

2,434 cases of Q fever From the French National reference center 1991-2016

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Q fever

Coxiella burnetii, gram negative intracellular bacteria Worldwide zoonosis (excepted in New Zealand) Endemic: French Guiana, Netherlands, Africa, France

Acute Q fever (hepatitis and pneumonia) and persistent C. burnetii infection (cardio-vascular infection)

Persistent C. burnetii infection: a changing paradigm

Organic lesion

+ Microbiological evidence (serology, PCR, culture)



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



Peacock, *Infect Imm*, 1983 Raoult, *Clin infect Dis*, 2017 Melenotte, *Int J infect dis*, 2018

National reference Center for Q fever Marseille

Serological test performed each year in the French National Reference Center of *Coxiella burnetii* infection.

Serological tests for Q fever each year in the French NRC





Questionnaire



First name First name Sex : Hospital (city and country) : Physician: Physician: <td< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></td<>											
fever diagnosis already known: ansthoracic echography result at the date of the first positive serology in the NRC for Q fever Acute Q fever Acute Q fever Acute Q fever Follow up fatigue post acute Q fever Date of the begining of symptoms Fever Acute Q fever on medical predisposition → Valvulopathy Thrombophiebitis Inflammatory disease Auto-antibodies Acute Q fever Acute andocarditis (ABC s Certain endocarditis (ABC s Cultivation date Neurological form → Meningitis Acute Hepatitis Lymphadenitis Meningitis Date Cultivation date Other clinical manifestation Serology Igg Igg Igg Igg Igg Igg Igg Igg Igg Igg Quitivation date Meningitis Date N* Igg Igg Igg Igg Igg Igg Igg Igg Igg Igg Igg Quitivation date Meningitis Date Serology Igg Igg Igg Igg Igg Igg Igg Igg Igg Mitoriolitis Meningitis Date <th>First name Family Name Date of Birth</th> <th>Sex :</th> <th>Hospi Physic Tel/Er</th> <th></th> <th colspan="4">QFever</th>	First name Family Name Date of Birth	Sex :	Hospi Physic Tel/Er		QFever						
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		Letter									

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Patients included

Primary (acute) C. burnetii infection

- -acute clinical symptoms -IgG titers II \ge 200 and IgM II \ge 50
- or seroconversion within three months of the primary symptoms.

Persistent C. burnetii focal infection

Persistence of clinical symptoms >3 monthsIdentification of an infectious focus



C. burnetii persistent infection

Systematic PETscan proposed Systematic TTE proposed Number of cases Date (year)

Persistent focalized C. burnetii infection

Q fever clinical presentation



Number of patients

Acute Q fever

Acute Q fever complication and anticardiolipins

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



Q fever complications



Acute Q fever endocarditis



50 cases of acute Q fever endocarditis

28 % had a preexisting valvulopathy

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

3 positive culture from blood

Persistent C. burnetii complications

C. burnetii persistent infection

Clinical presentation of persistent C. burnetii infections: 766 patients

	Endoca N=5	rditis 81	Vascular i N=1	nfection 45	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%	2.1		11	19.2%	
Osteoarticular infection	8	1.3%	11	7.5%		100	
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%	

Q fever the hidden pathogen of interstitial lung diseases



Table 1. Clinical Description of Patients With Q Fever and ILD

Patient Sex/Age, y	Geographic Origin	Medical History	Positive Autoimmune Imr Test Result	nunosuppressive Treatment	<i>C. burnetii</i> Focus Infection (in Addition to Lung)	C. burnetii Serology: IgGl, IgMl, IgAl IgGll, IgMll, IgAll Levels	<i>C. burnetii</i> Microbiological Analysis	Delay Between O Fever and ILD, mo ⁶	Radiological Feature	ILD C. burnetii Infection	Hospitalization	Q Fever Treatment	Outcome
1/M/72 (index patient)	Troyes, France	Asbestos exposure	ANCAs (MPO)	Corticoid and rituximab	Endocarditis (A183C2)	800, 0, 0, 400, 0, 0	IHC, FISH, and PCR ^o	-60°	Unclassified	Definite	ICU	HD	Partial clinical improvement at 71 mo
2/M/51	Reunion Island, France	Rheumatoid polyarthritis	RF/ANAs	Corticoids	Endocarditis (A0B1C2)	400, 0, 100, 800, 0, 200	No	-1 ^b	Unclassified	Possible	ICU	No	Died at 0.2 mo
3/F/70	Marseille, France	Tobacco	No	No	NI	800, 0, 0, 800, 0, 0	No	-24°	UIP	Possible	Medicine	No	Partial clinical improvement at 51 mo
4/M/57	French Guiana	Dermatopolymyositis	No	Corticoid and methotrexate	Endocarditis (A2B2C0)	51 200, 0, 3200, 102 400, 0, 6400	No	21	Unclassified	Possible	Medicine	HD	Partial clinical improvement a 51 mo
5/M/78	French Guiana	Asbestos exposure, amiodarone use, tobacco use	No	Na	NI	400, 0, 0, 400, 0, 0	No	0.5	Unclassified	Possible	Medicine	D	Partial clinical improvement at 2 mo
6/M/83	Toulouse, France	Amiodarone use	No	No	NI	1600, 0, 0 0, 0, 0	No	0.5	Unclassified	Possible	ICU	HD	Partial clinical improvement at 4 mo
7/F/59	Marseille, France	Tobacco use	ANCAs	Azathioprine	Granulomatous hepatitis	3200, 0, 100, 1600, 0, 200	IF ^d	0	NSIP	Possible	ICU	HD	Partial clinical improvement at 7.1 mo

Lymphadenitis

Focalized persistent *C. burnetii* lymphadenitis as the unique focus of *C. burnetii* persistent infection. Identification of the deep and persistent infective focus with PET-scan.



97 lymphadenitis

44% isolated with PET-scanner

associated with a risk of lymphoma HR=77.4, 95% CI [21.2-281.8], p<.001

Biopsy revealed positive FISH targeting the cpecific *C. burnetii* 16S rRNA A & B. PET scan with positive mediastinal lymphadenitis C. Positive FISH targeting *C. burnetii* 16S rRNA

Q fever and lymphoma



Patients with Q fever had a 25-fold increased risk of NHL

C. burnetii identified in macrophages and plasmacytoid dendritic cells

Gradiant IL-10 in patients with persistent C. burnetii infection, lymphadenitis and lymphoma

Q fever and lymphoma

Anatomical site of lymphoma

N=8-Lymph nodes 3-Cervical : 1 DLBCL, 1 T-cell lymphoma, 1 Marginal lymphoma 2-Abdominal: 1 DLBCL 1 & FL 1-Inguinal : 1 DLBCL 1-Mediastinal : DLBCL N=13 persistent focalized infection N=4 acute Q fever 1-Axillar : Lymphoplasmocytic lymphoma N=1-Lung 1-DLBCL 2-Pneumonia 9-Persistent Endocarditis N=1-Pectoral mass 1-DLBCL 1-Hepatitis N=2-Gastric 3-Vascular 1-MALT infection 1-NHL gastric lymphoma N=1-Spleen 1-Marginal zone lymphoma 1-Persistent N=3-Osteomedullar lymphadenitis 1-Isolated 1-Mantle cell lymphoma lymphadenitis 1-Marginal zone lymphoma 1-T cell lymphoma N=1 acute evolving to persistent C. burnetii

infection

Coxiella burnetii infectious foci

Mortality rate



Time from diagnosis (years)

	Number at risk									
Endocarditis	533	245	157	105	63	35	22	16	8	
Vascular infection	96	24	12	6	2	0	0	0	0	
Both (PEI and PVI)	49	18	9	5	2	2	0	0	0	
Other persistent focus	87	18	9	2	1	0	0	0	0	

Limitations

¹/₄ patients with acute Q fever were lost follow-up

C. burnetii cardio-vascular infections were probably over-represented

Conversely, the mortality rate might be underestimated because of potential loss to follow-up.

Conclusion

Cardio-vascular : fatal complication

Anticardiolipin antibodies associated with acute complications

Neglected rare foci

Alithiasic cholecystitis

Haemophagocytic syndrome

Acute Q fever endocarditis

Lymphadenitis

Lymphoma

Interstitial lung disease

Use TTE and PET !

Thank you

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