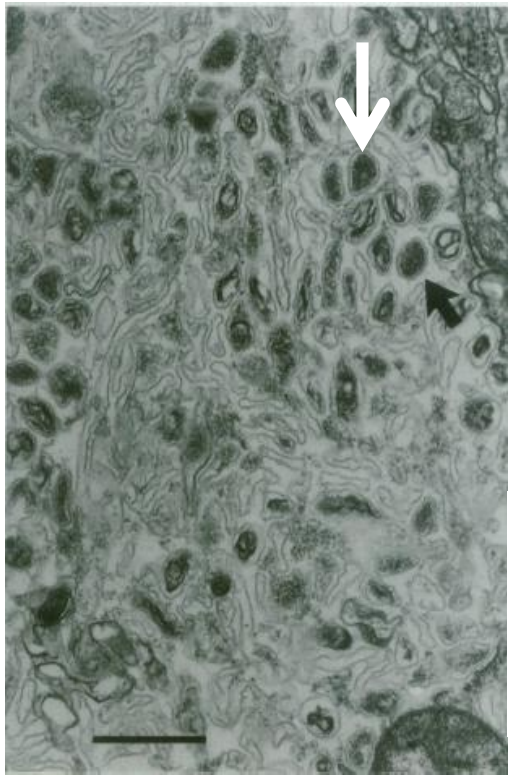
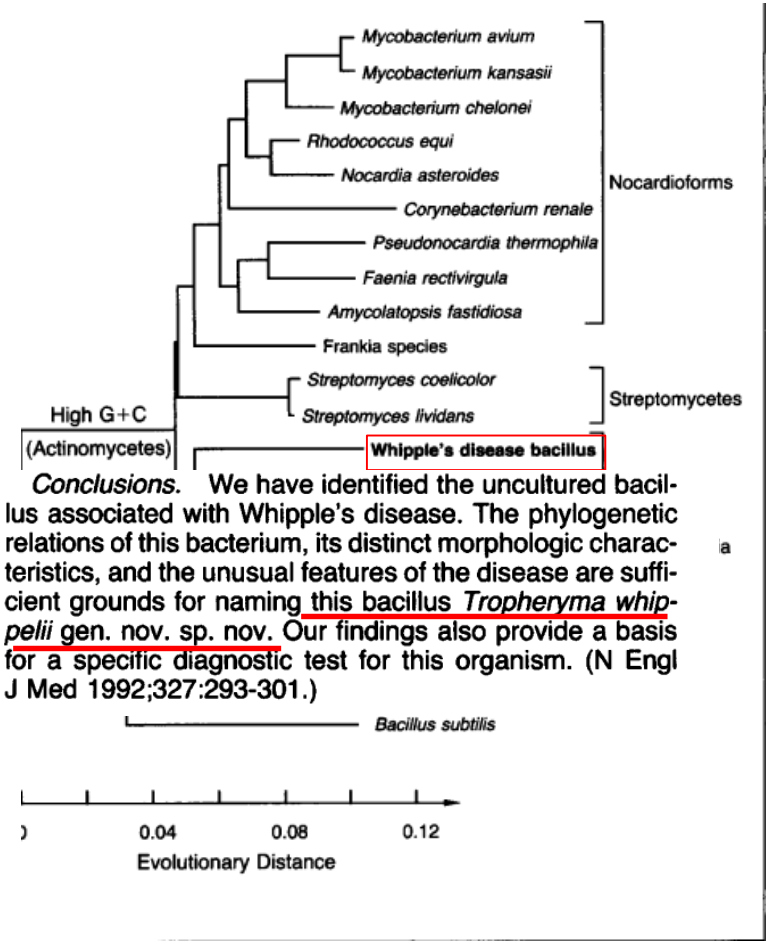


Figure 1. Histologic Evidence of Whipple's Disease in the Duodenum of Patient 5.

The lamina propria is packed with macrophages (Panel A; hematoxylin and eosin, ×400) with inclusions that are strongly PAS-positive (Panel B; ×400). These inclusions contain numerous bacillary forms (arrows) in various stages of degradation (Panel C; 2 percent uranyl acetate–lead citrate stain, ×33,000; bar equals 0.5 μm).

16S RNA : Gram positive actinobacteria



Conclusions. We have identified the uncultured bacillus associated with Whipple's disease. The phylogenetic relations of this bacterium, its distinct morphologic characteristics, and the unusual features of the disease are sufficient grounds for naming this bacillus *Tropheryma whippelii* gen. nov. sp. nov. Our findings also provide a basis for a specific diagnostic test for this organism. (N Engl J Med 1992;327:293-301.)

Relman, *NEJM*, 1992

Epidémiologie

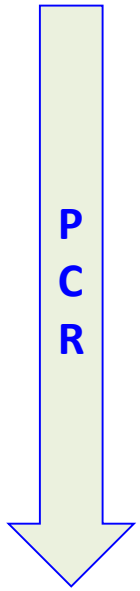
Prévalence et incidence

1000 cas décrit dans la littérature

In Europe incidence **<1/million/an** (**3 of 1,000,000** (95% IC[95% CI],2.1 -3.8)

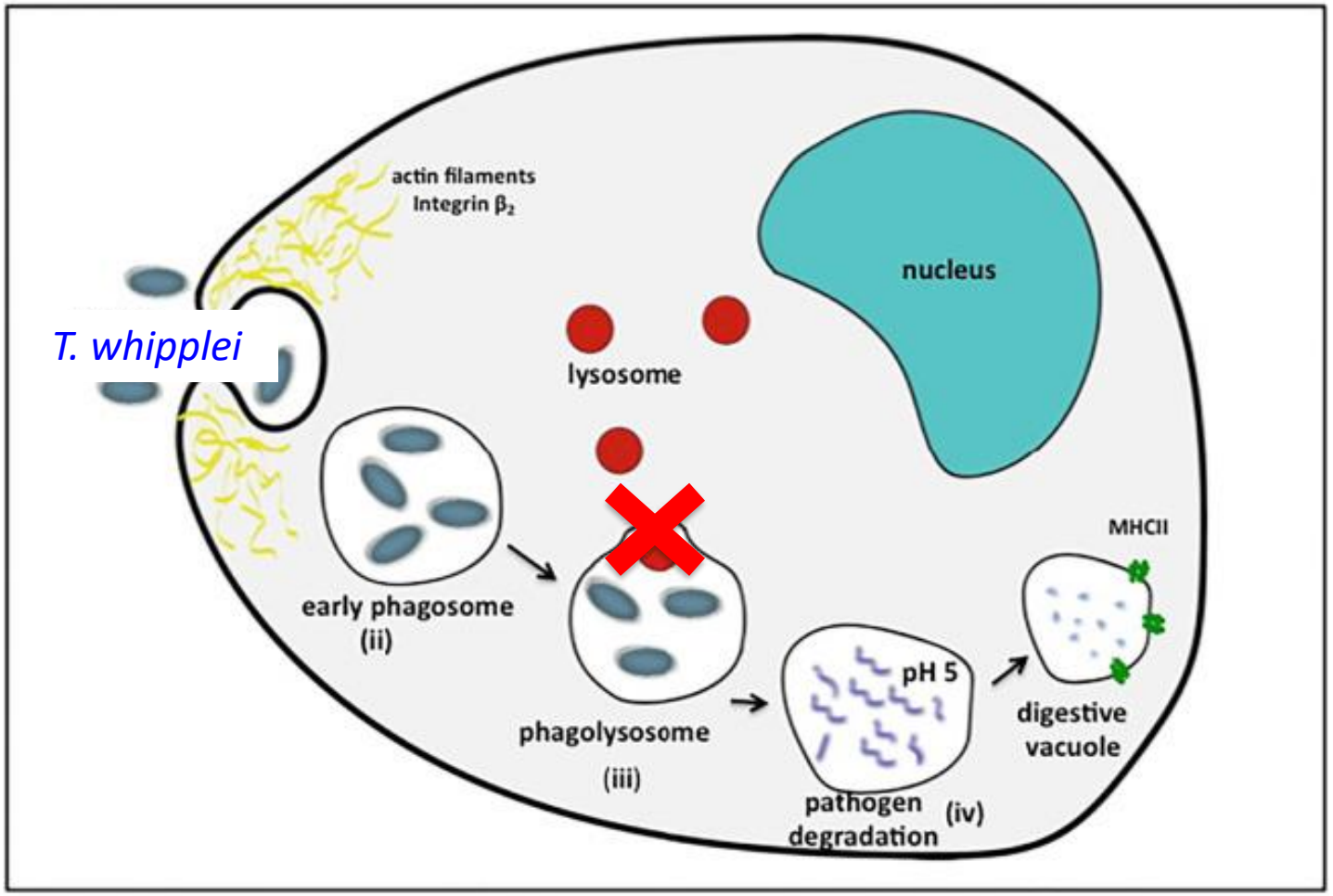
Incidence annuelle dans le monde : 12 nouveau cas

Actuellement : **1 à 6 nouveaux cas pour 10,000,000 personnes par an dans le monde**.



Dobbins, 1987
Elcher, *Dig dig sci*, 2020
Biagi, *Eur J Clin Microbiol Infect Dis*, 2015
Ruben, *CMR*, 2017

T. whipplei échappe au système immunitaire en empêchant la fusion du phagosome avec le lysosome



Gigho, *Infect Imm*, 2002
Mottola, *Plosone*, 2014

Présentation clinique de l'infection à *T. whipplei*

1-Maladie de Whipple classique

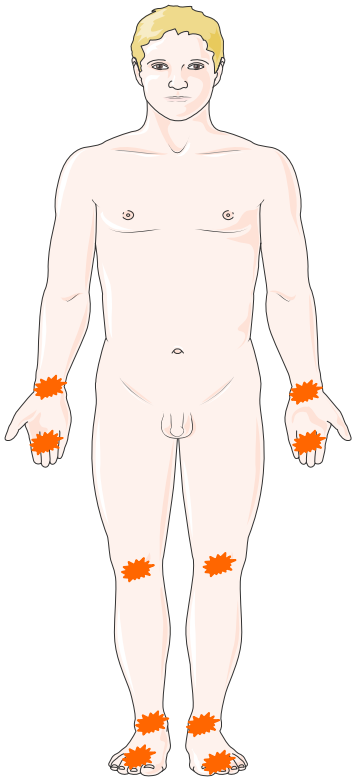
2-L'infection chronique focalisée à *T. whipplei*

Tableau clinique de la maladie de Whipple classique

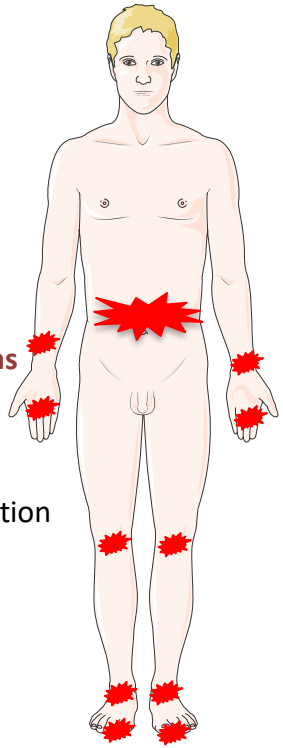
50% traitement IS

H, caucasien de 48 ans

Stade podromal
Poly-arthralgies
horaires inflammatoires
Migratrices, fluctuantes
Séronégative



Stade stationnaire 54 ans
Douleurs abdominales
Diarrhée chronique
Amaigrissement
Syndrome de malabsorption



+ 6.7 ans
Diagnostic de maladie de Whipple

Présentation clinique : polymorphe

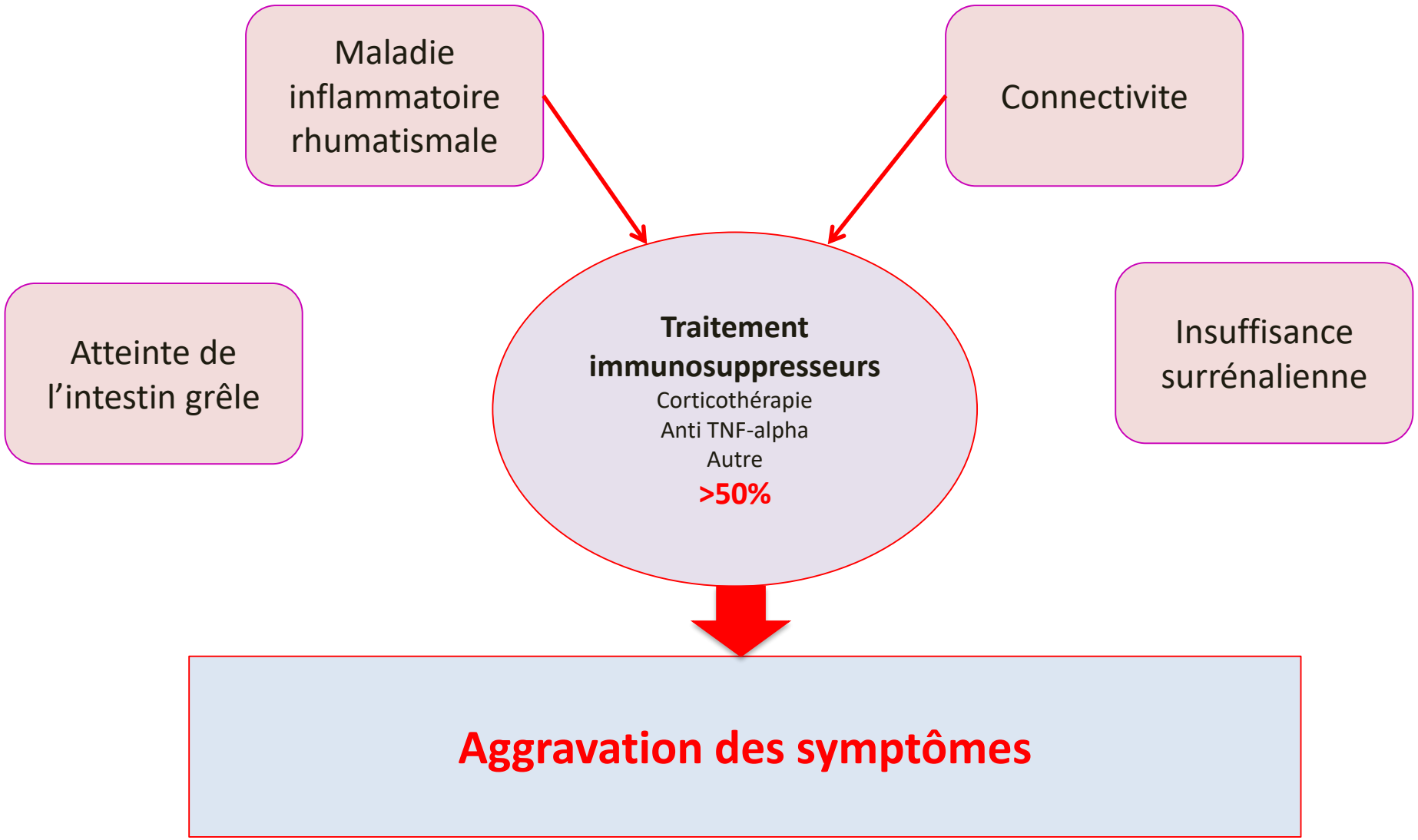
Table 2. Demographic and Clinical Features of Classic Whipple's Disease.*

Feature	Patients with Whipple's Disease *no./total no. (%)*
Male sex	770/886 (87)
Arthralgia or arthritis	244/335 (73)
Diarrhea	272/335 (81)
Weight loss	223/240 (93)
Fever	128/335 (38)
Adenopathy	174/335 (52)
Melanoderma	99/240 (41)
Neurologic signs†	33/99 (33)
Ocular signs†	6/99 (6)
Pleural effusion	26/190 (14)

Revue réalisée à partir de 7 études publiées depuis 1960

Fenollar, *NEJM*, 2007

Clinique
Rares sont les formes classiques



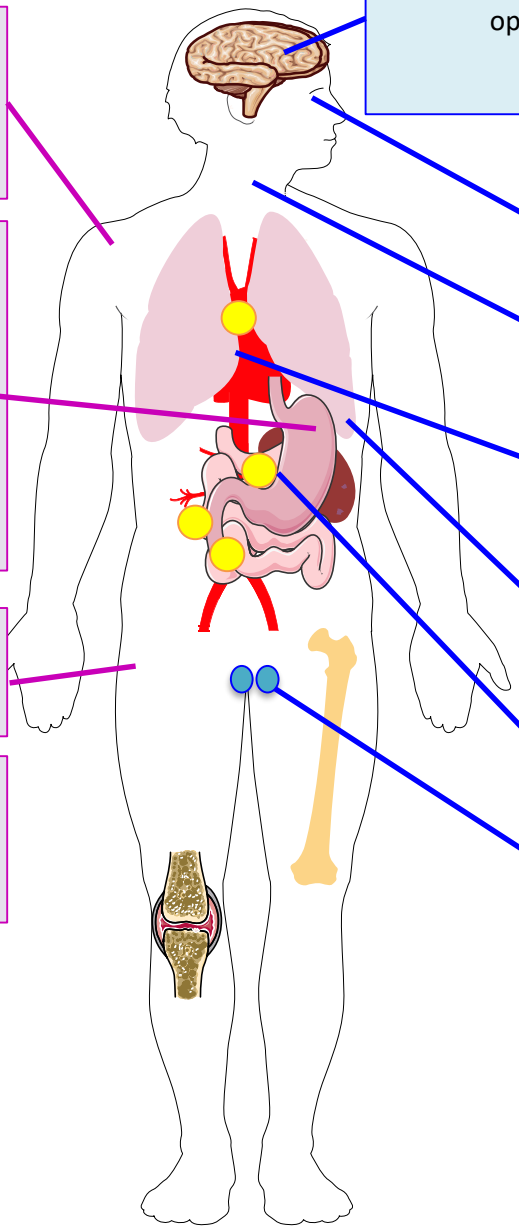
Maladie de Whipple classique

1-Arthralgies 80-90%
Poly/oligo arthrite ou inflammatoire, intermittente, migratrices, +/-destructrices

2-Signes digestifs:
douleurs abdominales/diarrhées/perte de poids
Syndrome de malabsorption
Phase avancée de la maladie
Saignement digestif
Ascite/anasarque

3-Cutanée 40-45%
Hyperpigmentation de la peau

3- Signes systémiques
Lymphadénopathies mésentériques 50%
Fièvre <20%



4-Atteinte neurologique 10-40%
Cognitive 71%/démence
ophtalmoplégie supranucléaire, nystagmus, myoclonus
Associée à des symptômes systémiques dans 80%

Uvéite

Hypothyroïdie

Cardiaque
péricardite endocardite

Pulmonaire
Pleuropneumopathie, HTAP, PID

Rénale (tardives)

Epididymitis & orchitis

Schneider, *Lancet*, 2008
Lagier, *Medicine*, 2010
Ruben, *CMR*, 2017

Biologie de la maladie de Whipple classique

Syndrome inflammatoire : CRP

Syndrome de malabsorption

Anémie 81%

Leucocytose 46%

Thrombocytose 69%

Thrombopénie

Eosinophilie

Hypo-albuminémie

Déficit en vitamine: B12, B9, D, K

Gunther, *Medicine*, 2015
Fenollar, *NEJM*, 2007

Atteinte articulaire

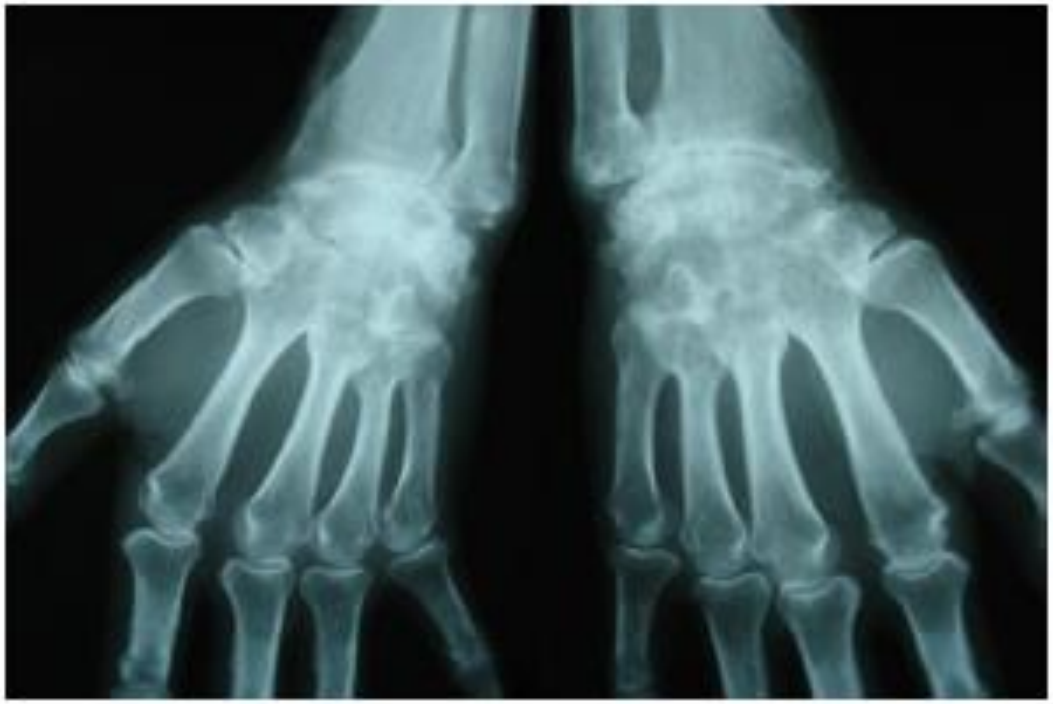


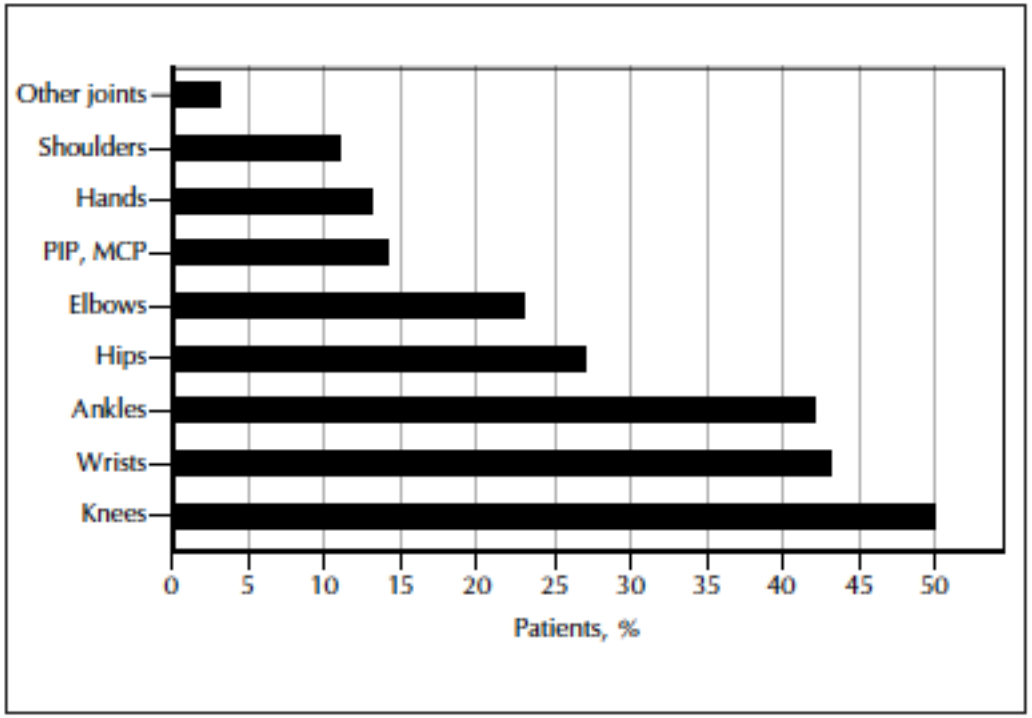
Fig. 1. Polyarthritis with joint destruction in a patient with Whipple's disease: symmetrical ankylosis of the carpal and carpometacarpal joints and bilateral narrowing of the radiocarpal joint space. The metacarpophalangeal joints are not affected (Courtesy of Puéchal et al. [16]).

Puechal, *Joint Bone Spin*, 2016

Atteinte articulaire

Figure 1. Joint involvement in Whipple disease, from a cumulative analysis of 131 patients

Data from [20–22,35]. MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints.



Puechal, *Rheumatol*, 2001

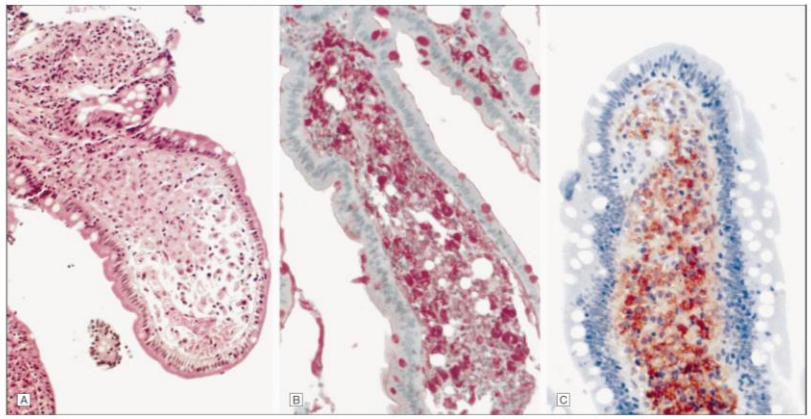
Atteinte digestive

Duodénum & Jéjunum

Amaigrissement
Malabsorption Anasarque

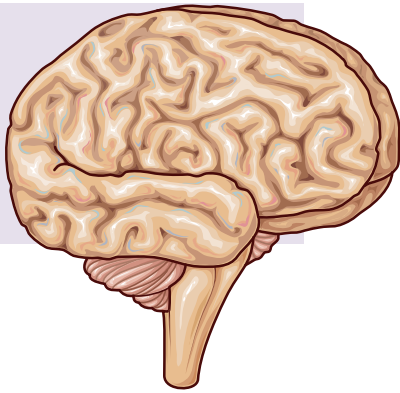
FIGURE 1: Whipple's disease: severe involvement of the distal duodenum (D4). Folds are low, and mucosa is swollen and grey-yellowish with multiple reddish spots (small mucosal haemorrhages).

Figure 2. Sections of a Villus Tip From a Patient With Whipple Disease



A, Inflammatory infiltrate seen in the lamina propria is made up of numerous foamy macrophages with a clear distended cytoplasm (hematoxylin-eosin, original magnification ×250). B, High-power magnification of foamy macrophages containing the characteristic rod-shaped inclusion bodies in the lamina propria. Mucous cells in

Atteinte neurologique



Maladie de Whipple classique
10-40%
Augmente avec le temps

Atteinte focalisée

Rechute après traitement

Asymptomatique le plus souvent l'atteinte du SNC se diagnostique sur la PCR positive sur le LCR

Démence, confusion, dysfonction cognitive

Bally, *Mov Disor*, 2018
Panegyres, *QJM*, 2006

NeuroWhipple

Table 3. Clinical Features of Neurologic Whipple's Disease and Blood Culture–Negative Endocarditis Associated with *T. whipplei*.

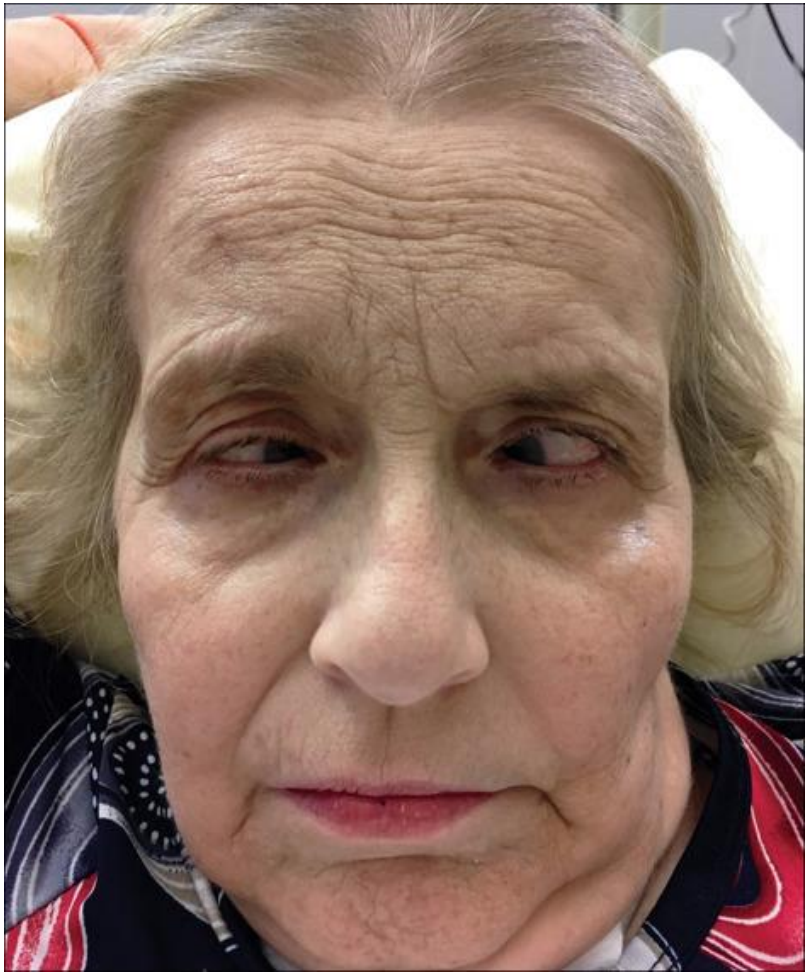
Feature	Value
Neurologic Whipple's disease[29]	
No. of patients	84
Cognitive change — %	71
Supranuclear ophthalmoplegia — %	51
Altered level of consciousness — %	50
Psychiatric signs — %	44
Upper motor neuron signs — %	37
Hypothalamic manifestations — %	31
Cranial nerve abnormalities — %	25
Myoclonus — %	25
Seizures — %	23
Oculomasticatory, or oculofacialskeletal, myorhythmia — %	20
Ataxia — %	20
Sensory deficits — %	12

pathognomonique

Hypersomnie, narcolepsie/cataplexie

Fenollar, *NEJM*, 2007

Oculomasticatory myorhythmia



Oculomasticatory myorhythmia is defined as **pendular vergence oscillations of the eyes that are synchronous with masticatory myorhythmia**.

Oculomasticatory myorhythmia

http://www.kaltura.com/index.php/extwidget/preview/partner_id/797802/uiconf_id/27472092/entry_id/0_yeuyrjyj/embed/auto

NeuroWhipple et LCR

LCR: normal avec **PCR *T. whipplei* +** chez les patients asymptomatiques

Patients symptomatiques: pléiocytose (5-10 /microL):
lymphocytes, monocytes et macrophages

Rarement PAS pos sur macrophages

Hyperprotéinorachie et bande oligoclonale

Uptodate

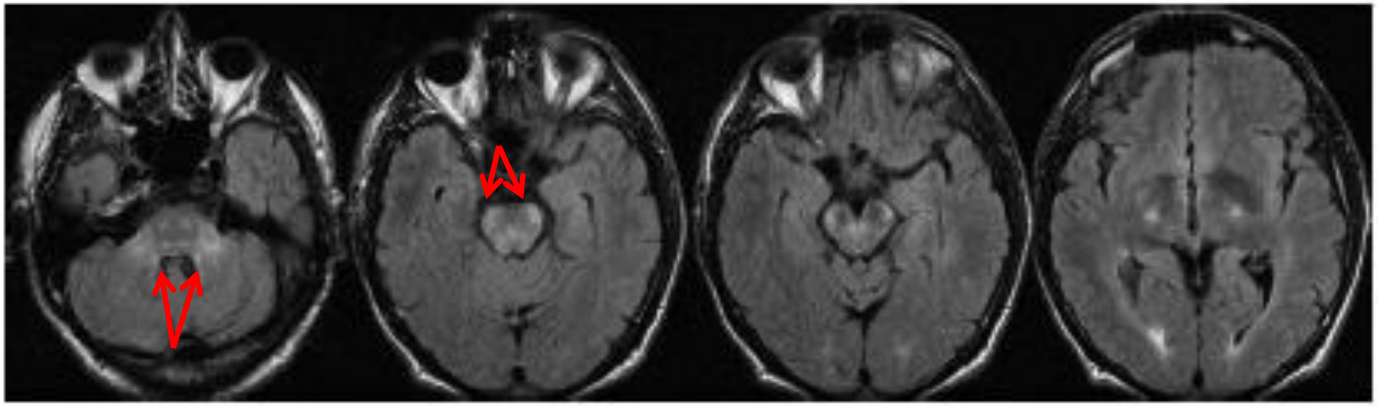
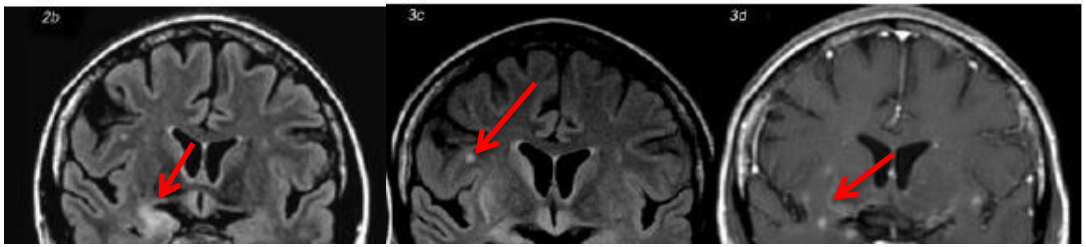


Fig 2. Axial noncontrast FLAIR MR images demonstrate bilaterally symmetric T2 signal-intensity abnormality without mass effect, involving the corticospinal tracts, brain stem, and brachium pontis.



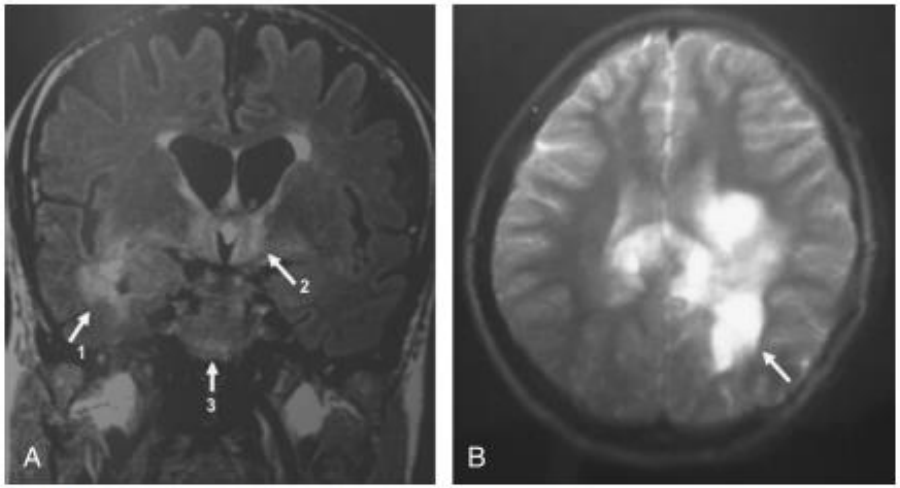
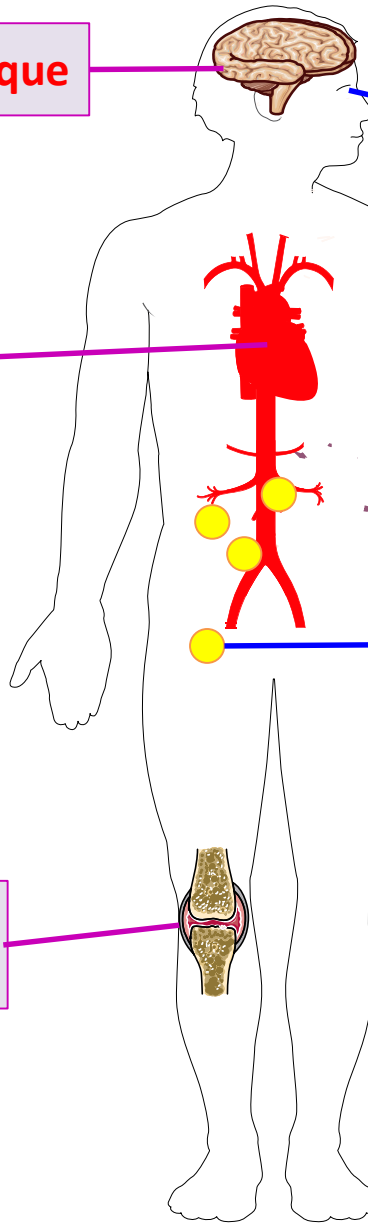


FIGURE 2. Brain MRI in WD with neurologic involvement. A, Flair-weighted MRI showed diffuse hyperintensities involving medial temporal lobes (arrow 1), hypothalamic regions (arrow 2), and a focal lesion of the left cerebral peduncle (arrow 3). B, T2-weighted MRI showed large pseudotumoral and nodular hyperintense lesions involving corpus callosum and periventricular white matter (arrow) with less mass effect than should be expected.

Symptômes neurologiques multiformes
Imagerie : multiples lésions nodulaires
Signes neurologiques focaux secondaires à une lésion nodulaire isolée

Black, *Clin report*, 2010
Panegyres, *QJM*, 2006
Compain, *Medicine*, 2013

L'infection chronique focalisée à *T. whipplei*



Atteinte neurologique

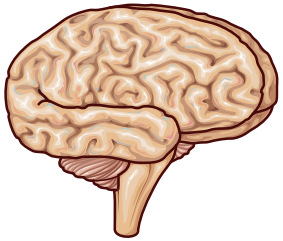
Uvéite

Cardiaque endocardite

Lymphadénite

Articulaire

Schneider, *Lancet*, 2008
Lagier, *Medicine*, 2010
Ruben, *CMR*, 2017
Puechal, *Joint bone spin*, 2016



Neurowhipple

Un nouveau cas de neuro-Whipple avec bilan digestif négatif

Cohen M., Bayreuther C., Chanalet S., Thomas P., Lebrun C.

Service de Neurologie — Hôpital Pasteur 06000 Nice — France.

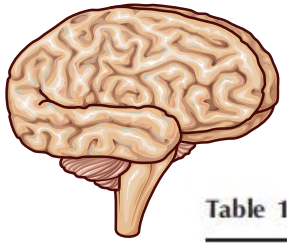
Introduction. Nous présentons un nouveau cas de forme pseudo-tumorale de Neuro-Whipple. Le tableau neurologique est au premier plan alors que le bilan digestif est resté négatif.

Observations. Il s'agissait d'une patiente de 38 ans, sans antécédents notables, adressée pour le bilan d'une hypersomnie. L'examen neurologique était normal. L'IRM encéphalique montrait un volumineux hypersignal du plancher du troisième ventricule d'allure tumorale, fortement rehaussé après injection de Gadolinium. Le bilan sanguin ne retrouvait qu'un très discret syndrome inflammatoire biologique. L'étude du LCR était normale (nombre d'éléments, protéinorachie, marqueurs inflammatoires : index d'immunoglobulines et immunofixation). La PCR Whipple sur le LCR était fortement positive, ce qui nous permit de poser le diagnostic de certitude. Une monothérapie par Bactrim® fut débutée rapidement. Une réaction allergique

Cohe, *Revue de neurologie*, 2007

Whipple disease is a rare infection caused by the bacterium *Tropheryma whippelii*. Patients usually present with gastrointestinal symptoms or migratory arthralgias. Although symptomatic central nervous system (CNS) involvement frequently occurs, Whipple disease confined to the CNS is rare. The authors present the case of a 40-year-old man who was surgically treated for a symptomatic left frontal tumor that had the neuroimaging features of a low-grade glioma (LGG). A histopathological investigation revealed a **perivascular accentuated inflammation with macrophages harboring PAS-positive diastase-resistant rods, which are distinctive features of cerebral Whipple disease.** The patient received cotrimoxazole for 1 year postoperatively and recovered well. This case is exceptional because it represents an isolated cerebral manifestation of Whipple disease that presented as a solitary frontal tumor, thus raising the differential diagnosis of LGG. A review of diagnostic and therapeutic options in suspected cases is presented

Löhr, *J neurosurg*, 2004



NeuroWhipple, F, 48 ans

Table 1 Cerebral Whipple's disease: laboratory data and MRI findings

Visit	Date	Findings
1	25 Nov 2003	Generalized tonic/clonic seizures
2	25 Nov 2003	Hyponatraemia—SIADH
3	28 Nov 2003	Atrophy and gliosis right hippocampal formation—MRI
4	29 Dec 2003	Severe amnesic syndrome including verbal and visuospatial memory
5	29 Mar 2004	Blepharospasm and complete paralysis of vertical gaze
6	31 Mar 2004	Development nodular enhancing lesions—MRI: right temporal lobe; caudate nuclei; anterior commissure; right globus pallidus; left insula cortex; left hippocampal formation; lenticular striate territory; mesencephalon and perivascular spaces
7	1 Apr 2004	Subacute deterioration with reduced consciousness, CSF pleocytosis (polymorphs) and decreased CSF protein
8	22 Jul 2004	Severe obstructive sleep apnoea
9	22 Jul 2004	Reduced sleep efficiency, frequent waking and sleep fragmentation
10	1 May 2004	Oligoclonal bands

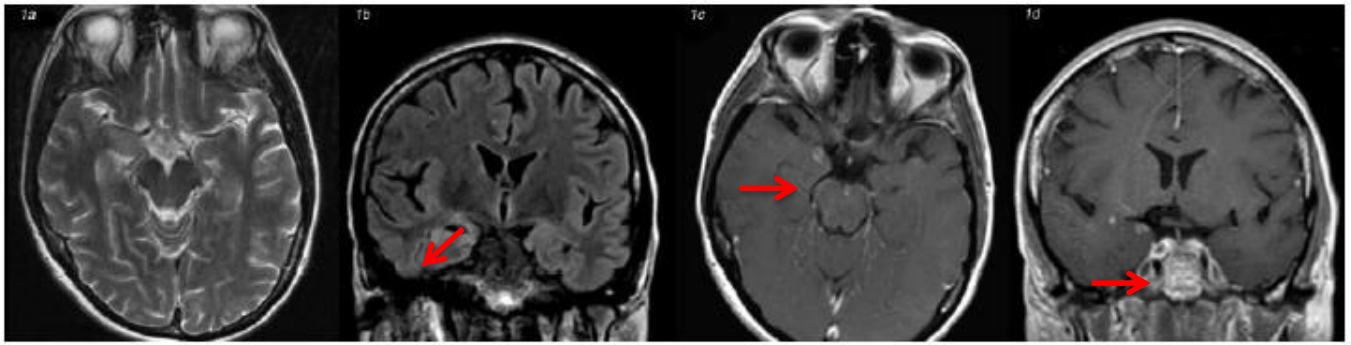
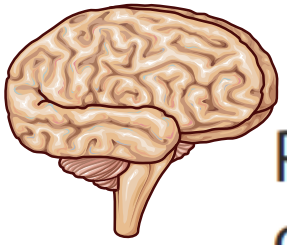


Figure 1. MR images obtained 3 days after presentation. **a** Transverse T2-weighted image showing right mesial temporal lobe oedema and swelling. **b** Coronal FLAIR image demonstrating right hippocampal oedema. **c,d** Transverse and axial contrast-enhanced T1-weighted images showing nodular mesial temporal enhancement.

Panegyres, *QJM*, 2006



Progressive dementia associated with ataxia or obesity in patients with *Tropheryma whipplei* encephalitis

Florence Fenollar[1], François Nicoli[2,3], Claire Paquet[4], Hubert Lepidi[1], Patrick Cozzone[3], Jean-Christophe Antoine[5], Jean Pouget[2] and Didier Raoult[1*]

Abstract

Background: *Tropheryma whipplei*, the agent of Whipple's disease, causes localised infections in the absence of histological digestive involvement. Our objective is to describe *T. whipplei* encephalitis.

Methods: We first diagnosed a patient presenting dementia and obesity whose brain biopsy and cerebrospinal fluid specimens contained *T. whipplei* DNA and who responded dramatically to antibiotic treatment. We subsequently tested cerebrospinal fluid specimens and brain biopsies sent to our laboratory using *T. whipplei* PCR assays. PAS-staining and *T. whipplei* immunohistochemistry were also performed on brain biopsies. Analysis was conducted for 824 cerebrospinal fluid specimens and 16 brain biopsies.

Results: We diagnosed seven patients with *T. whipplei* encephalitis who demonstrated no digestive involvement. Detailed clinical histories were available for 5 of them. Regular PCR that targeted a monocopy sequence, PAS-staining and immunohistochemistry were negative; however, several highly sensitive and specific PCR assays targeting a repeated sequence were positive. Cognitive impairments and ataxia were the most common neurologic manifestations. Weight gain was paradoxically observed for 2 patients. The patients' responses to the antibiotic treatment were dramatic and included weight loss in the obese patients.

Conclusions: We describe a new clinical condition in patients with dementia and obesity or ataxia linked to *T. whipplei* that may be cured with antibiotics.

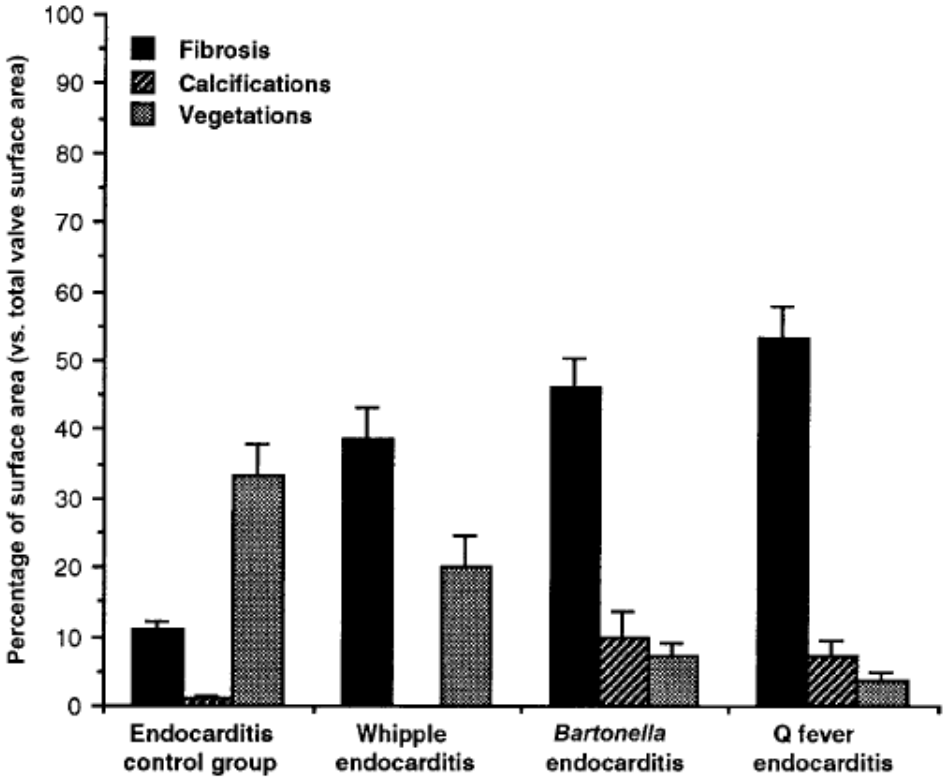
Endocardites à *T. whipplei*

Blood culture–negative endocarditis associated with *T. whipplei*[30-38]	
No. of patients	17
Male sex — no. (%)	14 (82)
Previous valvular disease — no. (%)	7 (41)
Acute rheumatic fever	3 (18)
Bicuspid aortic valve	2 (12)
Aortic bioprosthesis	2 (12)
Antecedent — no. (%)	12 (71)
Arthralgia or arthritis	8 (47)
Seronegative polyarthritis	2 (12)
Psoriatic arthritis	1 (6)
Myalgia	1 (6)
Interval between onset of symptoms and definite diagnosis — range (mean)	2 mo–20 yr (5 yr)
Involved valves — no. (%)	
Aortic	8 (47)
Mitral	4 (24)
Tricuspid	1 (6)
Aortic and mitral	3 (18)
Aortic and tricuspid	1 (6)
Fever — no. (%)	2 (12)
Cardiac vegetations — no. (%)	13 (76)
Congestive heart failure — no. (%)	10 (59)
Arterial emboli — no. (%)	10 (59)

Pas de fièvre
Pas de valvulopathie sous jacente

Fenollar, *NEJM*, 2007
Gubler, *Ann Intern Med*, 1999

Endocardites à *T. whipplei*



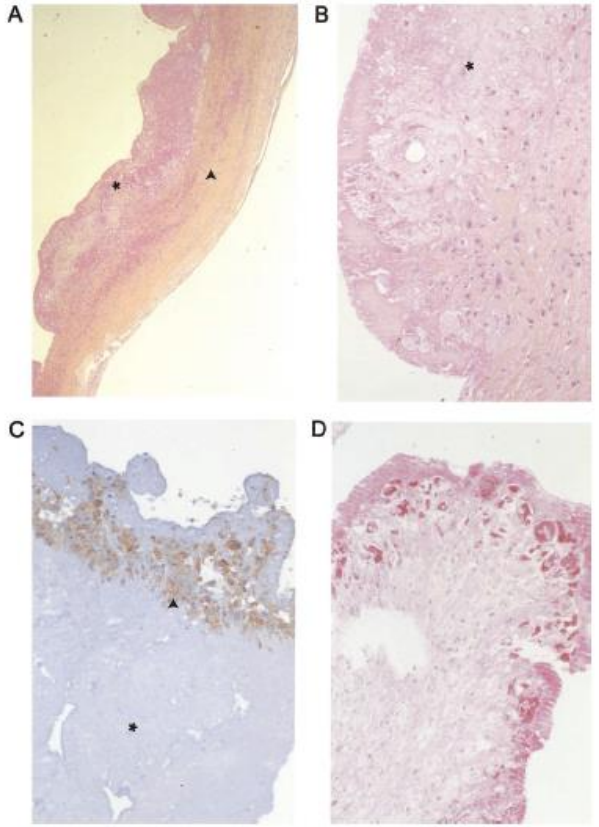
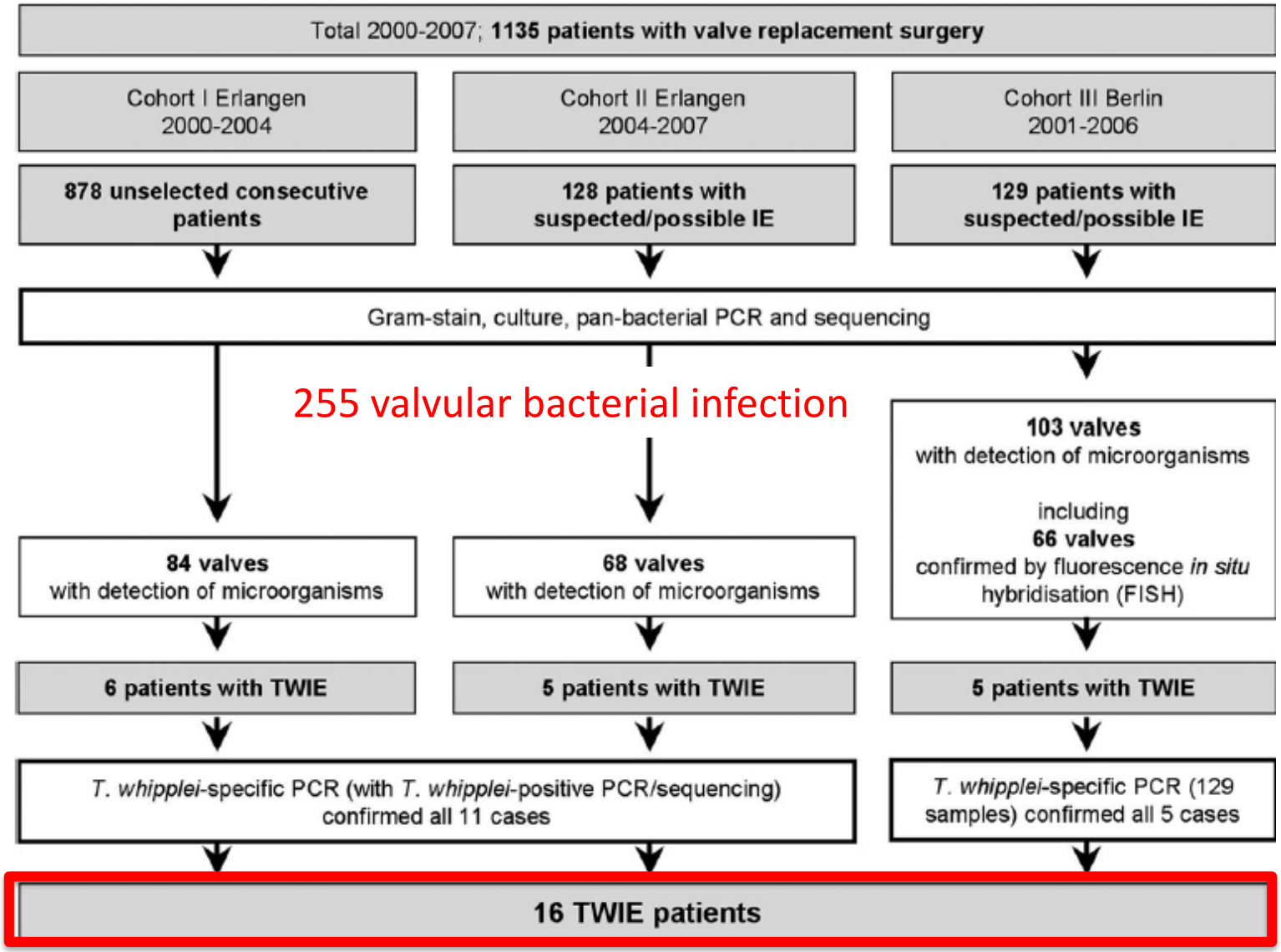


Figure 1. Aortic valve with Whipple endocarditis. *A*, Superficial vegetation (*) and fibrosis of the connective valve tissue (*arrowhead*) (hematoxylin-eosin-saffron; original magnification, ×40). *B*, Mononuclear inflammatory cell infiltrate with numerous foamy macrophages, with a clear distended cytoplasm (*) within the vegetation (hematoxylin-eosin-saffron; original magnification, ×250). *C*, Focal inflammatory infiltrate composed mainly of immunostained macrophages (*arrowhead*) representing a small area in the total valve tissue surface. The valve stroma is reorganized and fibrotic (*) (immunoperoxidase staining with an anti-CD68 monoclonal antibody; original magnification, ×250). *D*, High-power magnification of foamy macrophages containing the characteristic inclusion bodies (periodic acid–Schiff stain; original magnification, ×250).

Lepidi, *J Infect Dis*, 2004

EIHN et *T. whipplei*



Geißdörfer, *JCM*, 2012

EIHN et *T. whipplei*

"Classical" Whipple's disease (cWD) is caused by *Tropheryma whipplei* and is characterized by arthropathy, weight loss, and diarrhea. *T. whipplei* infectious endocarditis (TWIE) is rarely reported, either in the context of cWD or as isolated TWIE without signs of systemic infection. The frequency of TWIE is unknown, and systematic studies are lacking. Here, we performed an observational cohort study on the incidence of *T. whipplei* infection in explanted heart valves in two German university centers. Cardiac valves from 1,135 patients were analyzed for bacterial infection using conventional culture techniques, PCR amplification of the bacterial 16S rRNA gene, and subsequent sequencing. *T. whipplei*-positive heart valves were confirmed by specific PCR, fluorescence *in situ* hybridization, immunohistochemistry, histological examination, and culture for *T. whipplei*. Bacterial endocarditis was diagnosed in 255 patients, with streptococci, staphylococci, and enterococci being the main pathogens. *T. whipplei* was the fourth most frequent pathogen, found in 16 (6.3%) cases, and clearly outnumbered *Bartonella quintana*, *Coxiella burnetii*, and members of the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*). In this cohort, *T. whipplei* was the most commonly found pathogen associated with culture-negative infective endocarditis.

1-*Streptococcus*
2-*Staphylococcus*
3-*Enterococcus*
4-*Tropheryma whipplei* (6.3%)
Bar*tonella quintana*
Coxiella burnetii
HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)

Geißdörfer, *JCM*, 2012

EIHN et *T. whipplei*

TABLE 1 Characteristics of TWIE patients[a]

Patient	Sex	Age at diagnosis (yr)	Valve	Presence of gastrointestinal symptoms	Test result		
					PCR valve	PAS valve	*T. whipplei* IHC valve
1[b]	M	69	AV	Neg[e]	Pos	Pos	ND
2[c]	M	76	AV/XE	Neg	Pos	Pos	Pos
3	M	65	MV	Neg	Pos	Pos	Pos
4	F	60	AV	Neg	Pos	Pos	ND
5	M	69	AV	Neg	Pos	ND	ND
6	M	72	AV	Neg	Pos	ND	ND
7[d]	F	77	AV	Neg	Pos	Pos	Pos
8	M	63	AV	Neg	Pos	Pos	Pos
9	M	72	AV	Neg	Pos	Pos	Pos
10	M	46	AV	Neg	Pos	ND	ND
11	M	69	AV	Neg	Pos	Pos	Pos
12	F	57	MV	Neg	Pos	Pos	ND
13	M	56	AV	Neg	Pos	Pos	Pos
14	M	59	AV	Neg	Pos	ND	ND
15	F	79	AV	Pos[f]	Pos	ND	ND
16	F	73	MV	Pos[f]	Pos	ND	ND

Geißdörfer, *JCM*, 2012

EIHN et *T. whipplei*

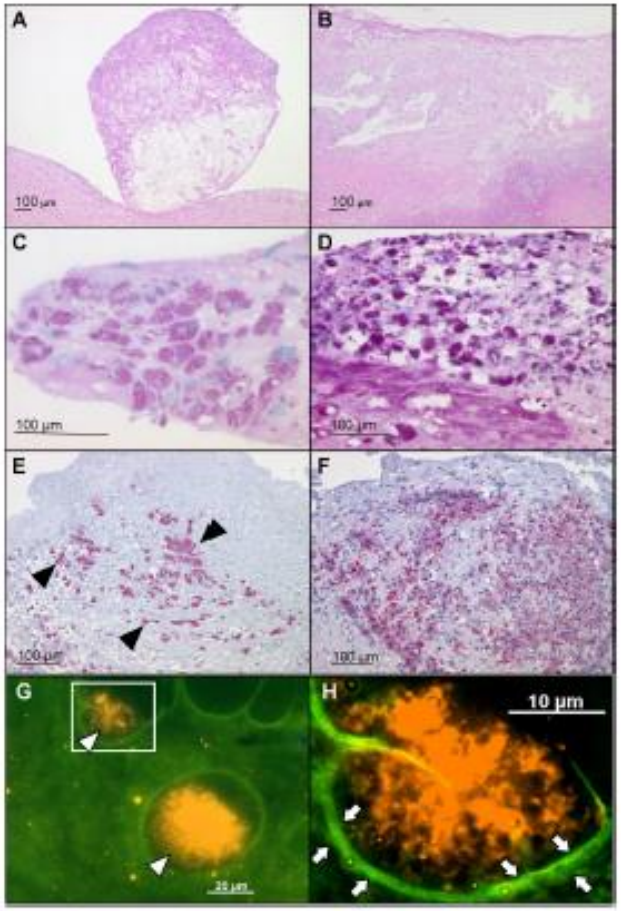


FIG 2 Histology and FISH of exemplary heart valves of patients with isolated *T. whipplei* IE. (A and B) HE stainings (C and D) PAS; (E and F) *T. whipplei*-specific immunohistochemistry. (G and H) FISH with the specific probe RE-WHIP3. (A) Polypoid vegetation. (B) Fibrotic valve with an infiltrate of foamy macrophages. (C and D) Red-stained PAS-positive macrophages in the stroma. (E and F) Numerous *T. whipplei*-infected macrophages stained red (exemplary ones are marked with black arrowheads) (alkaline phosphatase-anti-alkaline phosphatase [APAAP] method using Fast Red). (G) FISH with the specific probe RE-WHIP3 of the cardiac valve of a patient with isolated *T. whipplei* IE. The overlay of the fluorescein isothiocyanate (FITC) and Cy5 filter sets shows clusters of *T. whipplei* FISH-positive cells (orange, with open arrowheads) in the green autofluorescent background of the tissue. (H) Inset of panel G at a higher magnification. Fibrosis surrounding the bacteria is visible (bright green fluorescence and open arrows).

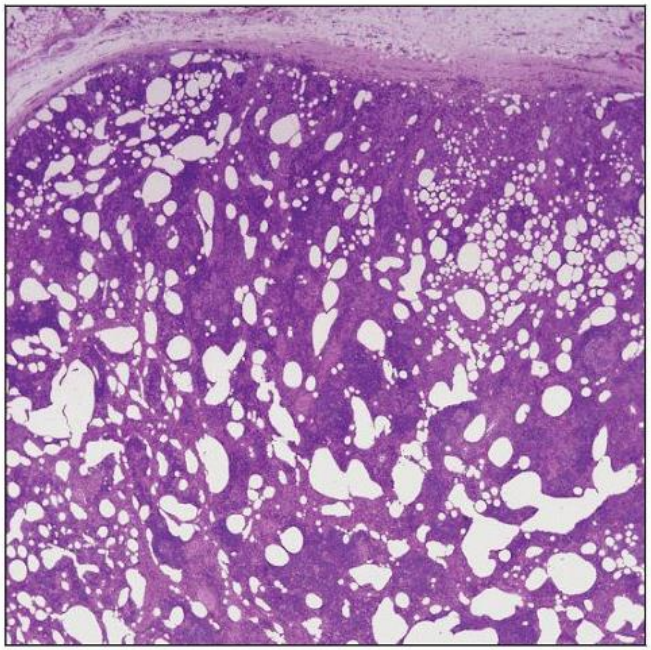
Geißdörfer, *JCM*, 2012

Caractéristiques histologiques ganglionnaires

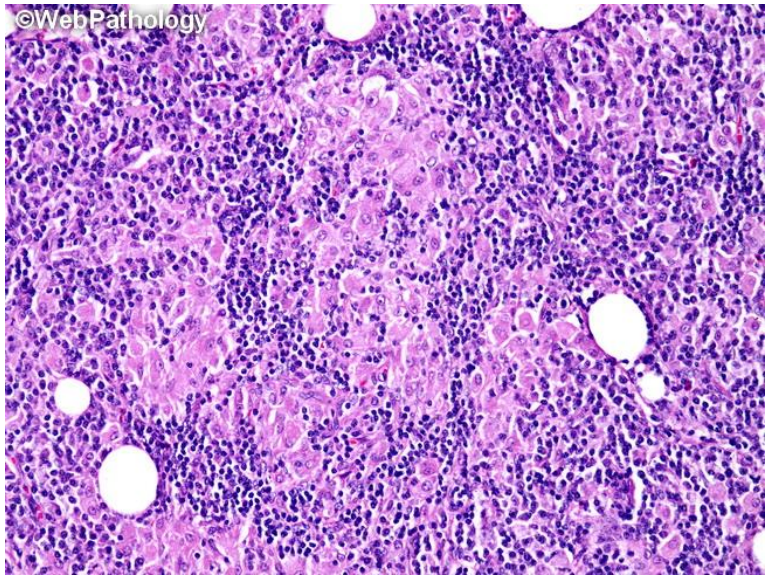
Dépôts extracellulaires d'adipocytes

Granulômes gigango-cellulaires non caséeux (médiastinal, mesentérique)

Lésions PAS négatives décrites dans 40% des cas



Whipple disease involving mesenteric lymph node. The nodal architecture is obscured by ill-defined lipogranulomas and cystic spaces.

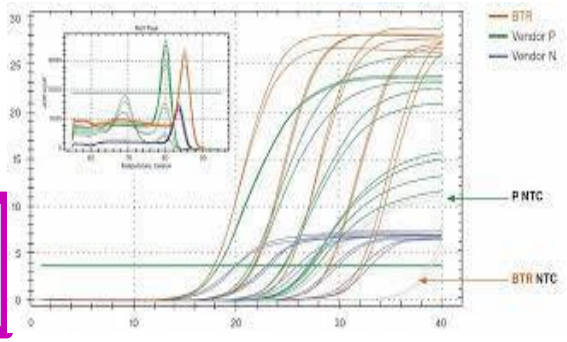


Webpathology, Whipple disease

Diagnostic

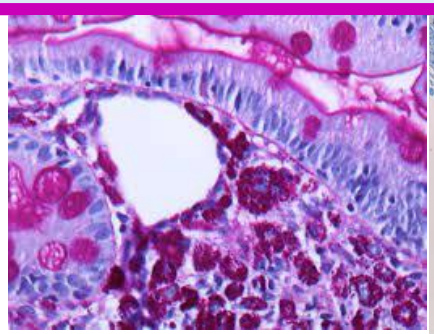
Outils microbiologiques

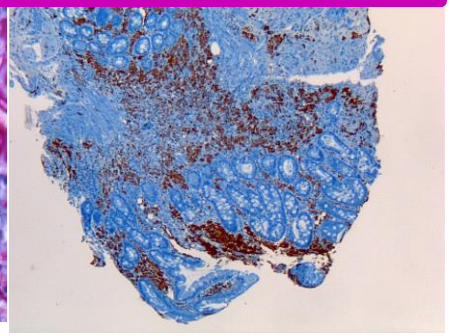
1-PCR *T. whipplei*: selles sang et salive



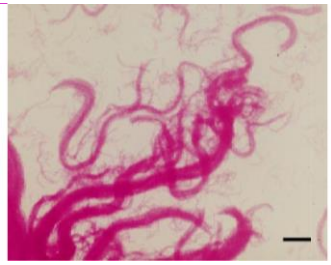
2-PCR *T. whipplei*: tissus profond

3-Histologie: HE, PAS et IHC





4-Culture sur milieu cellulaire



Lésion histologique endoscopies

Duodénum

FIGURE 1: Whipple's disease: severe involvement of the distal duodenum (D4). Folds are low, and mucosa is swollen and grey-yellowish with multiple reddish spots (small mucosal haemorrhages).

Couleur jaune pâle, vaisseaux lymphatiques ectasiés, inflammation, saignements

Jéjunum

FIGURE 2: Whipple's disease: jejunal mucosa is swollen and grey-pink with small whitish areas and multiple tiny mucosal haemorrhages.

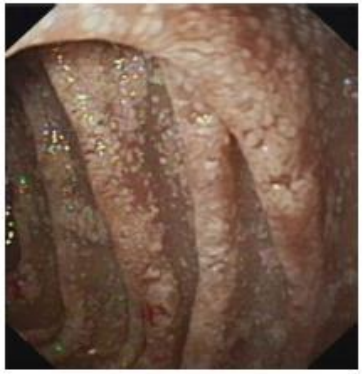
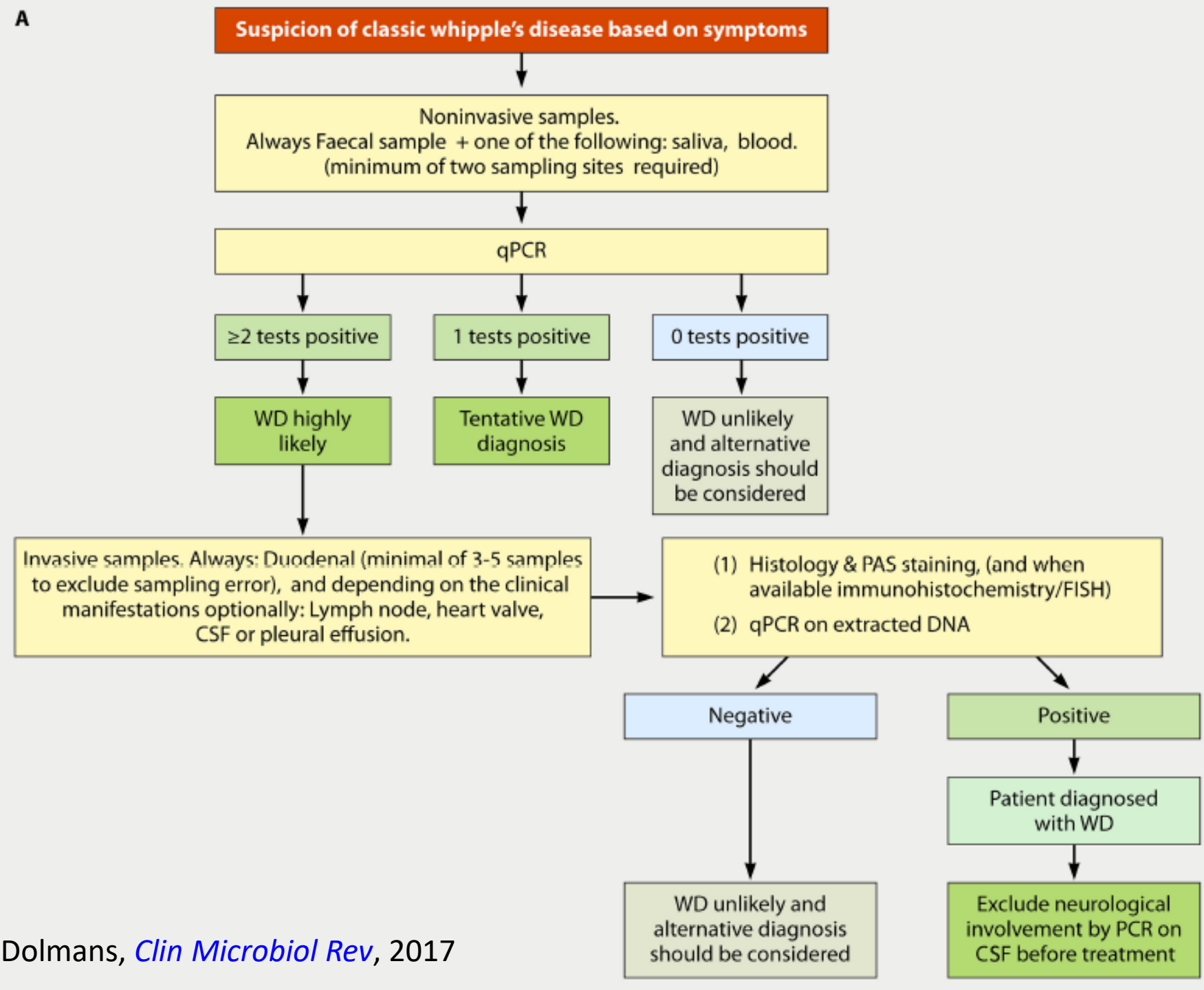


FIGURE 5: Whipple's disease: picture of the jejunum. Characteristic whitish areas protrude the above surrounding relief.

We typically obtain **seven to ten biopsies** from different parts of the **duodenum** and, if possible, sample the stomach and **proximal jejunum,** ileum.

BiopsieS DUODENALES
FIXEES (PAS et IHC) + CONGELEES (-80°C) ou fraîches (PCR et culture)



Dolmans, *Clin Microbiol Rev*, 2017

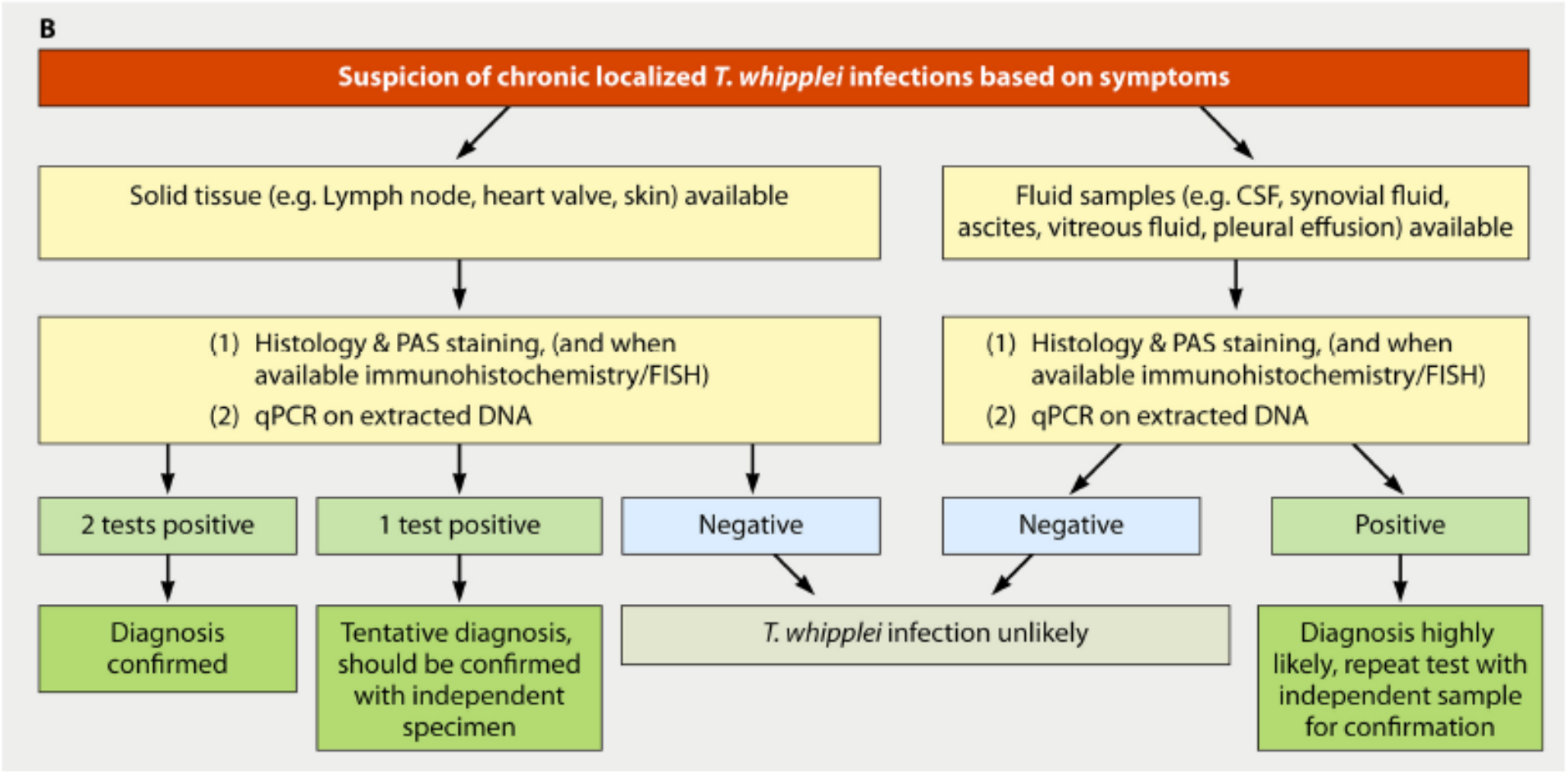


FIG 1 Schematic representation of the diagnostic algorithm. (A) Diagnostic strategy for classic Whipple's disease (WD). (B) Diagnostic strategy for chronic localized *T. whipplei* infection.

PAS pos non spécifique dans le SNC

Dolmans, *Clin Microbiol Rev*, 2017

Diagnostic différentiels PAS positive

Histologie

-Histoplasma spp

-Rhodococcus

-Mycobacterium

-Corynebacterium

-Bacillus cereus

Traitement

En l’absence de traitement

La maladie de Whipple est mortelle

In vitro

Doxycycline
Macrolide
Ketolides
Aminoglycosides
Trimethoprime-**sulfamethoxazole** (TW R T)

} MIC 0.25-2mcg/ml

Doxycycline
+ hydroxychloroquine

= bactéricide

Cephalosporine, polymixin, aztreonam

Moins actif sur *T. whipplei* intracellulaire

Fluoroquinolone

✘ Résistant

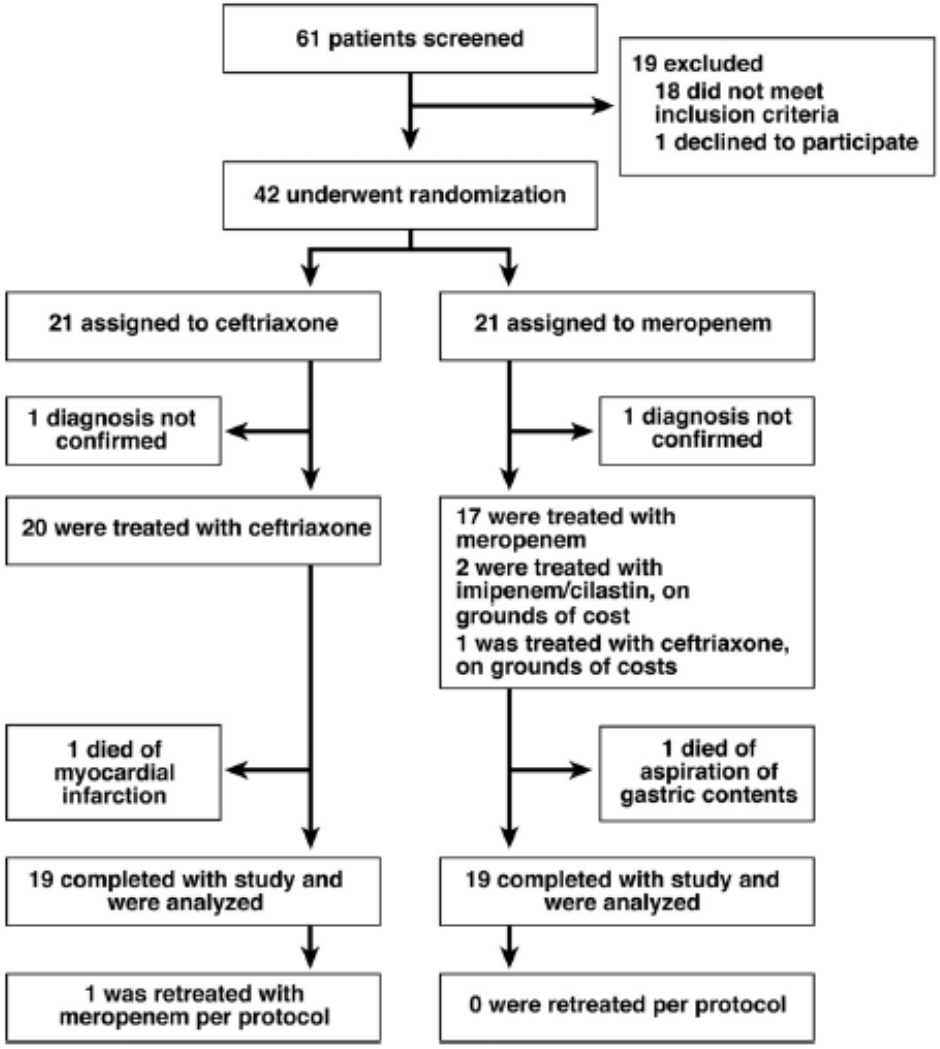
In vitro

TABLE 4 Value of different antibiotics in treatment of Whipple's disease

Antibiotic(s)	Success rate	Dose per day	Reference(s)
Streptomycin	Bad	1.0 g	205
Penicillin	Fair	1.2 million units	205
Tetracycline	Fair	600 mg	205, 231
Trimethoprim-sulfamethoxazole	Fair	160 mg/800 mg	201–204, 207
Ceftriaxone–trimethoprim-sulfamethoxazole	Fair	2 g/160 mg/800 mg	147
Meropenem–trimethoprim-sulfamethoxazole	Fair	3 g/160 mg/800 mg	147
Doxycycline-hydroxychloroquine	Good	200 mg/600 mg	207

Dolmans, *Clin Microbiol Rev*, 2017

La seule étude randomisée contrôlée évaluant l'efficacité thérapeutique du traitement antibiotique dans la maladie de Whipple



BACKGROUND & AIMS: Whipple's disease is a chronic infection caused by the actinomycete *Tropheryma whipplei*. We conducted a randomized controlled trial of the efficacy of antimicrobials that are able to cross the blood-brain barrier and to which *T whipplei* is susceptible. **METHODS:** Patients from central Europe with previously untreated Whipple's disease (n = 40) were assigned randomly to groups given daily infusions of either ceftriaxone (1 × 2 g, 20 patients) or meropenem (3 × 1 g, 20 patients) for 14 days, followed by oral trimethoprim–sulfamethoxazole for 12 months. The primary outcome measured was maintenance of remission for 3 years, determined by a composite index of clinical and laboratory data as well as histology. **RESULTS:** All patients were observed for the entire follow-up period (median, 89 mo; range, 71–128 mo); all achieved clinical and laboratory remission. Remission was maintained in all patients during the time of observation, except for 2 who died from unrelated causes. A single patient with asymptomatic cerebrospinal infection who was resistant to both treatments responded to chloroquine and minocycline. The odds ratio for the end point (remission for at least 3 years) was 0.95 (95% confidence interval, 0.05–16.29; $P = 1.0$). **CONCLUSIONS: This was a randomized controlled trial to show that treatment with ceftriaxone or meropenem, followed by trimethoprim–sulfamethoxazole, cures patients with Whipple's disease. One asymptomatic individual with infection of the cerebrospinal fluid required additional therapy.**

Feurle, *Gastroenterology*, 2010

La seule étude randomisée contrôlée évaluant l'efficacité thérapeutique du traitement antibiotique dans la maladie de Whipple

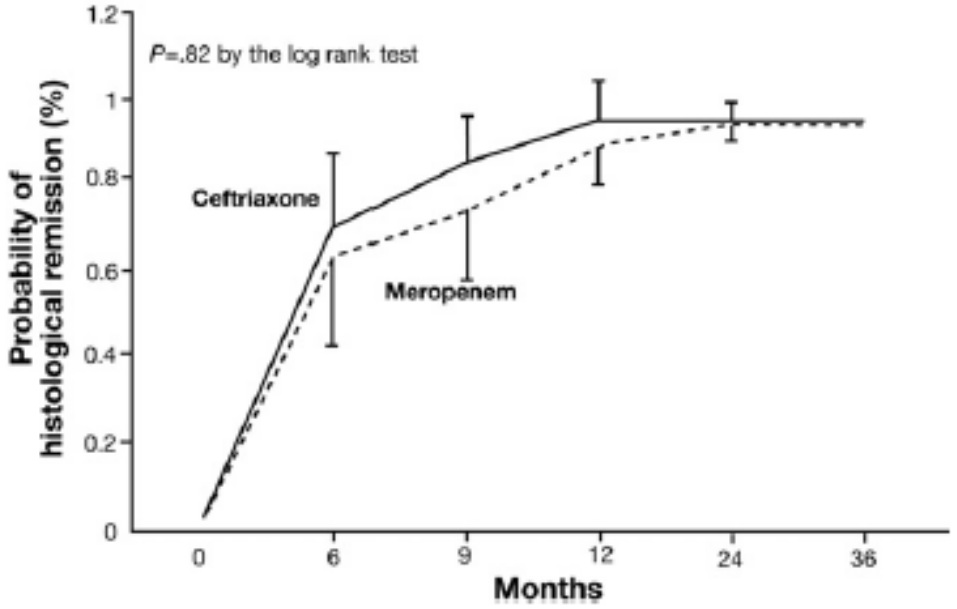


Figure 4. Kaplan–Meier estimate of the time course to remission in tissue samples in the 2 groups of the randomized controlled trial. Ongoing remission in the biopsy specimens is defined microscopically by transformation from the PAS-stained subtype 1 macrophages to the subtypes 2 and 3 (see text for detail). Vertical bars denote 95% confidence intervals, depicted in the Figure as one-sided to avoid overlapping. There is no significant difference in the time course of histological remission.

Feurle, *Gastroenterology*, 2010

Traitement

TTT empirique

Pas d’autre essai randomisé en double aveugle

Antimicrobial therapy in Whipple's disease

Indication	Agent	Duration
Initial therapy		
Initial phase*		
General infection	Ceftriaxone 2 g IV once daily **OR** Penicillin G 2 million units IV every four hours	Two weeks
Endocarditis	Penicillin G 2 million units IV every four hours **OR** Ceftriaxone 2 g IV once daily	Four weeks
Central nervous system disease¶	Ceftriaxone 2 g IV once daily **OR** Penicillin G 4 million units IV every four hours	Two to four weeks
If ceftriaxone and penicillin allergic	Meropenem 1 g IV every eight hours	Two to four weeks
Maintenance phase		
All infections	Trimethoprim-sulfamethoxazole one DS tablet twice daily	One year
If sulfa allergic	Doxycycline 100 mg PO twice daily **PLUS** Hydroxychloroquine 200 mg PO thrice daily	One year
Therapy for relapse		
Initial phase*	Penicillin G 4 million units IV every four hours **OR** Ceftriaxone 2 g IV twice daily	Four weeks
Maintenance phase	Doxycycline 100 mg PO twice daily **PLUS** hydroxychloroquine 200 mg PO thrice daily **OR** Trimethoprim-sulfamethoxazole one DS tablet twice daily for one year	One year

IV: intravenously; IM: intramuscularly; DS: double-strength (one double-strength tablet is equivalent to 160 mg trimethoprim and 800 mg sulfamethoxazole); PO: orally.

* The initial phase is followed by the maintenance phase.

¶ Central nervous system disease includes neurologically asymptomatic patients with a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) test for *Tropheryma whipplei* as well as patients with Whipple's disease and neurologic symptoms despite a negative CSF PCR test.

Graphic 65520 Version 5.0

Uptodate

Traitement

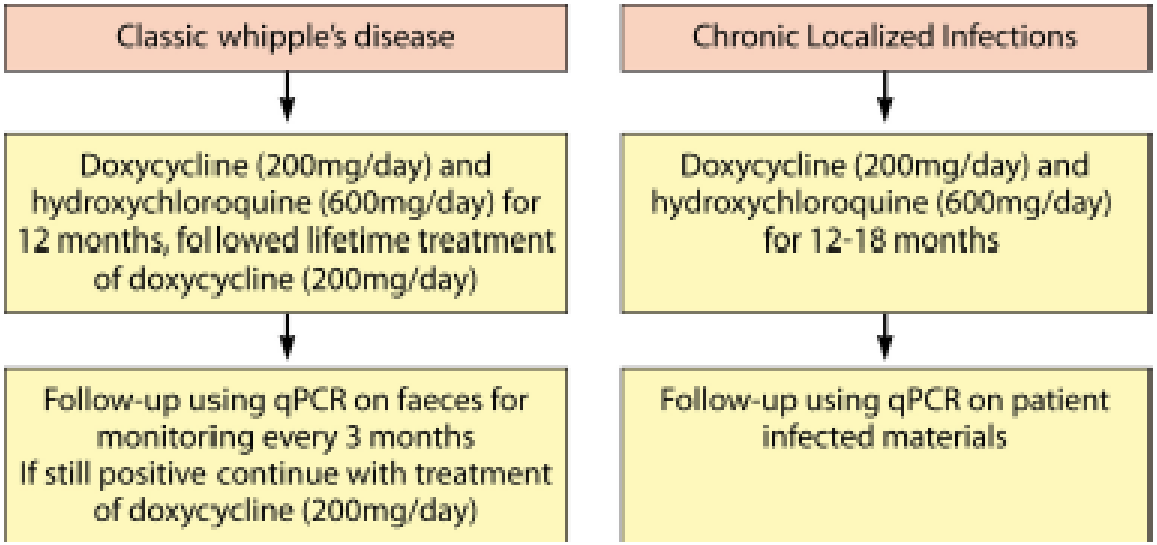


FIG 3 Latest proposed therapeutic strategy to treat *T. whipplei* infections. See the text for explanation.

Dolmans, *Clin Microbiol Rev*, 2017

IRIS

Table 2. **Characteristics of and Laboratory Findings in Patients With and Without IRIS After Treatment of Whipple Disease***

Characteristic	Patients Without IRIS	Patients With IRIS	*P* Value
Mean age (SD), *y*	57 (11) [55–60]	60 (10) [54–65]	0.43
Women/men, *n/n*	16/55	4/11	0.74
Mean BMI (SD), kg/m^2	21 (4) [21–22]	23 (3) [21–24]	0.055
Mean ESR (SD), *mm/h*	50 (27) [43–58]	32 (23) [12–51]	0.063
Lymphadenopathy, *n/n (%)*	23/71 (32.4) [21.8–44.5]	7/15 (46.7) [21.3–73.4]	0.37
Arthritis, *n/n (%)*	57/71 (80.3) [69.1–88.8]	14/15 (93.3) [68.1–99.8]	0.45
Diarrhea, *n/n (%)*	55/71 (77.5) [66.0–86.6]	5/15 (33.3) [11.8–61.6]	0.002
CNS infection with *Tropheryma whipplei*, *n/n (%)*	19/46 (41.3) [27.0–56.8]	7/9 (77.8) [40.0–97.2]	0.069
Weight loss, *n/n (%)*	58/69 (84.1) [73.3–91.8]	5/15 (33.3) [11.8–61.6]	<0.001
Previous immunosuppressive treatment, *n/n (%)*	11/71 (15.5) [8.0–26.0]	12/15 (80.0) [51.9–95.7]	<0.001

BMI = body mass index; CNS = central nervous system; ESR = erythrocyte sedimentation rate; IRIS = immune reconstitution inflammatory syndrome.
* Data in square brackets are 95% CIs.

Feurle, *Ann Med*, 2010

IRIS

10% des patients (15/142)

Symptomes : fièvre, Arthrite, pleurésie, erythème noueux, orbithopathie inflammatoire, perforation intestinale, syndrome hypothalamique

2 décès

Les patients initialement traités par IS sont plus à risque d'IRIS

Traitement par **corticostéroides**

Traitement alternatif **Thalidomide**

Moos, *J Immunol*, 2013
Feurle, *Ann Med*, 2010

Suivi

Clinique

PCR selles et salive

Pas de biopsie duodénale (invasif et NS)

Suivi à vie (pas de guérison de la maladie de Whipple)

Rechute plusieurs année après (2-20 ans)

Proposition d’un traitement par doxycycline au long court

Antibiotic Treatment and Relapse in Whipple's Disease

Long-Term Follow-up of 88 Patients

R. D. KEINATH, D. E. MERRELL, R. VLIETSTRA, and W. O. DOBBINS III

Departments of Medicine, Sections of Gastroenterology, University of Michigan, Duke University, Mayo Clinic, and Veterans Administration Medical Center, Ann Arbor, Michigan

Reports of clinical relapse occurring after apparently successful antibiotic treatment of Whipple's disease prompted this review of long-term follow-up of treated patients. Follow-up of at least 1 yr after completion of treatment or 2 yr after diagnosis was obtained on 88 patients with documented Whipple's disease by a review of the medical literature, correspondence with the authors as needed, and questionnaires mailed to academic gastroenterology programs in the United States. Relapse was defined on the basis of morphology (preferably) or clinically, or both. Thirty-one patients relapsed, 6 of whom relapsed twice. Fifty-seven patients did not relapse. The mean time to relapse was 4.2 yr. The mean follow-up period of patients who did not relapse was

88 patients
-16 rechute neurologique
-13 arthrites
-5 gastrointestinales

patients treated with other regimens relapsed. Nine of the 13 patients with central nervous system relapse had been initially treated with tetracycline, 2 were treated with penicillin, and 2 were treated with combinations of antibiotics. Results of treatment of central nervous system relapse were poor in 10 of the 11 patients for whom details were available. Results of treatment of non-central-nervous-system relapse were excellent in 19 of 20 patients. It is concluded that tetracycline alone, or penicillin alone, is not adequate initial therapy for Whipple's

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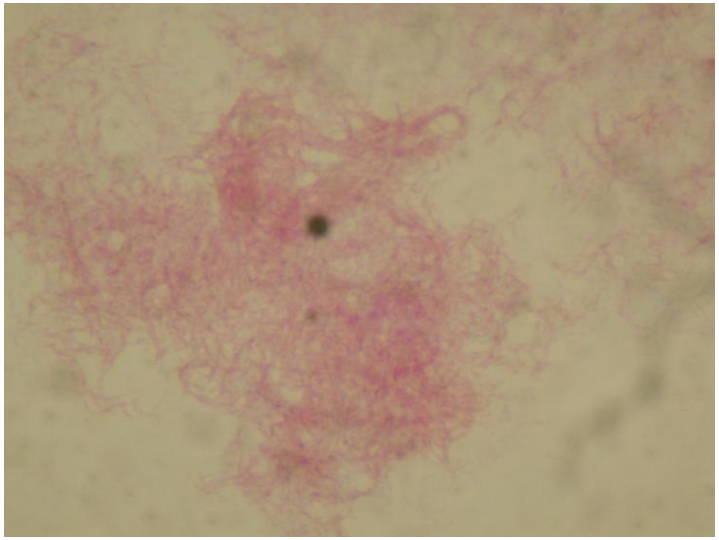
Rechute NeuroWhipple
F/ 75

2003: Maladie de Whipple classique diagnostiquée sur BDU

2015: amaigrissement AEG et ataxie, Sd extrapyramidal, sd cérébelleux cinétique troubles cognitifs, dysautonomie

2015: PCR *T. whipplei* positive sur le LCR
Culture sur milieu axénique du LCR trouble à J104



Parmi les propositions suivantes concernant la maladie de Whipple, lesquelles sont vraies?

A. Le diagnostic repose sur la PCR positive sur la biopsie duodénale
B. Il existe jusqu'à 20% de portage de T. whipplei asymptomatique dans les selles dans certaines populations
C. La PCR positive sur le LCR permet de poser le diagnostic de neurowhipple
D. Le PAS positif sur biopsie duodénale est suffisant au diagnostic d'infection à *T. whipplei*
E. Les rechutes tardives sous forme d'atteintes neurologiques isolées ont été décrites dans la littérature

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Conclusion

Infection à Bactéries intracellulaires

1-Il faut y penser !

2- Sérologie et PCR sont utiles au diagnostic

3- Utiliser des antibiotiques efficaces, sur les intracellulaires et le compartiment intra-cellulaire

4- Dépister les complications (ETT, PET si suspicion d'atteinte vasculaire)

5- Suivi prolongée pour les infections persistantes

6- Suivi à vie pour les rechutes (infections vasculaires à *C. burnetii*, et infections à *T. whipplei*)