

# **Neurobartonelloses**

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# Disclosures

**I disclose the following relevant financial or non-financial relationships:**

In conjunction with Dr. S. Sontakke and North Carolina State University, E. B. Breitschwerdt holds US Patent No. 7,115,385; Media and Methods for Cultivation of Microorganisms, which was issued on October 3rd, 2006.

I am a co-founder, shareholder and Chief Scientific Officer for Galaxy Diagnostics, a company that provides advanced diagnostic testing for the detection of *Bartonella* spp. infections.

**I do not intend to reference any off-label or non-FDA approved usage in this presentation.**

# *Bartonella* Cell Tropisms & Neurological Disease

Intracellular Infection:

Endothelial Cells

Pericytes

Macrophages

Microglial Cells

Accessing the nervous system:

- Penetrate blood brain barrier via endothelial cells or pericytes.
- Migrate into the nervous system via macrophages (Trojan horse).
- Maintained within the brain by microglial cells.
- Isolation from cerebrospinal fluid

# *Bartonella* Virulence Factors

## Immune Evasion and Intracellular Survival

### Lipopolysaccharide

TLR4 signaling activated 1000x less by *Bh* LPS than *Salmonella* LPS  
(Zahringer *J Biol Chem* 2004)

Antigenic variation

Adhesins- *Vomps Bq* & *BadA* in *Bh*

### Type IV Secretion System (translocate effector proteins (Beps) into cells)

BepA - inhibits apoptosis thereby facilitating vascular tumor formation

BepC - facilitates invasome-mediated cellular entry

Bep D - induces STAT3 activation of immune cells to downregulate inflammation (TNF-alpha) and promotes an anti-inflammatory IL-10 response

# Neurological & Psychological Manifestations

## Review Article

Breitschwerdt, Sontakke & Hopkins. (2012)

Neurological Manifestations of Bartonellosis in Immunocompetent Patients: A Composite of Reports from 2005–2012

J of Neuroparasitology, Vol. 3

## Diseases Described:

Recurrent expressive aphasia in a 15-year-old male

Encephalitis lethargica in a 16-year-old girl

Encephalopathy - 9-year-old girl during admin antibiotics

Fatal encephalopathy in a 6-year-old male

Transverse myelitis in a 46-year-old man

Transverse myelitis in a 13-year-old boy

Expressive Aphasia in a 59-year-old male

MS-like disease in a 27-year-old-man

Psychiatric illness in a 41-year-old male

Meningitis in a 47-year-old woman

Neurological disease in a 50-year-old male

Headaches and insomnia in a 7-year-old female

Hallucinations and visual defects in an 18-year-old female

# Patient #1

*Breitschwerdt et al. J Clin Micro 2011*

## 18 Year-old Woman

- Four-year history of progressive peripheral visual loss, sensory neuropathy, and hallucinations
- Other symptoms: headaches, joint pain, back pain, mood swings, dizziness
- Neurologist, Psychiatrist, Neuro-ophthalmologist

1. Would you test this patient for bartonellosis?
2. What test for bartonellosis would you request?

# Patient #2

*Maggi et al. Med Microbiol & Immunol 2019*

## 14 Year-old Girl

- Five-year history of intermittent fever, ocular pain, balance problems, headaches, irritability, blurred vision, disorientation, hallucinations, memory loss, insomnia, tremors, anxiety and panic attacks.
- Other symptoms included fatigue, joint pain involving the elbows, shoulders, hips, knees and ankles, muscle weakness and pain, tachycardia and diarrhea.

1. Would you test this patient for bartonellosis?
2. What test for bartonellosis would you request?

# Patient #3

*Breitschwerdt et al J Central Nerv Syst Dis 2019*

## 14-Year-old Boy

- 18-month history of progressive neuropsychiatric symptoms
- Diagnoses included major depression, psychoses and schizophrenia
- Evaluated by four psychiatrists
- Hospitalized for two months in a specialty hospital for detailed medical and neuropsychiatric testing
- Complete resolution of neuropsychiatric symptoms with Bartonella-directed antimicrobial therapy

1. Would you test this patient for bartonellosis?
2. What test for bartonellosis would you request?



# *Bartonella* spp. Infections & Neuropsychiatric Illnesses

**Patient #1:** *Bartonella koehlerae*

**Patient #2:** *Bartonella quintana* and *Bartonella vinsonii* subsp. *vinsonii* co-infection

**Patient #3:** *Bartonella henselae*

Results for all three patients confirmed by PCR amplification & DNA sequencing. Negative controls- negative.

# Rapid Expansion of *Bartonella* Species

3 species in 1990



>45 species in 2023

*B. henselae*      *B. quintana*      *B. bacilliformis*      *B. rochlimae*

*B. birtlesii*      *B. koehlerae*      *B. doshiae*      *B. talpae*      *B. clarridgeiae*

*B. vinsonii arupensis*      *B. bovis*      *B. chomelii*      *B. grahamii*      *B. vinsonii berkhoffii II*

*B. alsatica*      *B. taylorii*      *B. peromysci*      *B. schoenbuchensis*      *B. rudakovii*

*B. elizabethae*      *B. naantaliensis*      *B. capreoli*      *B. washoensis*      *B. volans*

*B. mayotimonensis*      *B. eldjazairii*      *B. tamiae*      *B. merieuxii*      *B. vinsonii berkhoffii III*

*B. rattimassiliensis*      *B. vinsonii vinsonii*      *B. melophagi*      *B. thailandensis*

*B. vinsonii berkhoffii I*      *B. vinsonii berkhoffii IV*      *B. tribocorum*      *B. rondoniense*

White color shaded *Bartonella* spp. reported in association with infection in dogs or humans.  
Yellow color indicates *Bartonella* spp. in mammalian reservoir hosts.

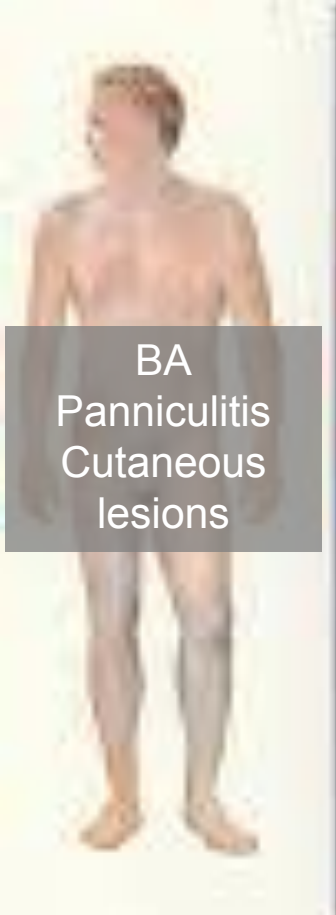
# Patient #1: *Bartonella koehlerae* & Neurocognitive Abnormalities

Breitschwerdt et al. J Clin Microbiol 2011

<u>Sample Day</u>	<u>Blood PCR</u>	<u>BAPGM PCR</u>	<u>Bk IFA</u>	<u>Bh IFA</u>	<u>Bvb IFA</u>
0	<i>Bspp</i>	Neg	64*	<16	<16
294	Neg	<i>Bk</i>	256	<16	<16
507	Neg	<i>Bk</i>	256	<16	<16
801	Neg	Neg	<16	<16	<16

\*- denotes retrospective testing after development of a *B. koehlerae* IFA

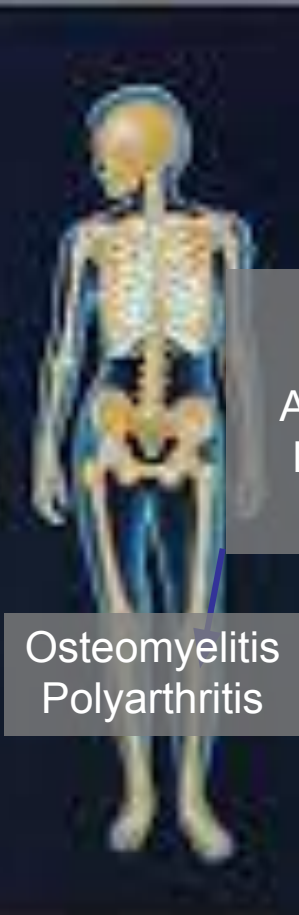
# Clinical Manifestations of Bartonellosis



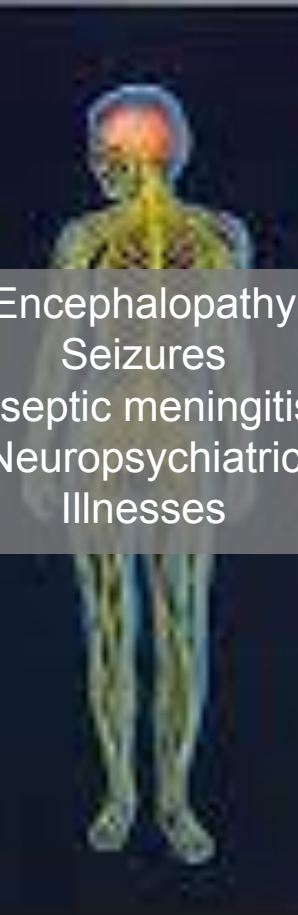
BA  
Panniculitis  
Cutaneous  
lesions



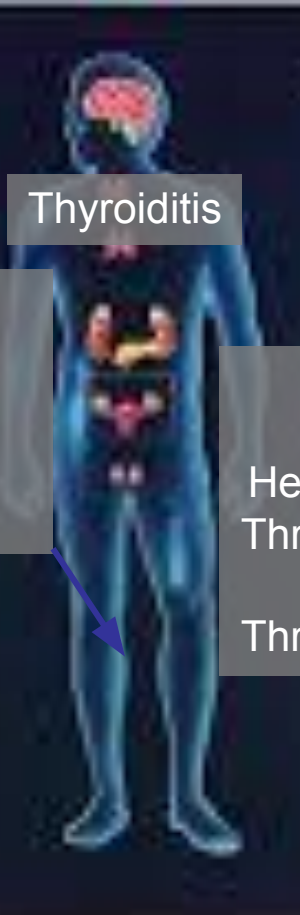
Myalgia



Osteomyelitis  
Polyarthrits



Encephalopathy  
Seizures  
Aseptic meningitis  
Neuropsychiatric  
Illnesses



Thyroiditis



Endocarditis  
Myocarditis  
Hemolytic anemia  
Thrombocytopenia  
Vasculitis  
Thromboembolism

Integumentary  
System

Muscular  
System

Skeletal  
System

Nervous  
System

Endocrine  
System

Circulatory  
System

# **Bartonella Bacteremia & Neurological Dysfunction**

*Breitschwerdt et al. J Clin Microb 2008*

<u>Patient</u>	<u>Age</u>	<u>Gender</u>	<u>Neuro Abnor</u>	<u>Bartonella sp.</u>
1	23	F	Seizures	<i>B. henselae</i>
2	41	F	H/I/ML	<i>B. henselae</i>
3	44	F	H/I/ML	<i>Bh/Bvb</i>
4	54	F	H/I/ML	<i>B. henselae</i>
5	49	M	Partial Paralysis	<i>B. henselae</i>
6	14	M	Migraines	<i>B. henselae</i>

H/I/ML= Headache, Insomnia, Memory Loss

# Seizures with Persistent *B. henselae* Bacteremia and CSF Infection

Breitschwerdt et al J Clin Microb 2008

<u>Sample</u> <u>Day</u>	<u>Blood</u> <u>PCR</u>	<u>BAPGM</u> <u>PCR</u>	<u>Bh</u> IFA	<u>Bq</u> IFA	<u>Bvb</u> IFA
0	<i>Bh</i> (H1)	Neg	256	128	256
31 *Isolate	<i>Bh</i> (H1)	<i>Bh</i> (H1)*	1024	256	256
256 (CSF)	Neg	<i>Bh</i> (H1)	NT	NT	NT
458	Neg	Neg	64	64	64

\**Bartonella henselae* Houston I strain type confirmed by DNA sequencing,  
Serology performed by the Centers for Disease Control & Prevention

# Co-infection with *Anaplasma platys*, *Bartonella henselae* and *Candidatus Mycoplasma haematoparvum*

*Maggi et al. Parasites and Vectors 2013*

## 27-Year-old female veterinarian

Migraines, seizures, status epilepticus, & a history of neuro cognitive abnormalities for 2 years.

Worked in Grenada, Ireland, South Africa.

April 2013: *B. vinsonii* subsp. *berkhoffii* and *B. henselae* seroreactive.  
All 16 *Bartonella* PCRs (blood and 7, 14, and 21-day cultures x4) were negative.

May 2013: *B. henselae* BAPGM enrichment blood culture positive.  
Co-infected with *A. platys* and *Candidatus M. haematoparvum*

November 2013: 6 mo doxycycline therapy failed to clear *B.henselae*.

# Occupational Risk: Veterinary Workers

*Lantos et al. Vector Borne and Zoonotic Dis 2014*

## Cross Sectional Study:

BAPGM Enrichment blood culture/PCR & DNA sequencing

*Bartonella* spp. DNA amplified from 32/114 (28%) veterinary workers

*B. henselae* 15 (56%)

*B. vinsonii* subsp. *berkhoffii* 7 (26%)

*B. koehlerae* 6 (22%)

*B. volans*-like 1 (4%)

Co-infection 2 (6%)

Controls: 32 non-veterinary medical professionals: All BAPGM enrichment PCR negative.



# Occupational Risk: Veterinary Workers

*Lantos et al. Vector Borne & Zoonotic Disease 2014*

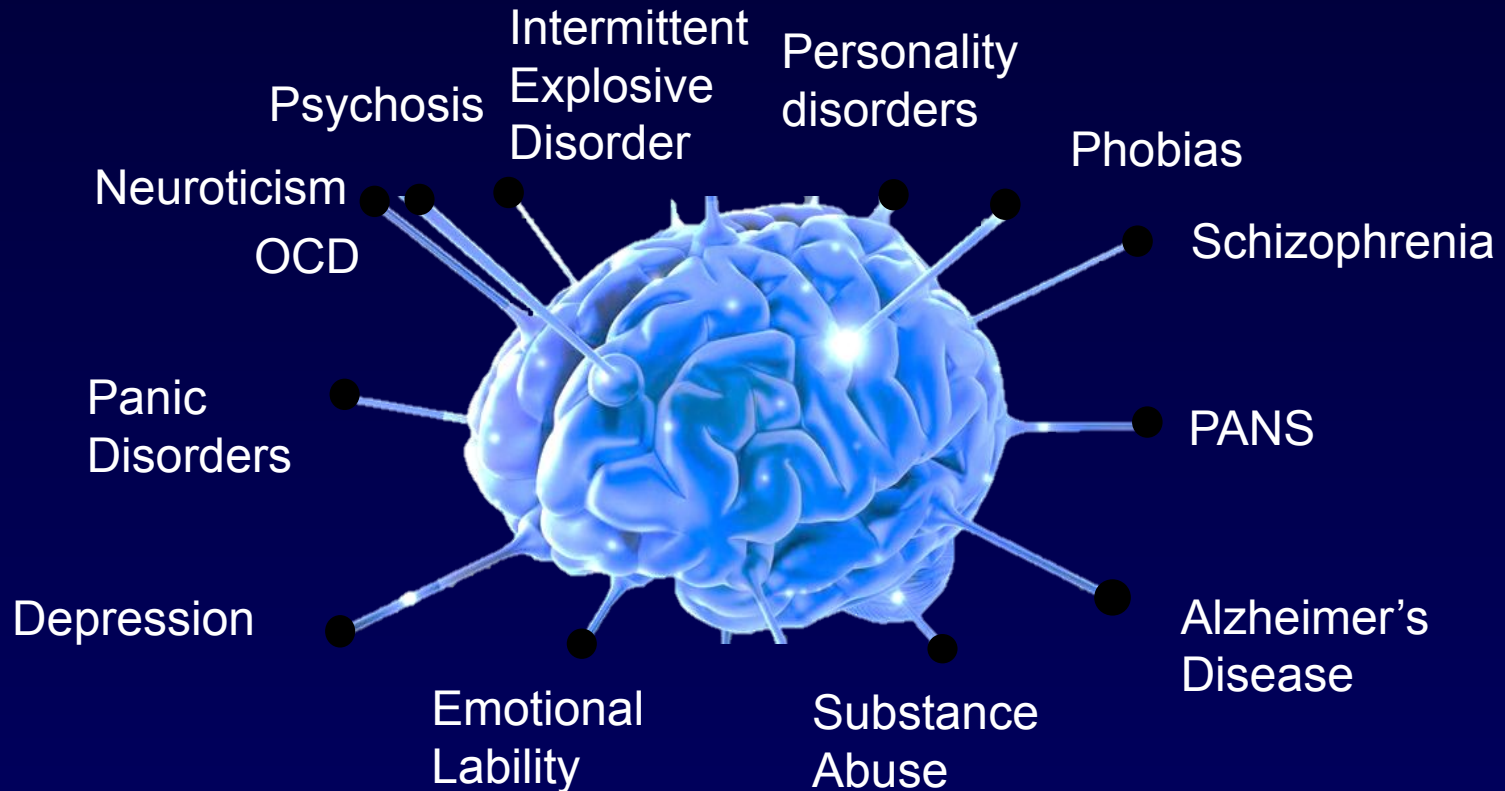
## Clinical findings associated with positive BAPGM-ePCR

Headache	(70% vs 40%, $p = 0.009$ )
Irritability	(68% vs 44%, $p = 0.04$ )
Headache and Irritability	(56% vs 29%, $p = 0.03$ )
Muscle pain and joint pain	(63% vs 35%, $p = 0.03$ )
Antibiotic treatment in last year	(59% vs 35%, $p = 0.04$ )

## Epidemiologic associations with positive BAPGM-PCR

Age / gender	not associated
Travel to Asia	(33% vs 9%, $p = 0.006$ )

# Bartonella & Neuropsychiatric Dysfunction?



# Bartonella and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

*Breitschwerdt et al. J Cent Nerv Syst Dis 2019*

## 14-year-old Boy

Sudden Onset psychotic behavior

Hallucinations, delusions, suicidal and homicidal ideation

Failed 18 months psychiatric medications and immunosuppression for autoimmune encephalitis.

*Bartonella henselae* amplified and sequenced from blood and BAPGM enrichment blood cultures.

*B. henselae* IFA seronegative

# Bartonella-associated Cutaneous Lesions

Left Medial Thigh



Medial Right Axilla



# Pediatric Acute-Onset Neuropsychiatric Syndrome

1. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake.
  - ✓ Went from highly functional (gifted school) to dysfunctional in a very brief timeframe with a rapid onset of OCD symptoms of intrusive thoughts, phobias, unfounded fears, and repetitive behaviors. Severely restricted food intake was not noted.
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories:
  - ✓ Anxiety (severe);
  - ✓ Emotional lability and/or depression;
  - ✓ Irritability, aggression, and/or severely oppositional behaviors;
  - ✓ Behavioral (developmental) regression;
  - ✓ Deterioration in school performance (could not attend school during illness);
  - ✓ Sensory or motor abnormalities;
  - ✓ Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.
3. Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder, or others.
  - ✓ No known neurological or medical disorder to explain symptoms.Plus persistent psychosis and visual, auditory, and tactile hallucinations.

OCD, obsessive-compulsive disorder; PANS, pediatric acute-onset neuropsychiatric syndrome.  
The check marks reflect specific symptoms reported in the patient that supported the criteria.

- *Bartonella henselae* grew in BAPGM after 2 months of doxycycline administration
- Family endured a substantial emotional, social and financial price
- Cost of medical interventions prior to documentation of *B. henselae* \$400,000
- Mother quit her job to provide home care for her son.

# Two Major Innovations for *Bartonella* spp. Diagnosis

**Sample  
Enrichment**



**Bio-Rad QX One  
Droplet Digital PCR**






# Bartonella & Neuropsychiatric Illnesses



Article

## ***Bartonella* Associated Cutaneous Lesions (BACL) in People with Neuropsychiatric Symptoms**

Edward B. Breitschwerdt <sup>1,\*</sup>, Julie M. Bradley <sup>1</sup>, Ricardo G. Maggi <sup>1</sup>, Erin Lashnits <sup>1</sup>  
and Paul Reicherter <sup>2</sup>

VECTOR-BORNE AND ZOO NOTIC DISEASES  
Volume 21, Number 6, 2021  
© Mary Ann Liebert, Inc.  
DOI: 10.1089/vbz.2020.2729

## Schizophrenia and *Bartonella* spp. Infection: A Pilot Case–Control Study

Erin Lashnits,<sup>1</sup> Ricardo Maggi,<sup>1</sup> Fredrik Jarskog,<sup>2</sup> Julie Bradley,<sup>1</sup>  
Edward Breitschwerdt,<sup>1</sup> and Flavio Frohlich<sup>2–5</sup>

# Cat Scratch, Refractory Seizures, *Bartonella henselae* DNA in Brain Enrichment Cultures

December 2016, 2 years-old: Scratch by a Feral Cat (Rt. Cheek)

August 2018, “Insect bite” and rash (Rt wrist)

September 2018, Seizure onset,

Seizures increase in frequency through 2022 and are refractory to medications.

Sequential MRIs: Diagnosis Rasmussen Encephalitis-  
“immune-mediated unilateral (Rt side) hemispheric atrophy leading to neurological dysfunction and intractable seizures”

Serial EEGs and PET Scan in 2021- abnormal Rt hemisphere brain activity.



# Cat Scratch, Refractory Seizures, *Bartonella henselae* DNA in Brain Enrichment Cultures



# Cat Scratch, Refractory Seizures, *Bartonella henselae* DNA in Brain Enrichment Cultures

Armin Laboratory (Germany)- *Bartonella* & *Borrelia*

NCSU Research Testing:

January 2022: Bvb I-32, Bvb II-64, Bh-64, Bk-32, Bq- 16

BAPGM enrichment blood culture triple draw- Negative

June 2022: Rt Cortical Brain Biopsy

BAPGM enrichment brain biopsy culture- *B. henselae*

Bruge Medium Culture- ddPCR+ 21 days of incubation

*Borrelia* spp. ddPCR from blood, serum and enrichment cultures- negative

December 2022: Doxycycline escalating dose

February 2023: Attending school, first time in a year

# Neurobartonelloses: Concluding Thoughts

- It seems likely that infections with *Bartonella* species are a more important cause of neurologic and neuropsychiatric diseases than is currently appreciated.
- Our understanding of the neuropathogenesis of bartonellosis is minimal and lacking in detail.
- Sensitive detection of *Bartonella* spp. DNA in the blood, CSF or brain tissues of patients with neurological diseases often requires serial blood testing (triple draw), enrichment blood or CSF culture, and ddPCR.
- In the context of causation or secondary opportunistic infection, treatment studies are needed to assess the medical importance of this genus in patients with neurological illnesses.

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  - Dr. Janice Bush

## NCSU-CVM Comparative Medicine Institute



# References 1

- Breitschwerdt, E.B., Mascarelli, P.E., Schweickert, L.A., Maggi, R.G., Hegarty, B.C., Bradley, J.M. and Woods, C.W., 2011. Hallucinations, sensory neuropathy, and peripheral visual deficits in a young woman infected with *Bartonella koehlerae*. *Journal of clinical microbiology*, 49(9), pp.3415-3417.
- Breitschwerdt, E.B., Maggi, R.G., Nicholson, W.L., Cherry, N.A. and Woods, C.W., 2008. *Bartonella* sp. bacteremia in patients with neurological and neurocognitive dysfunction. *Journal of clinical microbiology*, 46(9), pp.2856-2861.
- Maggi, R.G., Mascarelli, P.E., Pultorak, E.L., Hegarty, B.C., Bradley, J.M., Mozayeni, B.R. and Breitschwerdt, E.B., 2011. *Bartonella* spp. bacteremia in high-risk immunocompetent patients. *Diagnostic microbiology and infectious disease*, 71(4), pp.430-437.
- Maggi, R.G., Mozayeni, B.R., Pultorak, E.L., Hegarty, B.C., Bradley, J.M., Correa, M. and Breitschwerdt, E.B., 2012. *Bartonella* spp. bacteremia and rheumatic symptoms in patients from Lyme disease–endemic region. *Emerging infectious diseases*, 18(5), p.783.
- Maggi, R.G., Richardson, T., Breitschwerdt, E.B. and Miller, J.C., 2020. Development and validation of a droplet digital PCR assay for the detection and quantification of *Bartonella* species within human clinical samples. *Journal of Microbiological Methods*, 176, p.106022.
- Oliveira, A.M., Maggi, R.G., Woods, C.W. and Breitschwerdt, E.B., 2010. Suspected needle stick transmission of *Bartonella vinsonii* subspecies *berkhoffii* to a veterinarian. *Journal of veterinary internal medicine*, 24(5), pp.1229-1232.

# References 2

- Mascarelli PE, Maggi RG, Hopkins S, Mozayeni BR, Trull CL, Bradley JM, Hegarty BC, Breitschwerdt EB. 2013. *Bartonella henselae* infection in a family experiencing neurological and neurocognitive abnormalities after woodlouse hunter spider bites. Parasites and Vectors 6, p. 98.
- Bradley JM, Mascarelli PE, Trull CL, Maggi RG, Breitschwerdt EB. *Bartonella henselae* infections in an owner and two Papillon dogs exposed to tropical rat mites (*Ornithonyssus bacoti*). 2014. Vector Borne Zoonotic Dis. 14: pp. 703-9.
- Breitschwerdt EB, Sontakke S, Hopkins S. 2012. Neurological manifestations of bartonellosis in immunocompetent patients: A composite of reports from 2005-2012. J Neuroparasitology 3, pp. 1-15.
- Kaufman DL, Koegnik AM, Mozayeni RB, Cherry NA Breitschwerdt EB. 2017. Neurological and immunological dysfunction in two patients with *Bartonella henselae* bacteremia. Clin Case Reports 5, pp. 931-935.
- Breitschwerdt EB, Maggi RG. *Bartonella quintana* and *Bartonella vinsonii* subsp. *vinsonii* bloodstream infection in a girl from North Carolina, USA. 2019. Med Microbiol Immunol 28, pp.101-107.
- Breitschwerdt EB, Greenberg R, Maggi RG, Lews A, Bradley JM. *Bartonella henselae* infection in a boy with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). 2019. Journal of Nervous System Disease. 11, pp. 1-8.
- Breitschwerdt EB, Bradley JM, Maggi RG, Lashnits E, Reicherter P. *Bartonella* Associated Cutaneous Lesions (BACL) cutaneous lesions in people with neuropsychiatric symptoms. 2020. Pathogens 9, p.1023.
- Lashnits E, Maggi R, Jaraskog LF, Bradley J, Breitschwerdt EB, Frohlich F. Schizophrenia and *Bartonella* spp. infection: a pilot case-control study. 2021. Vector Borne Zoonotic Dis. 21, pp. 413-421.