Q Fever in the USA - Diagnosis, Treatment and Management

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Q Fever in the USA

- Nationally notifiable disease – reported to CDC
- National seroprevalence 3.1% = 10 million exposures
- <200 cases reported per year
- Reasons for underreporting:
  - Lack of awareness/recognition
    - Medical community
    - Public
  - Asymptomatic infections – cattle strains predominant
- Endemic disease – prevalence?
- MMWR Reports & Recommendations on Q fever diagnosis, treatment and management – published fall 2012

Q Fever Diagnostic Algorithm. *This algorithm is intended for use as a general guide and does not replace the physician's clinical judgment.*

Patient has clinical evidence of **acute Q fever** infection (e.g., fever, headache, rigors, weight loss, myalgia, arthralgia, pneumonia, or hepatitis). If suspect case, perform diagnostic testing and initiate empiric treatment with doxycycline. Do NOT wait for laboratory results to begin treatment and do NOT stop treatment based on negative acute serology results.

Patient has laboratory evidence of **acute Q fever** infection:

- Four-fold increase in Phase II IgG or IgM antibody titer by IFA test in paired serum samples; or
- Convalescent Phase II IgG antibody titer by IFA of ≥1:128; or
- Detection of DNA in a clinical specimen by PCR assay; or
- IHC staining of organism in a clinical specimen; or
- Isolation of *C. burnetii* from a clinical specimen by culture

No

No further treatment; further testing only for highly suspect laboratory-negative cases

Yes

Acute Q fever case

Perform clinical evaluation to determine if high-risk patient for chronic disease: heart valve or vascular defect. *Pregnant patient see footnote.

Yes

Repeat clinical assessment and serology at 3, 6, 12, 18 and 24 months..

No

Repeat clinical assessment and serology in ~6 months

Patient has clinical evidence of **chronic Q fever** infection with organ involvement

AND

Patient has laboratory evidence of **chronic Q fever** infection:

- Demonstration of Phase I IgG antibody titer by IFA ≥1:1024; or
- Detection of DNA in a clinical specimen (e.g. heart valve) by PCR assay; or
- IHC staining of organism in a clinical specimen (e.g. heart valve); or
- Isolation of *C. burnetii* from a clinical specimen by culture

No

NOT A CASE unless clinical ***and*** laboratory evidence is present. Continue serologic and clinical monitoring. If nonspecific clinical findings present with laboratory evidence, perform thorough search for focus of infection (e.g., echocardiogram, PET/CT scan).

Yes

Chronic Q fever case. Treat appropriately (minimum 18 months [native valves] and 24 months [prosthetic valves] for endocarditis); monitor clinically and serologically throughout treatment.

Serologic monitoring demonstrates four-fold decrease in Phase I IgG **AND** Clinical recovery.

Yes

Discontinue antibiotic treatment and continue twice yearly serologic monitoring for potential relapse (minimum 5 years).

No

Continue antimicrobial treatment and serologic monitoring. Consult Q fever expert.

*Acute infection in pregnant woman, treat accordingly and monitor throughout pregnancy.

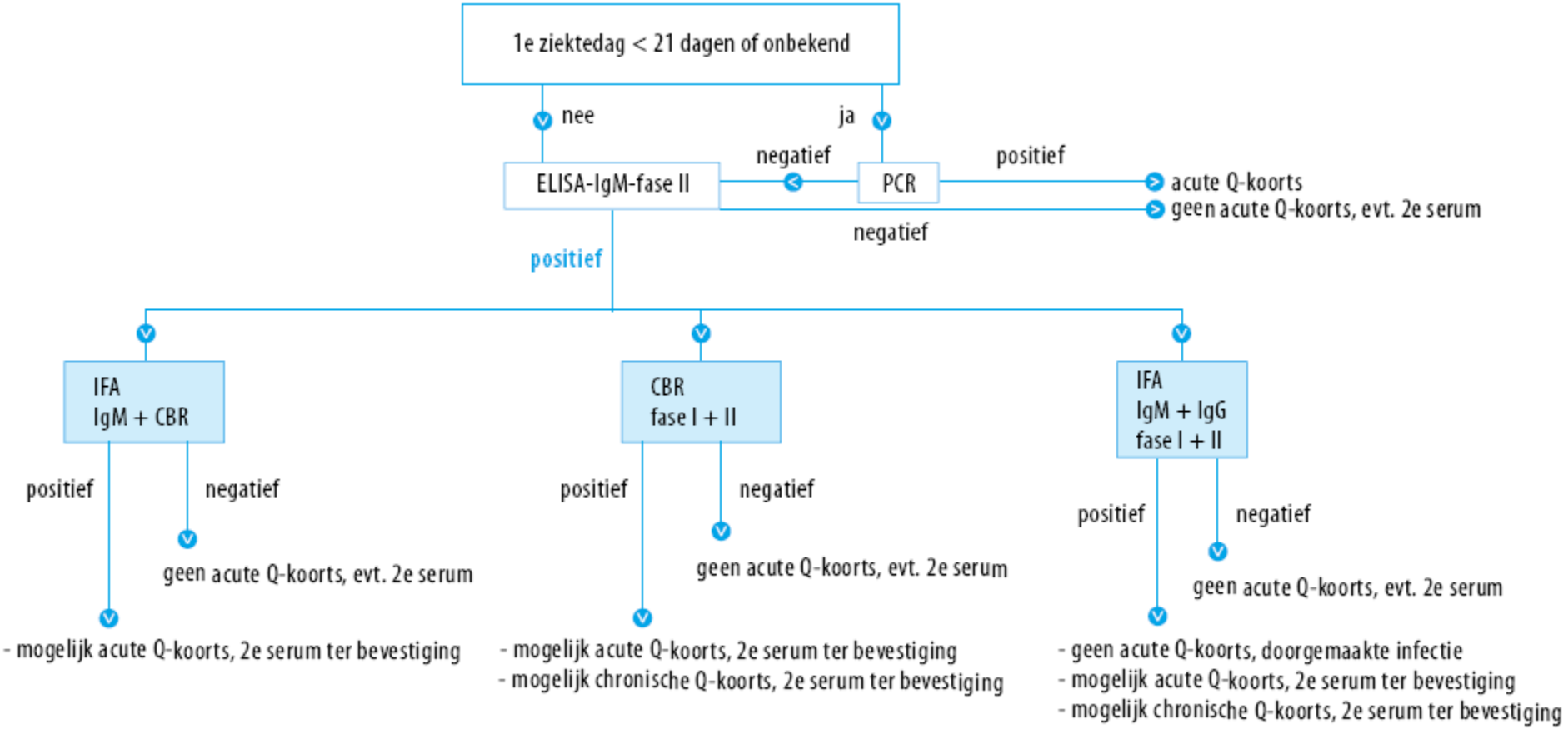
Q Fever Diagnostic Testing Recommendations

Type of sample	Interval since onset of symptoms	Type of Analysis
Acute – whole blood	Until day 14	PCR
Acute – serum	Until day 21 for IFA Until day 14 for PCR	IFA for Phase I and II IgG and IgM ; PCR
Convalescent – serum	3-6 weeks after acute sample	IFA for Phase I and II IgG and IgM
Chronic – whole blood	>6weeks after acute illness	PCR
Chronic – serum	>6weeks after acute illness	IFA for Phase I and II IgG and IgM ; PCR
Heart valve and other tissues	Chronic illness (occurring 6 weeks to years later)	PCR, culture, IHC

Diagnostic Testing Summary

- PCR of whole blood or serum useful to diagnose acute Q fever in the first two weeks of symptom onset; a negative result does not rule out Q fever.
- IFA of paired acute and convalescent specimens remains gold standard to confirm diagnosis of acute Q fever. ELISAs useful for population screening but generally lack specificity of IFA.
- For patients initially evaluated late in disease progression, a single convalescent sample may be tested using IFA, but will lack diagnostic capacity of paired serum samples (probable case, not confirmed).
- Diagnosis of chronic Q fever requires demonstration of a elevated Phase I IgG antibody ($\geq$1:1024) *and* an identifiable persistent infection (e.g. endocarditis).
- PCR, IHC, or culture of affected tissue can provide definitive confirmation of acute or chronic infection by *C. burnetii*.

Dutch Acute Diagnostic Algorithm



Wegdam et al (Consensus beraad),NTVG, 2010:154:A2388

USA Q Fever Treatment Recommendations

Indication	Recommended drug and adult dose	Recommended drug and pediatric dose	Drug and dosage for pregnant women
Acute Q fever	Doxycycline 100 mg bid x 14 days	**≥8years**:Doxycycline: 2.2 mg/kg per dose bid x 14 days (maximum, 100 mg per dose) **<8 years with high risk criteria:** Doxycycline: 2.2 mg/kg per dose bid x 14 days (maximum, 100 mg per dose) **<8 years with mild or uncomplicated illness:** Trimethoprim/sulfamethoxazole 4-20 mg/kg bid x14 days (maximum, 800 mg per dose) or doxycycline 2.2 mg/kg per dose bid x 3 days past defervescence (maximum 5 days)	trimethoprim/sulfamethoxazole: 960 mg bid throughout pregnancy
Chronic Q fever			
Endocarditis or vascular infection	Doxycycline 100 mg bid and hydroxychloroquine 200 mg tid ≥18 months	Recommend consultation	Recommend consultation
Non-cardiac organ Disease	Doxycycline 100 mg bid and hydroxychloroquine 200 mg tid	Recommend consultation	Recommend consultation
Postpartum with chronic serologic profile	Doxycycline 100 mg bid and hydroxychloroquine 200 mg tid x 12 months		
Post-Q fever fatigue Syndrome	No current recommendations	No current recommendations	No current recommendations

Summary of Q Fever Treatment

- Acute Q fever: doxycycline 2 weeks treatment recommended for adults, children ≥ 8 years old, and for severe infections in patients of any age.

- Children < 8 years of age with uncomplicated illness may be treated with trimethoprim/sulfamethoxazole, or a shorter duration (≤ 5 days) of doxycycline.

- Women who are pregnant when diagnosed with acute Q fever should be treated with co-trimoxazole (trimethoprim/ sulfamethoxazole) throughout duration of pregnancy.

- Chronic Q fever: doxycycline and hydroxychloroquine for ≥18 months.

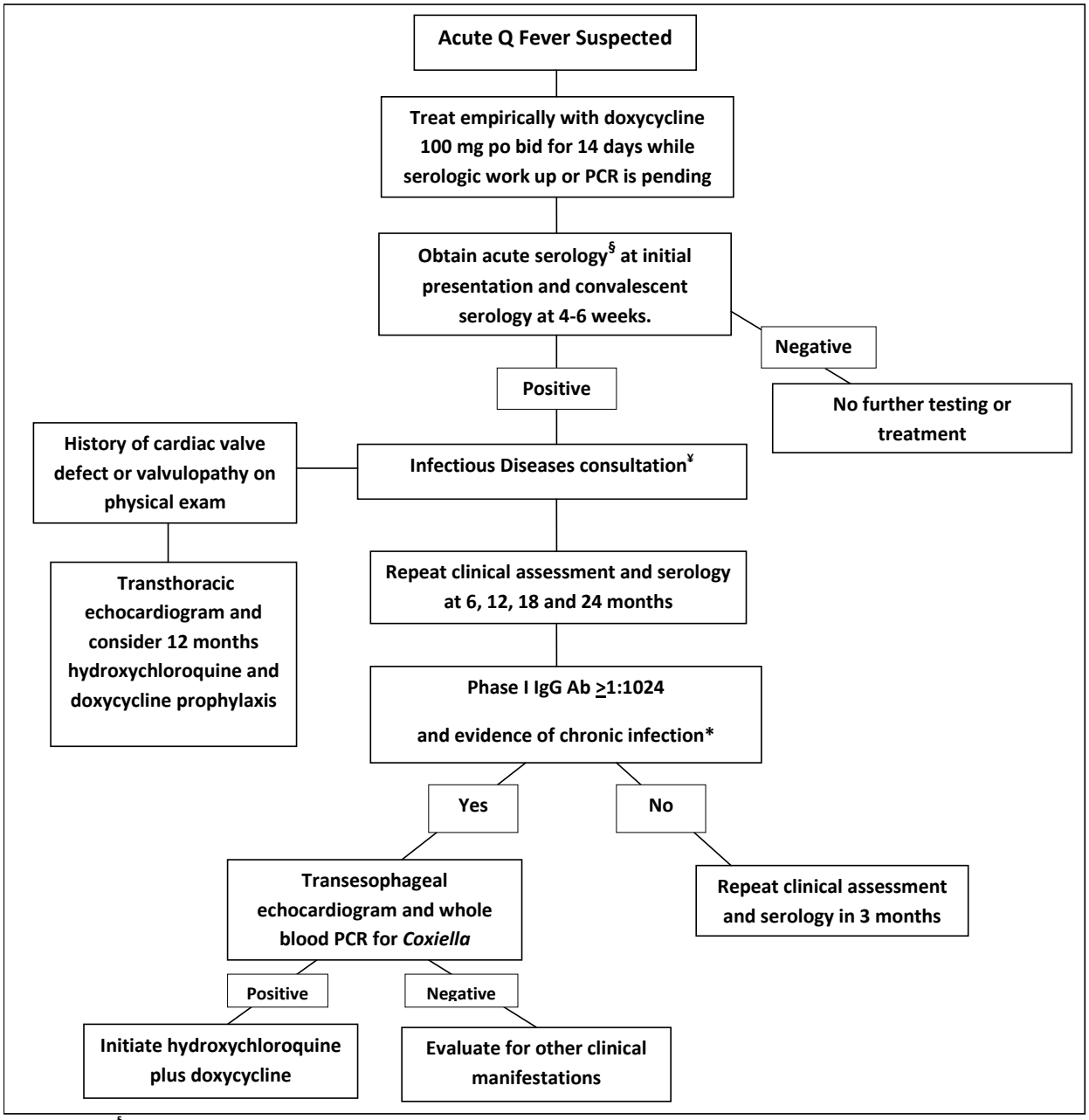
Summary of Q Fever Management

- Treatment for acute or chronic Q fever should only be given in clinically compatible cases and not based on elevated serologic titers alone (pregnancy would be exception where seroconversion without clinical symptoms may warrant treatment).

- Because of the delay in seroconversion often necessary to confirm diagnosis, antibiotic treatment should be initiated promptly in suspected acute Q fever cases without waiting for laboratory confirmation. Treatment of chronic Q fever should be initiated following diagnostic confirmation.

- Clinical and serologic monitoring is recommended following acute Q fever infection in order to assess possible progression to chronic disease. The recommended schedule for monitoring is based on the patient's risk for chronic infection.

US Military Guidelines



§ Serology should be performed at the same reference lab to minimize interlaboratory variability as results may be markedly different. ¥ Confirmed cases should be reported to the appropriate public health command. *Note: Clinical signs or symptoms consistent with possible chronic infection (fevers, chills, weight loss, shortness of breath, new heart murmur, elevated inflammatory markers) at anytime should prompt referral to Infectious Diseases.

Case Definitions
Diagnostic versus Surveillance

- Q fever is nationally notifiable disease in USA
- States required to report cases to CDC
- Purpose of surveillance case definitions is to provide guidelines to US states for reporting cases to CDC, and are not intended for clinical diagnostic use
- CDC typically initiates revisions to surveillance case definitions based on changes in diagnostic criteria and knowledge base
- Surveillance case definitions:
  - USA - confirmed or probable
  - EU - confirmed or probable

USA Surveillance Case Definitions

	Acute Q fever	Chronic Q fever
Clinical evidence of infection	Fever and one or more of the following: rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzymes.	Newly recognized culture-negative endocarditis (particularly in a patient with previous valvulopathy or compromised immune system), suspected infection of a vascular aneurysm or vascular prosthesis, or chronic hepatitis, osteomyelitis, osteoarthritis, or pneumonitis in the absence of other known etiology.
Laboratory Criteria	<u>Laboratory Confirmed:</u> - Four-fold change in IgG antibody titer to C. burnetii phase II antigen by IFA between paired sera - Detection of C. burnetii DNA in clinical specimen by PCR - Demonstration of C. burnetii in clinical specimen by IHC - Isolation of C. burnetii from clinical specimen by culture <u>Laboratory Supportive:</u> - Single IgG titer ≥ 1:128 to C. burnetii phase II antigen by IFA (phase I titers may be elevated as well)	<u>Laboratory Confirmed:</u> - IgG titer ≥ 1:800* to C. burnetii phase I antigen by IFA - Detection of C. burnetii DNA in a clinical specimen by PCR - Demonstration of C. burnetii in a clinical specimen by IHC - Isolation of C. burnetii from a clinical specimen by culture <u>Laboratory Supportive:</u> - IFA IgG titer ≥ 1:128 and < 1:800* to C. burnetii phase I antigen
Case classification	<u>Confirmed Acute Q fever</u>: a laboratory confirmed case that either meets the clinical case criteria or is epidemiologically linked to a lab-confirmed case. <u>Probable Acute Q fever:</u> a clinically compatible case that has laboratory supportive results.	<u>Confirmed Chronic Q fever</u>: a case with clinical evidence of infection that is laboratory confirmed. <u>Probable Chronic Q fever:</u> a case with clinical evidence of infection that has laboratory supportive results.

EU vs USA Surveillance Case Definitions

EU	USA CDC – Acute	USA CDC - Chronic
a. Clinical criteria Any person with at least one of the following three: — Fever — Pneumonia — Hepatitis	**Clinical evidence of infection** Fever and one or more of the following: rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzymes.	**Clinical evidence of infection** Newly recognized culture-negative endocarditis (particularly in a patient with previous valvulopathy or compromised immune system), suspected infection of a vascular aneurysm or vascular prosthesis, or chronic hepatitis, osteomyelitis, osteoarthritis, or pneumonitis in the absence of other known etiology.
b. Laboratory criteria At least one of the following three: — Isolation of *Coxiella burnetii* from a clinical specimen — Detection of *Coxiella burnetii* nucleic acid in a clinical specimen — ***Coxiella burnetii* specific antibody response (IgG or IgM phase II)**	*Laboratory Confirmed:* **- Four-fold change in IgG antibody titer to *C. burnetii* phase II antigen by IFA between paired sera** - Detection of *C. burnetii* DNA in a clinical specimen by PCR **- Demonstration of C. burnetii in a clinical specimen by IHC** - Isolation of *C. burnetii* from a clinical specimen by culture *Laboratory Supportive:* **- Single IgG titer ≥ 1:128 to *C. burnetii* phase II antigen by IFA (phase I titers may be elevated as well)**	*Laboratory Confirmed:* **- IgG titer ≥ 1:800* to *C. burnetii* phase I antigen by IFA** - Detection of *C. burnetii* DNA in a clinical specimen by PCR **- Demonstration of *C. burnetii* in a clinical specimen by IHC** - Isolation of *C. burnetii* from a clinical specimen by culture *Laboratory Supportive:* **- IFA IgG titer ≥ 1:128 and < 1:800* to *C. burnetii* phase I antigen**
c. Epidemiological criteria At least one of the following two epidemiological links: — Exposure to a common source — Animal to human transmission	**Not Applicable**	**Not Applicable**
d. Case classification		
Probable case: Any person meeting the clinical criteria and with an epidemiological link	**Probable Acute Q fever:** a clinically compatible case that has laboratory supportive results.	**Probable Chronic Q fever:** a case with clinical evidence of infection that has laboratory supportive results.
Confirmed case: Any person meeting the clinical and the laboratory criteria	**Confirmed Acute Q fever:** a laboratory confirmed case that either meets the clinical case criteria or is epidemiologically linked to a lab-confirmed case.	**Confirmed Chronic Q fever:** a case with clinical evidence of infection that is laboratory confirmed.

EU vs USA Surveillance Case Differences

- EU does not define chronic cases
- IHC not a diagnostic criteria – primarily used on tissue specimens from chronic cases
- EU laboratory criteria does not define serology titer level or assay type
- USA has no epidemiological criteria
- EU confirmed case = fever + single titer; probable or not a case in USA depending on titer
- EU probable case = fever + epidemiological criteria; not a case in USA

Q Fever – USA Summary

- Few cases reported despite 3.1% seroprevalence
- Increasing awareness in medical community
- Diagnostics available at commercial and few specialty laboratories
  - IFA and PCR – commercial
  - IFA, PCR, IHC, isolation – specialty (CDC)
- No human vaccine licensed
- No veterinary vaccine licensed
- USA livestock
  - Cattle – 92.6 million
  - Sheep – 5.5 million
  - Goats – 3 million