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

Dr Cléa Melenotte
Marseille
IHU Méditerranée Infection
**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)

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**Persistent *C. burnetii* infection: a changing paradigm**

- Organic lesion
  - + Microbiological evidence (serology, PCR, culture)

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

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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

<table>
<thead>
<tr>
<th>First name</th>
<th>Family Name</th>
<th>Sex</th>
<th>Hospital (city and country):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Tel/Email:</td>
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</tbody>
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**Q Fever**

- Acute Q fever
- Follow up fatue post acute Q fever
- Date of the beginning of symptoms
- Fever
- Acute Q fever on medical predisposition
- Thrombophlebitis
- Vascular
- Pericarditis
- Myocarditis
- Immunosuppression
- HIV
- Neurological form
- Meningitis
- Pneumonia
- Encephalitis
- Acute Hepatitis
- Lymphadenitis
- Other clinical manifestation

**Serology**

<table>
<thead>
<tr>
<th>Date</th>
<th>N</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
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</table>

**Polymerase chain reaction**

<table>
<thead>
<tr>
<th>Date</th>
<th>Sample</th>
<th>Smarlab</th>
<th>IS1111</th>
<th>IS30</th>
<th>Actine</th>
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**CULTURE and PCR**

<table>
<thead>
<tr>
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<th>No</th>
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<tbody>
<tr>
<td>MIC</td>
<td></td>
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</tbody>
</table>

Second serum request

| Yes | No |

Anticardiolipin antibodies

Letter

Treatment

- Yes
- Antibiotic use:
- Date of beginning:
- Date of the end:

Inflammatory disease
- Auto-antibodies
- Treatment resistance
- Corticoids

Acute endocarditis
- Follow up of acute Q fever
- Possible endocarditis (ABC score)
- Certain endocarditis (ABC score)
- Possible vascular infection
- Certain vascular infection
- Lung pseudo tumor
- Osteoarticular infection
- Other:
Patients included

**Primary (acute) *C. burnetii* infection**
- acute clinical symptoms
- IgG titers II ≥ 200 and IgM II ≥ 50
- or seroconversion within three months of the primary symptoms.

**Persistent *C. burnetii* focal infection**
- Persistence of clinical symptoms >3 months
- Identification of an infectious focus
C. burnetii persistent infection

Persistent focalized C. burnetii infection

Systematic TTE proposed

Systematic PET-scan proposed
Q fever clinical presentation
Acute Q fever
Acute Q fever complication and anticardiolipins

**eTable 13. ROC analysis of IgG anticardiolipin antibodies and acute Q fever complications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Q fever endocarditis</td>
<td>.67</td>
<td>.58</td>
<td>.76</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
<td>.78</td>
<td>.67</td>
<td>.89</td>
</tr>
<tr>
<td>Meningitis</td>
<td>.68</td>
<td>.56</td>
<td>.79</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>.72</td>
<td>.6</td>
<td>.85</td>
</tr>
<tr>
<td>Alithiasic cholecystitis</td>
<td>.75</td>
<td>.6</td>
<td>.9</td>
</tr>
</tbody>
</table>

AUC: area under curve, CI: confidence interval

**Q fever complications**

- Women
- Men

French Guiana

Metropolitan France
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 |
|---|---|---|---|
|               | 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%                        |
Q fever the hidden pathogen of interstitial lung diseases

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age, y</th>
<th>Geographic Origin</th>
<th>Medical History</th>
<th>Positive Autoimmune Test Result</th>
<th>Immunosuppressive Treatment</th>
<th>C. burnetii Focus Infection (in Addition to Lung)</th>
<th>C. burnetii Serology: IgG1, IgM1, IgAl Levels</th>
<th>C. burnetii Microbiological Analysis</th>
<th>Delay Between Q Fever and ILD, mo¹</th>
<th>Radiological Feature</th>
<th>ILD C. burnetii Infection</th>
<th>Hospitalization</th>
<th>Q Fever Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/72</td>
<td>3/70</td>
<td>Troyes, France</td>
<td>Asbestos exposure</td>
<td>ANCA, MPO</td>
<td>Corticoid and rituximab</td>
<td>Endocarditis A1B3C2</td>
<td>800, 0, 0, 400, 0, 0</td>
<td>IHC, FISH, and PCR ¹</td>
<td>−60</td>
<td>Unclassified</td>
<td>Definite</td>
<td>ICU</td>
<td>HD</td>
<td>Partial clinical improvement at 71 mo</td>
</tr>
<tr>
<td>2/M/51</td>
<td>2/51</td>
<td>Reunion Island, France</td>
<td>Rheumatoid polyarthritis</td>
<td>RF/ANAs</td>
<td>Corticoids</td>
<td>Endocarditis A0B1C2</td>
<td>400, 0, 100, 800, 0, 200</td>
<td>No</td>
<td>−1</td>
<td>Unclassified</td>
<td>Possible</td>
<td>ICU</td>
<td>No</td>
<td>Died at 0.2 mo</td>
</tr>
<tr>
<td>3/F/70</td>
<td>3/F/70</td>
<td>Marseille, France</td>
<td>Tobacco</td>
<td>No</td>
<td>No</td>
<td>NI</td>
<td>800, 0, 0, 800, 0, 0</td>
<td>No</td>
<td>−24</td>
<td>UIP</td>
<td>Possible</td>
<td>Medicine</td>
<td>No</td>
<td>Partial clinical improvement at 51 mo</td>
</tr>
<tr>
<td>4/M/57</td>
<td>4/M/57</td>
<td>French Guiana</td>
<td>Dermatomyositis</td>
<td>No</td>
<td>No</td>
<td>Corticoid and methotrexate</td>
<td>A1B2C0</td>
<td>No</td>
<td>21</td>
<td>Unclassified</td>
<td>Possible</td>
<td>Medicine</td>
<td>HD</td>
<td>Partial clinical improvement at 51 mo</td>
</tr>
<tr>
<td>5/M/78</td>
<td>5/M/78</td>
<td>French Guiana</td>
<td>Asbestos exposure</td>
<td>No</td>
<td>No</td>
<td>NI</td>
<td>400, 0, 0, 400, 0, 0</td>
<td>No</td>
<td>0.5</td>
<td>Unclassified</td>
<td>Possible</td>
<td>Medicine</td>
<td>D</td>
<td>Partial clinical improvement at 51 mo</td>
</tr>
<tr>
<td>6/M/83</td>
<td>6/M/83</td>
<td>Toulouse, France</td>
<td>Amiodarone use</td>
<td>No</td>
<td>No</td>
<td>NI</td>
<td>1600, 0, 0, 0, 0</td>
<td>No</td>
<td>0.5</td>
<td>Unclassified</td>
<td>Possible</td>
<td>ICU</td>
<td>HD</td>
<td>Partial clinical improvement at 51 mo</td>
</tr>
<tr>
<td>7/F/59</td>
<td>7/F/59</td>
<td>Marseille, France</td>
<td>Tobacco use</td>
<td>ANCA</td>
<td>Azathioprine</td>
<td>Granulomatous hepatitis</td>
<td>3200, 0, 100, 1600, 0, 200</td>
<td>IF²</td>
<td>0</td>
<td>NSIP</td>
<td>Possible</td>
<td>ICU</td>
<td>HD</td>
<td>Partial clinical improvement at 71 mo</td>
</tr>
</tbody>
</table>

Melenotte, *Clin infect dis*, 2018
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
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

Gradient 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
- 1-Axillar: Lymphoplasmocytic lymphoma

**N=1-Lung**
- 1-DLBCL

**N=1-Pectoral mass**
- 1-DLBCL

**N=2-Gastric**
- 1-MALT
- 1-NHL gastric lymphoma

**N=1-Spleen**
- 1-Marginal zone lymphoma

**N=3-Osteomedullar**
- 1-Mantle cell lymphoma
- 1-Marginal zone lymphoma
- 1-T cell lymphoma

Coxiella burnetii infectious foci

**N=4 acute Q fever**
- 2-Pneumonia
- 1-Hepatitis

**N=13 persistent focalized infection**
- 9-Persistent Endocarditis
- 3-Vascular infection
- 1-Persistent lymphadenitis

**N=1 acute evolving to persistent C. burnetii infection**
Mortality rate

58 patients died due to 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)

Kaplan-Meier survival estimates:

<table>
<thead>
<tr>
<th>Condition</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
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<tbody>
<tr>
<td>Persistent endocarditis (PEI)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Persistent vascular infection (PVI)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Persistent endocarditis and vascular infection (PEI + PVI)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other persistent focus</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</table>

Number at risk:

<table>
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<tr>
<th></th>
<th>533</th>
<th>245</th>
<th>157</th>
<th>105</th>
<th>63</th>
<th>35</th>
<th>22</th>
<th>16</th>
<th>8</th>
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<tbody>
<tr>
<td>Endocarditis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular infection</td>
<td>96</td>
<td>24</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Both (PEI and PVI)</td>
<td>49</td>
<td>18</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other persistent focus</td>
<td>87</td>
<td>18</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Limitations

¼ 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

Marseille
Didier Raoult
Camélia Protopopescu
Patrizia Carrieri
Matthieu Million
Sophie Edouard
Jean-Louis Mège
Philippe Parola

Cayenne
Félix Djossou
Loïc Epelboin
Aba Mahamat
You