



# A long-lasting FUO

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- Martial, 34, carpenter
- No significant medical history
- Married, wife pregnant
- 2 healthy children
- Lives in a rural area
- Biking, jogging, parachuting
- 1 pet cat
- No travel abroad



# A long story - 1

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- Oct 2009 : arthromyalgia, fever, fatigue, rigors
  - Pandemic flu ? → TAMIFLU®
- Transient improvement, and then relapses
  - Intermittent spiking fever
- 25 Dec 2009, acute high-grade fever
  - PCP : working diagnosis CAP → AUGMENTIN® 7 days
  - Lab : CRP 8 mg/L, WBC 6000/mm<sup>3</sup> (6 G/L)



## A long story - 2

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- No improvement
- 27 Jan 2010 : thoracic suffocation
  - ➔ first admission to ID department
- Weight gain (4 kg !) over the past 4 months
- Mild fatigue
- Temperature : 37,9°C
- Mild dry cough, atypical chest pain
- Physical examination strictly normal



# A long story - 3

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- Lab

- Iono, BUN, creat N
- ASAT 29 UI/L
- **ALAT 62 UI/L**
- **GGT 120 UI/L**
- AP 86 UI/L
- Bili N

- **CRP : 47 mg/L**

- Plt 265 G/L

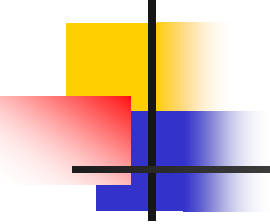
- Hb 15 g/dl

- WBC: 6500/mm<sup>3</sup>  
normal distribution

- Chest Xray N

- Urinalysis N

# What diagnosis tests would you need?



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- Blood cultures
- LDH
- PCT
- Coagulation
- Serologies
  - EBV, CMV, HIV
  - Hepatitis
  - C. pneumoniae
  - M. pneumoniae
  - Q fever
- Negative
- Normal
- 0.33 ng/mL (N < 0.1)
- Prolonged aPTT
- All negative



# Follow-up - 1

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- No Rx started
- Fever subsides but nocturnal sweats persist
- CRP goes down to 35 mg/L
- Patient wants to go home
  
- Diagnosis examinations performed at the outpatient clinic
  - Orthopantomogram and dental examination unremarkable
  - TAP CTscan normal except for mild splenomegaly



# Follow-up - 2

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- 6 Feb 2010, fever relapses → hospital
- Clinical examination still normal except for a new mild aortic systolic murmur
- CRP 53 mg/L
- WBC 5.6 G/L, Hb 15,8 g/dl, plt 289 G/L

# What would you do next?



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- Microbiology
  - Repeat BC
    - Neg
  - Q fever, Bartonella, Brucella
    - Neg
  - Quantiferon TB-Gold
    - Neg
- Ferritin
  - Normal
- Auto-immunity tests
  - Neg
- Tumor markers
  - Neg
- Bone marrow biopsy
  - Normal
- TTE + TEE
  - Bicuspid AV
  - no evidence of IE





# Follow-up - 3

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- 20 Feb 2010
  - Temperature back to normal
  - Serum inflammatory markers back to normal...
  - ... and patient back to home
- 3 Apr 2010
  - Acute left lumbar pain
  - No fever, normal CRP and WBC
  - Abdominal CT: hypodensity left kidney (nephritis, infarct?)
  - Admission to Urology dpt. Rx with ceftriaxone
  - CT final diagnosis: renal infarct (Ceftriaxone d/c after 4 days)



# What would you do next?

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- What we did
  - PET-CT: normal
  - Auto-inflammatory disorders: FMF, HIDS, ...
  - 3rd TTE/TEE: no change, likelihood of IE very low
  - Prolonged aPTT persists: extensive search for thrombophilia negative
- End of April 2010
  - Resolution of all symptoms
  - Patient feels "healed"



# Summary as of May 2010

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- Intermittent "naked" FUO
- No deterioration of general status
- Bicuspid AoV, no sign of IE
- 1 renal infarct
- Mild splenomegaly
- All BC (n  $\approx$  30) neg
- Max CRP 53 mg/L, below 15 since Feb 2010
- 4 TTE, 2 TEE: no IE
- All serologies for BCNE negative
- Prolonged aPTT
- PET CT normal



# What is your diagnosis?

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- FUO, resolved
- APLS
- Do not know...
- IE (BCN)
- FTBS
- ...
- the residents
- the internists
- the cardiologists
- Dr H (knows nothing else)
- Dr DG (female fellow)



# Follow-up - 4...

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- 29 Jul 2010: new admission for TIS
  - Hemiparesia, resolute within 24 hours
  - No fever, serum inflammatory markers N
- Diagnosis
  - Dr H: BCN IE, redo TEE
  - Cardiologists: unchanged TTE, no IE, no TEE
  - Dr H: BCN IE, f... the cardiologists



# Follow-up - 5

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- TTE + TEE
  - Evidence of IE on bicuspid AoV
  - Aortic ring cleansed abscess
  - Visualisation of all previous tapes in a batch
    - "Abnormalities should have been seen before"
    - "Bicuspid Aov made them difficult to see"
- 10 000 € Question

What pathogen?

# BCNE shampoo

- Dental consult
- Repeat BC
- Serologies for syphilis, leptospirosis, brucellosis, *Coccidioides immitis*, *Yersinia enterocolitica*, *Q fever*, *Chlamydia pneumoniae*
- PCR *Bartonella*
- Whipple disease
  - Upper/lower IT enzymes
  - Specific *T. whipplei* PCR on stools, saliva, blood, CSF

**NEGATIVE**



# Follow-up - 6

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- Worsening valve damages
  - Valve replacement indicated
- Would you start antibiotics? If yes, which one(s)?
  - Ceftriaxone + Gentamicin 14 jours
  - Followed by Ceftriaxone alone until surgery
- 28 Oct 2010: valve replacement
  - Insertion of a St-Jude mechanical prosthesis
  - Macro: typical of IE
  - Histo: typical of IE
  - Culture: negative
  - 16sRNA PCR + sequencing :





# Conclusion - 1

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- All this because of a pet cat
- My personal record for time to diagnosis of IE
  - 9 months up to positive diagnosis
  - 3 more months up to microbiological diagnosis
  - ... in an ID department specialized in IE!
- Fever + bicuspid AoV + renal infarct + TIA (34 y-o)
- APLS and FTBS ruled out...



# Follow-up - 7

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- Six months later
- Nine months later
- Jan 2013: so far so good

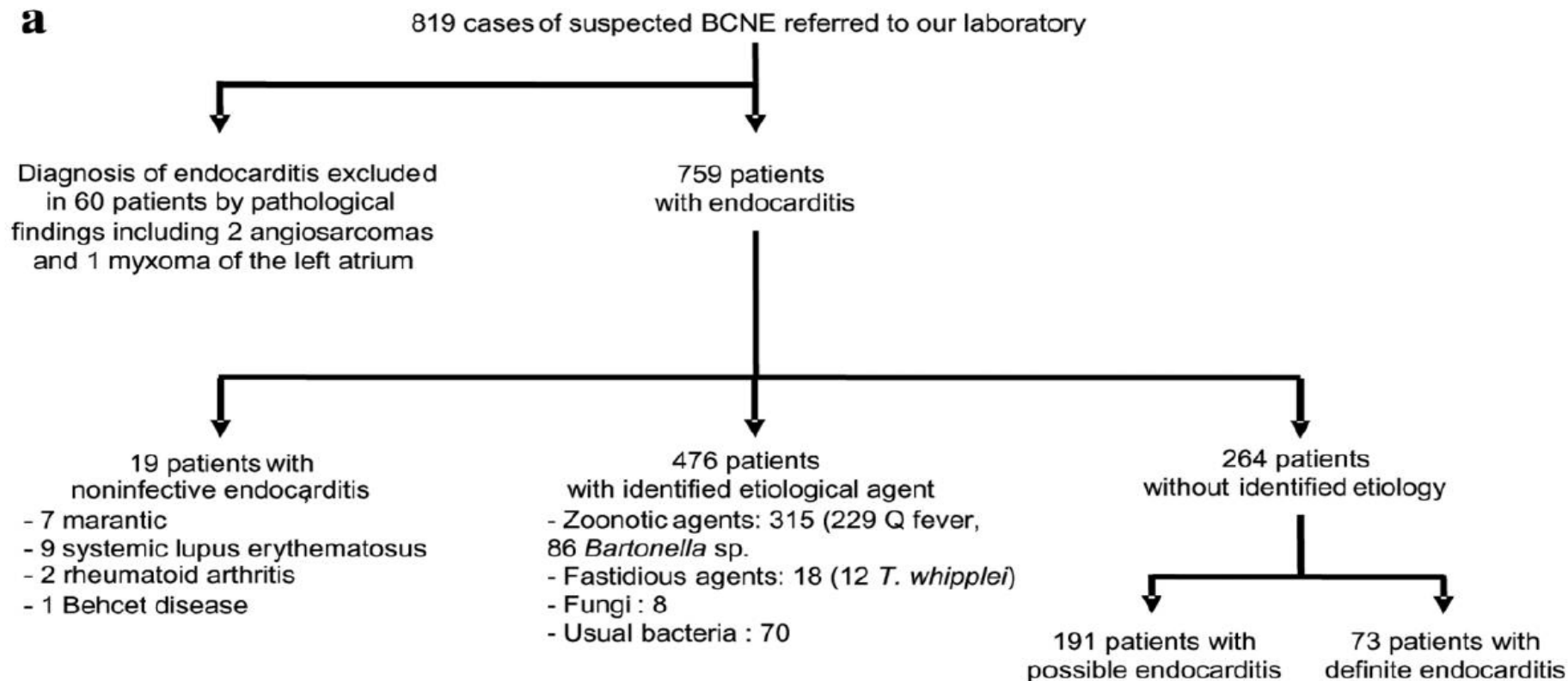
# BCNE-causing organisms

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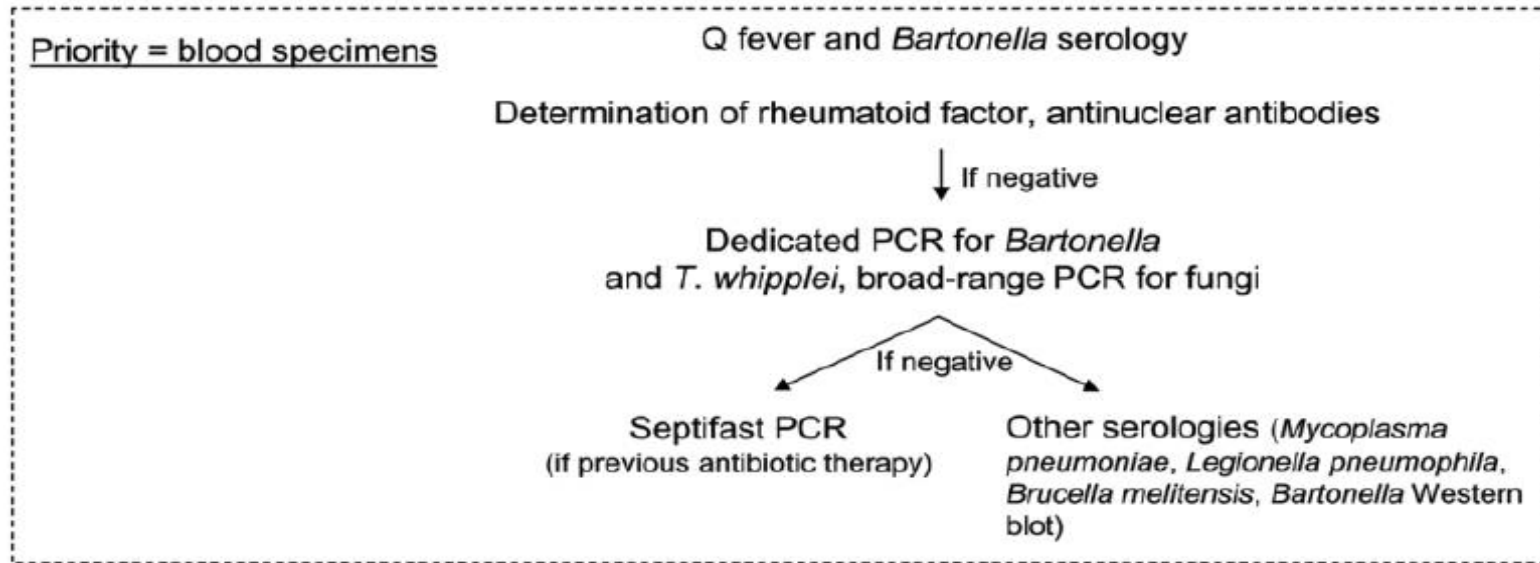
- ▶ Single most frequent
  - ▶ *Coxiella burnetii*
- ▶ Other most frequent
  - ▶ *Abiotrophia*
  - ▶ *Aggregatibacter (former Actinobacillus) actinomycetemcomitans*
  - ▶ *Bartonella*
  - ▶ *Brucella*
- ▶ Rare
  - ▶ *Cardiobacterium hominis*
  - ▶ *Erisipelothrix rhusiopathiae*
  - ▶ *Haemophilus aphrophilus*,
  - ▶ *Haemophilus parainfluenzae*
  - ▶ *Listeria monocytogenes*
- ▶ Very rare
  - ▶ *Campylobacter*
  - ▶ *Eikenella*
  - ▶ *Francisella*
  - ▶ *Gemella*
  - ▶ *Granulicatella*
  - ▶ *Kingella*
  - ▶ *Legionella*
  - ▶ *Mycobacteria*
  - ▶ *Mycoplasma*
  - ▶ *Neisseria*
  - ▶ *Pasteurella*
  - ▶ *Tropheryma whippiei*



# Comprehensive Diagnostic Strategy for Blood Culture–Negative IE: A Prospective Study of 819 New Cases



# Comprehensive Diagnostic Strategy for Blood Culture–Negative IE: A Prospective Study of 819 New Cases



# Serology (MIF) in the diagnosis of *Coxiella burnetii* infections

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Ac #phase II Ag		Ac #phase I Ag		Interpretation
IgG	IgM	IgG	IgA	
≤ 100				Active Q fever unlikely
≥ 200	≥ 50			Acute Q fever
		≥ 800 - 1600	≥ 100	Chronic Q fever



# *Bartonella* and endocarditis

Small bacteria, intracellular facultative (none or few are intracellular in IE)  
Target cells: erythrocytes, endothelial cells

	<i>B. quintana</i>	<i>B. henselae</i>
Ratio M/F	5.3	1.5
Contact with cat	20%	70%
Homeless	60%	0%
Body lice	40%	0%
Alcohol abuse	65%	10%
Prior valve disease	40%	90%



# IE due to *T. whipplei*, *Bartonella* et *C. burnetii*

## Distinctive clinical features

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Characteristics, %	<i>T. whipplei</i>	<i>Bartonella</i> <i>a</i>	<i>C. burnetii</i>
Male	90	85	65
Preexisting valve disease	15	50	90
Fever	40	90	90
Diarrhea	80	-	-
Weight loss	90	-	60
Arthralgia	70	-	-



# IE due to *T. whipplei*, *Bartonella* et *C. burnetii*

## ESC 2015 guidelines

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Pathogens	Proposed therapy <sup>a</sup>	Treatment outcome
<i>Brucella</i> spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months <sup>b</sup> orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
<i>C. burnetii</i> (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) <sup>c</sup> orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50.
<i>Bartonella</i> spp. <sup>d</sup>	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%.
<i>Legionella</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
<i>Mycoplasma</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months <sup>e</sup>	Optimal treatment unknown.
<i>T. whipplei</i> (agent of Whipple's disease) <sup>f</sup>	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) <sup>c</sup> orally for ≥18 months	Long-term treatment, optimal duration unknown.

