Chronic Q fever

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Radboud Expertise Center for Q fever
## Conflict of interest

<table>
<thead>
<tr>
<th>(potential) conflict of interest</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially relevant relationships with companies</td>
<td>None</td>
</tr>
<tr>
<td>• Sponsorship or grant for research</td>
<td>• Research grants Q-support</td>
</tr>
<tr>
<td>• Fee or other (financial) compensation</td>
<td>• None</td>
</tr>
<tr>
<td>• Shareholder</td>
<td>• None</td>
</tr>
<tr>
<td>• Other relationship</td>
<td>• None</td>
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</table>

Q fever outbreak the Netherlands

- Q fever:
  - zoonotic infection
  - *Coxiella burnetii*

- 2007 to 2010: Q fever outbreak the Netherlands:
  - >4000 patients notified with acute Q fever
  - >40,000 people infected
  - Localized in the southeastern part of the Netherlands

- Clinical syndromes:
  - Acute Q fever
  - Q fever fatigue syndrome
  - Chronic Q fever
Definition chronic Q fever

Proven chronic Q fever
- Phase 1 IgG ≥ 1024
- Endocarditis
- Vascular infection
- OR
- Positive PCR Q fever
- blood or tissue

Probable chronic Q fever
- Phase 1 IgG ≥ 1024
- Risk factors
- Symptoms chronic infection
- Atypical focus

Possible chronic Q fever
- Phase 1 IgG ≥ 1024

Follow-up

Treat

Kampschreur et al., J Infect. 2012;64(3):247-59
Q fever endocarditis

- 70-80% of all chronic Q fever patients
- The Netherlands: 35% of all chronic Q fever patients
- Usually in patients with underlying valve disease
- Vegetations often absent: difficult diagnosis!
- Revised Duke criteria: high anti-phase I antibody level
- Important cause of culture-negative endocarditis
Vascular chronic Q fever

- <10% of all chronic Q fever cases in France
- 60% of all chronic Q fever cases in the Netherlands

Frequent complications:
- Aneurysm rupture
- Aorto-enteric fistulas with gastrointestinal bleeding
- Paravascular abscesses
- Spondyl(odisc)itis
Dutch Chronic Q fever Database

- Data of all known Dutch chronic Q fever patients

- Patients identified by:
  - Microbiology labs
  - Infectious diseases specialists

- Last complete update May 2016, planned in 2018

- 249 patients with proven chronic Q fever
  - 27% endocarditis
  - 50% vascular infection
  - 16% endocarditis and vascular infection

- 74 patients with probable chronic Q fever
Complications

Update May 2016 database:
• 439 patients with chronic Q fever (until May 2012: 284 patients)

• Complications present:
  • 61% proven chronic Q fever
  • 15% probable chronic Q fever
  • 2% possible chronic Q fever

  • 60% vascular chronic Q fever
  • 48% Q fever endocarditis

Kampschreur et al., J Clin Microbiol. 2014;52(5):1637-43
Van Roeden et al., submitted (update 2016)
## Complications and mortality

<table>
<thead>
<tr>
<th></th>
<th>Complications (OR, 95% CI)</th>
<th>Mortality Q fever (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.02-1.06)</td>
<td>1.03 (1.00-1.06)</td>
</tr>
<tr>
<td>Prosthetic valve or vascular prosthesis</td>
<td>1.79 (1.07-2.99)</td>
<td>Ns</td>
</tr>
<tr>
<td>Positive serum PCR</td>
<td>2.25 (1.36-3.72)</td>
<td>Ns</td>
</tr>
<tr>
<td>Four-fold titer decrease</td>
<td>Ns</td>
<td>0.27 (0.12-0.58)</td>
</tr>
<tr>
<td>Complications</td>
<td>NA</td>
<td>8.20 (3.65-18.45)</td>
</tr>
</tbody>
</table>
Mortality chronic Q fever

Van Roeden et al., poster ECCMID 2017, submitted
Mortality chronic Q fever

- Proven chronic Q fever: 25%
- Probable chronic Q fever: 4%
- Possible chronic Q fever: none

- Endocarditis and vascular infection: 33%
- Vascular infection: 25%
- Endocarditis: 12%

Van Roeden et al., poster ECCMID 2017, submitted
Screening for chronic Q fever

**General population:**

- 2014 (7 years after the start of the outbreak)
- Screening Q fever serology 1517/2161 adult inhabitants of Herpen
- Seroprevalence 33.8%
- 2 known chronic Q fever patients
- 1 new chronic Q fever patient

- 4.4% chronic Q fever in 69 patients with a known cardiovascular risk factor

Morroy et al., PLOS one, 2015 Jul 1;10(7):e0131777
Screening risk groups

Vascular infections:
- Jeroen Bosch Hospital and Bernhoven Hospital,
- November 2009 until January 2012
- Screening chronic Q fever (IFA) in all patients with:
  - AAA ≥30 mm
  - Aneurysm iliac artery >12 mm
  - EVAR
  - Vascular prosthesis aorta or iliac arteries
- Seroprevalence Q fever among 770 patients: 16.9%
- Chronic Q fever in 30.8% of all patients with positive Q fever serology

Hagenaars et al., J Inf 2014;69:154-60
Screening risk groups

Endocarditis:
• November 2010 until January 2011 in Jeroen Bosch Hospital
• Screening of all patients with previous heart valve surgery

• Seroprevalence among 568 patients: 20.4%
• Chronic Q fever in 7.8% of all patients with positive Q fever serology

Screening risk groups

Reumatoid arthritis:
- Area of Q fever outbreak, December 2011 until June 2012
- Screening of all patients with reumatoid arthritis
- Seroprevalence among 759 patients: 14.8%
- Chronic Q fever in 8.9% of all patients with positive Q fever serology

Dutch chronic Q fever database

• ~75% of all patients diagnosed with proven or probable chronic Q fever have a risk factor and can be identified by screening

• 68% of all patients has a complication before start of antibiotic therapy, so diagnosis came “too late”
FDG-PET/CT in chronic Q fever

- Localizing infection is difficult in chronic Q fever:
  - Vegetations often not seen on echocardiography
  - Chronic low-grade vascular infection easily missed on CT

- FDG-uptake in all activated inflammatory cells: sensitive imaging technique

- FDG-PET/CT has proven its diagnostic value in:
  - Diagnosing vascular infection
  - Prosthetic valve endocarditis (EASC guideline 2015)

- Low sensitivity of FDG-PET/CT for diagnosing native valve endocarditis (but high specificity)

Granados et al., JNM 2016;57:1669-71
European Society of Cardiology guideline endocarditis 2015
FDG-PET/CT at diagnosis

230 FDG-PET/CT scans

Change of diagnosis: probable → proven n = 31 (13.5%)

New complications:
• Psoas abscess: n = 8 (3.5%)
• Spondylodiscitis n = 3 (1.3%)
• Spondylodiscitis and psoas abscess n = 4 (1.7%)

Effect on treatment decision:
• Start antibiotic treatment: n = 37 (16.1%)
• Change antibiotic treatment: n = 2 (0.9%)
• Surgical intervention: n = 6 (2.6%)

PET/CT helpful in 47 patients (20.4%)

Kouijzer et al., JNM 2017 May 25 Epub, poster ESCCAR 2017
FDG-PET/CT during follow-up

• 218 FDG-PET/CT scans performed in 143 patients

• Reason for follow-up scans:
  • Suspected new complications: n=175 (80.3%)
  • End of treatment evaluation: n=43 (19.7%)

• Change of diagnosis probable to proven chronic Q fever: n=2 (0.9%)
• Change of treatment: n=125 (57.3%)
FDG-PET/CT: patient

2012 abdominal aneurysm → EVAR

2015-01: malaise, weight loss 10kg, backache, no fever.
IFA phase I IgG antibodies: 1:4096.
FDG-PET/CT: minimally increased uptake around EVAR, psoas abscess.
Positive PCR psoas abscess.

2015-04: FDG-PET/CT:
FDG uptake around EVAR, psoas, muscles, and spondylodiscitis L4.
Treatment of chronic Q fever

- Tetracycline effective, but long-term treatment needed, many relapses
- Tetracyclines combined with quinolones more effective
- *C. burnetii* replicates within acidified phagolysosome in macrophages and monocytes decreasing bactericidal activity of antibiotics
- Alkalizing agent such as hydroxychloroquine increases pH in phagolysosome

Maurin et al., J Infect Dis 1992;166:1097-102
Treatment of chronic Q fever

First-line treatment of chronic Q fever: doxycycline with hydroxychloroquine

Raoult et al., Arch Int Medicatie: 1999;167-73
Treatment of chronic Q fever

- Doxycycline with hydroxychloroquine many side effects:
  - Gastrointestinal
  - Phototoxicity (>90%)
  - Cutaneous hyperpigmentation
  - Retinopathy

- Treatment failure in some cases
- Need for alternative regimens

Treatment of chronic Q fever

- Descriptive retrospective observation cohort study with data from Dutch National Chronic Q fever Database

- Time-dependent Cox proportional hazards analysis to compare efficacy of different treatment regimens

- Reference regimen: doxycycline with hydroxychloroquine

- Comparator regimens:
  - Doxycycline with quinolone (with or without hydroxychloroquine)
  - Quinolone monotherapy
  - Doxycycline monotherapy
Treatment of chronic Q fever

• Outcome: overall mortality and therapy failure defined as:
  • New complication >6 weeks after initiation of treatment
  • New positive PCR having been negative >3 months
  • PCR-positivity persisting >6 months during treatment
  • Chronic Q fever related mortality
Treatment of chronic Q fever

• Outcome: overall mortality and therapy failure defined as:
  • New complication >6 weeks after initiation of treatment
  • New positive PCR having been negative >3 months
  • PCR-positivity persisting >6 months during treatment
  • Chronic Q fever related mortality

• 276 patients included:
  • 227 proven chronic Q fever (82%)
  • 49 probable chronic Q fever (18%)

• Mean treatment duration 2.0 years
• Doxycycline plus hydroxychloroquine used by 254 patients (92%)
• 160 patients (58%) used multiple regimens
Treatment of chronic Q fever

- Treatment with doxycycline plus quinolone or treatment with quinolone alone not associated with the primary outcome compared to tetracycline plus hydroxychloroquine

<table>
<thead>
<tr>
<th></th>
<th>DOX/HCQ</th>
<th>DOX/QNL</th>
<th>QNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>254 (92%)</td>
<td>71 (26%)</td>
<td>93 (34%)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>27 (11%)</td>
<td>8 (11%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>Chronic Q fever related mortality</td>
<td>22 (9%)</td>
<td>5 (7%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Complications</td>
<td>34 (13%)</td>
<td>11 (15%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Therapy failure</td>
<td>61 (24%)</td>
<td>12 (17%)</td>
<td>21 (23%)</td>
</tr>
</tbody>
</table>

- Treatment with quinolone or doxycycline monotherapy frequently discontinued due to subjective insufficient clinical response (29% and 59%)
Doxycycline levels

TABLE 1. Serum doxycycline concentration, MIC, and outcome for 16 patients with Q fever endocarditis

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>No. of dilution decrease</th>
<th>Serum doxycycline level (μg/ml) after 1 yr of treatment</th>
<th>Doxycycline MIC (μg/ml)</th>
<th>Serum/MIC ratio</th>
<th>Outcome</th>
<th>Duration of treatment (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>3.8 ± 0.4</td>
<td>4</td>
<td>1.0</td>
<td>Still under therapy</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2.5 ± 0.1</td>
<td>4</td>
<td>0.6</td>
<td>Cured</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3.9 ± 0.5</td>
<td>4</td>
<td>1.0</td>
<td>Dead*</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2.2 ± 0.1</td>
<td>4</td>
<td>0.6</td>
<td>Cured</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2.1 ± 0.2</td>
<td>4</td>
<td>0.5</td>
<td>Cured</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2.7 ± 0.4</td>
<td>4</td>
<td>0.7</td>
<td>Still under therapy</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>4.0 ± 0.4</td>
<td>4</td>
<td>1.0</td>
<td>Cured</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>5.9 ± 0.6</td>
<td>2</td>
<td>3.0</td>
<td>Cured</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>3.9 ± 0.4</td>
<td>2</td>
<td>2.0</td>
<td>Cured</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>4.0 ± 1.4</td>
<td>2</td>
<td>2.0</td>
<td>Cured</td>
<td>29</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>3.2 ± 0.6</td>
<td>2</td>
<td>1.6</td>
<td>Cured</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>4.7 ± 0.8</td>
<td>2</td>
<td>2.4</td>
<td>Cured</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>8.3 ± 1.1</td>
<td>4</td>
<td>2.1</td>
<td>Dead*</td>
<td>19</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>2.9 ± 0.1</td>
<td>2</td>
<td>1.5</td>
<td>Cured</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>4.5 ± 0.7</td>
<td>1</td>
<td>4.5</td>
<td>Still under therapy</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>3.5 ± 0.6</td>
<td>8</td>
<td>0.4</td>
<td>Dead</td>
<td>14</td>
</tr>
</tbody>
</table>

*a These patients died without suffering an evolutive Q fever.

*b Patients 1 to 5 had decreases of IgG and/or IgA phase I antibody titers of ≥2 dilutions (group B). Patients 7 to 15 had decreases of IgG and/or IgA phase I antibody titers of ≥2 dilutions (group A). Patient 16 died during the course of treatment.

- High ratio serum doxycyclin concentration/MIC (>1) associated with rapid decline in antibody levels
Doxycycline levels

• 201 patients with chronic Q fever treated with doxycycline >12 weeks:
  • In 167 patients (83%): treatment based on doxycycline concentrations
  • In 34 patients (17%): treatment not based on doxycycline concentrations

• Primary outcome: first disease-related event (new complication or Q fever related mortality) during or within one year after end of treatment

• Multivariable analysis with a Cox proportional hazards model adjusted for the intensity of patient care
Doxycycline levels

- Target level between 5 and 10 μg/ml
- In 145 patients (87%) serum concentration >5 μg/ml reached

Van Roeden et al., poster ESCCAR 2017, submitted
Doxycycline levels

- Disease-related events HR (95%CI): 0.50 (0.26-0.96)

- Advice for all patients treated with doxycycline for chronic Q fever:
  - measurement of serum doxycycline concentrations
  - titration of doxycycline dosage up to serum doxycycline concentrations >5 µg/ml
Treatment chronic Q fever

- Treatment duration endocarditis at least 18 months
- Prosthetic heart valve at least 24 months
- Treatment duration in vascular infection unknown, in clinical practice (much) longer
- Treatment duration for other than preferred regimes longer (how long?)

Treatment can be stopped:
- Minimal treatment duration has been reached
- Four-fold titer decrease or phase I IgG ≤ 1024
- Serum PCR negative
- No active infection on imaging
Chronic Q fever: a complicated disease

• Think of chronic Q fever!

• Difficult diagnosis: FDG-PET/CT useful for diagnosis and during follow-up

• Difficult treatment:
  • Many side effects
  • Doxycycline with a quinolone appears to be a safe alternative to doxycycline with hydroxychloroquine
  • Determining doxycycline levels needed during doxycycline therapy
Thanks to:

• University Medical Center Utrecht, the Netherlands
  • Sonja van Roeden
  • Jan-Jelrik Oosterheert

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  • Peter Wever

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  • Ilse Kouijzer

• All hospitals, doctors, and patients participating in the Dutch Chronic Q fever Database

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