ANAPLASMA PHAGOCYTOPHILUM INFECTION IN CATS
A literature review to raise clinical awareness

Ingo Schäfer and Barbara Kohn

Practical relevance: Granulocytic anaplasmosis is a disease in humans and animals caused by the Gram-negative bacterium Anaplasma phagocytophilum within the family Anaplasmataceae. The pathogen is transmitted by ticks of the Ixodes species. Infections with A phagocytophilum have often been described in dogs but reports on natural infections in cats are rare. An infection with A phagocytophilum should be considered as a differential diagnosis in cats if the history reveals tick infestation and/or outdoor access in combination with the relevant clinical signs.

Global importance: A phagocytophilum is also important in human medicine because of its zoonotic potential. Due to the risk of vector-borne infections for both feline and public health, cats should be protected with ectoparasiticides, especially in endemic areas.

Aim: The aim of this review is to give an overview of the published data and summarise the epidemiology, pathogenesis, diagnosis, clinical signs and therapy of feline granulocytic anaplasmosis. As clinical signs are vague and non-specific, this review aims to raise awareness of A phagocytophilum infection, both among clinicians, so that they consider testing potentially exposed cats, and scientists, in order to prompt further research.

Evidence base: Sixteen publications describing 55 cats have been reviewed. Thirty-four cats were well diagnosed based on guidelines of the European Advisory Board on Cat Diseases and blood analyses were performed to varying extents for these cats. Because of the limited number of studies and a lack of knowledge in cats, clinical signs and blood analyses are compared with available data in dogs.

Keywords: Anaplasma phagocytophilum; vector-borne; anaplasmosis; granulocytic anaplasmosis; zoonosis

Introduction

Anaplasma phagocytophilum is a Gram-negative, obligate intracellular bacterium within the family Anaplasmataceae. The pathogen was formerly variously known as Ehrlichia equi, Ehrlichia phagocytophila and human granulocytic ehrlichiosis (HGE) agent, thus making literature reviews challenging. A phagocytophilum causes granulocytic anaplasmosis in humans and animals and is transmitted by ticks of the Ixodes species within 24–48 h of tick attachment. Rodents and wild ruminants are the most common reservoirs.

While infections with A phagocytophilum occur commonly in dogs, the literature only rarely describes natural infections in cats. Case reports of A phagocytophilum infection in cats, based on detection by PCR, have been published in Germany, Austria, Poland, Switzerland, Italy, the UK, Finland, Sweden and the USA.

Epidemiology

Infections with A phagocytophilum have been described in humans and a number of animal species including cats. The first case report of an infected cat was published in Sweden in 1999. Prior to this, the pathogen had already been described via microscopic detection of morulae in sheep in Scotland in 1932 (cited by Woldehiwet and Scott and Foggie), in cattle in the UK in 1950, as well as in other domestic ruminants such as goats and deer, in horses in the USA in 1968, in dogs in the USA in 1982 and in humans in the USA via PCR in 1994.

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The species of tick that transmits *A phagocytophilum* varies geographically.

*A phagocytophilum* is transmitted by ticks, with the species of tick varying based on geography. In the USA, *Ixodes pacificus* (West) and *Ixodes scapularis* (Midwest and Northeast) have been described as vectors. In Europe, *Ixodes ricinus* is the most important vector, followed by *Ixodes trianguliceps*, *Ixodes hexagonus* and *Ixodes ventulatus*. In Asia and Russia, *Ixodes persulcatus* and *Dermacentor silvarum* are the most common vectors.

In humans, rare infections without vector contact have been diagnosed; for example, nosocomial infections in China, infections transmitted via blood transfusion and transplacental infections. Transplacental infections have also been described in cows but not in cats. The natural and experimental transmission of *A phagocytophilum* via blood/blood transfusion has been described in dogs, as well as in cats (MR Lappin, unpublished data). In a study performed in Berlin, Germany, 5/42 clinically healthy blood donor cats were serologically positive for *A phagocytophilum*; direct pathogen detection via PCR was negative in all cats. Consensus guidelines from the American College of Veterinary Internal Medicine (ACVIM), as well as the European Advisory Board on Cat Diseases (ABCD), recommend methods of detection for *A phagocytophilum* in blood donor cats (see later).

In European cats, antibody prevalences for *A phagocytophilum* have been described, ranging from 4.3% to 37.6% have been reported (Table 1). Direct pathogen detection via PCR or within a blood smear was positive in 0–23.1% of cats in Europe, and in 0–6.9% of cats in the USA (Table 1). Direct methods of detection of *A phagocytophilum* in European dogs showed a prevalence of 0–21.7% in different countries, via indirect detection methods, 2.7–56.5% of dogs tested positive. In the USA, prevalences in dogs ranged from 3% to 37% using direct detection methods and 0% to 55.4% via antibody testing.

These wide ranges in prevalence of *A phagocytophilum* infection in dogs and cats could be explained by the large geographical areas studied, with their varying climates and environments, tick populations and reservoir host populations. The different study populations also have an impact on the prevalence rates. Stray cats and dogs will have received little or no veterinary care and prophylactic measures against vector-borne infections will not have been implemented. Living outdoors all the time, they also have an increased risk of vector contact and infection.

Some studies have been performed in areas not endemic for *Ixodes* species and, as expected, these studies showed a dramatically lower prevalence compared with areas in which *Ixodes* species are endemic. Cats with and without outdoor access have also been studied (Table 1). Compared with cats with outdoor access (and also with dogs), cats living only indoors are less likely to have vector contact. Moreover, the intensive grooming behavior of cats might lead to the removal of ticks before the transmission of pathogens. Furthermore, cats may show lower numbers of *A phagocytophilum* in circulating neutrophil granulocytes in comparison with dogs, potentially leading to false-negative PCR results.

### Screening for *A phagocytophilum* in blood donor cats is recommended using both direct and indirect methods.

Pathogenesis

Based on studies in humans and dogs, *A phagocytophilum* is known to be spread by *Ixodes* species ticks via transstadial transmission. For the pathogen to be transmitted, it is assumed that the vector has to be in direct contact with the host for 24–48 h. The pathogen then spreads via blood and lymphatic circulation, and the incubation time ranges from 1 to 2 weeks. Neutrophil granulocytes are infected via endocytosis following P-selectin-mediated adhesion. After the pathogen has penetrated the cell membrane of the phagosome, it proliferates by forming morulae. The pathogen inhibits some of the vital functions of the neutrophilic granulocytes, such as neutrophilic motility, phagocytosis, release of reactive oxygen radicals (oxidative burst) and interaction of neutrophilic granulocytes with endothelial cells, in order to survive and ensure its own proliferation. The breakdown of the phagosomes and the host’s cell membrane releases the pathogen and leads to infection of further cells and organs. The bacterium is able to prevent its recognition by the immune system by activating certain pathogenic mechanisms and delaying apoptosis.

There is little information on the specific pathogenesis of *A phagocytophilum* infection in cats. In an experimental study with six cats, mild clinical signs (transient fever) were triggered by intraperitoneal administration of infected blood. Blood tests showed a slight decrease in leukocytes (neutrophilic granulocytes and lymphocytes), significant reduction of mean cell volume and elevated liver enzymes (alanine aminotransferase and aspartate trans-
| Country    | Region                | n     | Study population                                                                                                                                  | Detection method | Prevalence | Period        | Reference |
|------------|-----------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------|---------------|-----------|
| Germany    | North East Germany    | 265   | 150/265 indoor, 99/265 outdoor access, 16/265 stray cats, 49/265 clinically healthy, 216/265 with clinical signs (96/265 with ectoparasitic treatment), 72/265 with tick infestation | IFAT             | 24/265 (9.1%) | 11/2007–11/2008 | 6         |
|            | (Berlin/Brandenburg)  |       |                                                                                                                                                    | PCR              | 1/265 (0.4%) |              |           |
| Bavaria,   | Lower Saxony          | 326   | 238/326 domestic cats, 58/326 animal shelter cats, 20/326 laboratory cats, 10/326 suspected *A. phagocytophilum* infection 24 domestic cats, 6 animal shelter cats and 2 cats with suspected infection tested positive 306 238/306 domestic cats, 58/306 stray cats (clinically healthy), 10/306 suspected *A. phagocytophilum* infection; 1 cat, with a history of travel to Denmark 6 months earlier, tested positive | IFAT             | 53/326 (16.3%) | 05/2006–08/2008 | 7         |
|            |                       |       |                                                                                                                                                    | PCR              | 1/306 (0.3%)  |              |           |
| Southern   | Germany               | 479   | Domestic cats                                                                                                                                     | PCR              | 2/479 (0.4%) |              |           |
| Europe     |                       |       |                                                                                                                                                    |                  |            |              |           |
| UK         | England               | 60    | Domestic cats with clinical signs indicative of suspected vector-borne infections                                                               | PCR              | 1/60 (1.7%)  | 08/2001–10/2001 | 14        |
| Ireland    | Dublin and surrounding area | 116  | 75/116 stray cats, 41/116 domestic cats                                                                                                             | PCR              | 0/116      | 01/2008–05/2008 | 42        |
| Sweden     | Central Sweden        | 90    | Domestic cats presented to a veterinary clinic                                                                                                      | IFAT             | 19/90 (21.1%) | 2010–2011    | 43        |
| Greece     | Crete, Mykonos, Skopelos, Athens | 148  | Cats with outdoor access                                                                                                                       | PCR              | 0/148      | Summer 2015  | 44        |
|            | Northern and central Greece | 100  | Domestic cats: 40/100 indoor, 60/100 with outdoor access 50/100 clinically healthy, 50/100 with clinical signs                                                                 | IFAT             | 0/100      |              | 45        |
|            |                       |       |                                                                                                                                                    | PCR              | 0/100      |              |           |
| Italy      | Northern and central Italy | 250  | Cats with outdoor access                                                                                                                        | Morulae          | 15/250 (6%) | 1997–2000  | 46        |
|            | Central Italy         | 560   | Clinically healthy cats: 176/560 animal shelter cats, 384/560 domestic cats 7/176 animal shelter cats and 18/384 domestic cats tested positive (21 cats with tick attachment in the previous 3–6 months) | IFAT             | 25/560 (4.5%) | 01/2005–12/2011 | 47        |
|            |                       |       |                                                                                                                                                    | PCR              | 2/320 (0.6%) |              |           |
| Portugal   | Lisbon and Évora      | 37    | 22/37 domestic cats, 13/37 animal shelter cats, 2/37 stray cats (3 animal shelter cats and 2 domestic cats tested serologically positive) | IFAT             | 5/37 (13.5%) | 08/2007–04/2008 | 51        |
|            |                       |       |                                                                                                                                                    | PCR              | 0/37       |              |           |
|            | Northern and central Portugal | 320  | Domestic cats: 192/320 outdoor access, 124/320 indoor, 4/320unknown 2/192 cats with outdoor access clinically healthy and tested positive | PCR              | 2/320 (0.6%) |              | 52        |
|            |                       |       |                                                                                                                                                    |                  |            |              |           |
| Southern   | Portugal              | 649   | 329/649 stray cats, 320/649 domestic cats 35/649 tested positive (26/35 stray cats, 9/35 domestic cats; 8/35 clinically healthy, 3/35 with suspected infection) | PCR              | 35/649 (5.4%) | 01/2012–08/2013 | 53        |

**Table 1: Prevalence of feline *Anaplasma phagocytophilum* infections in selected studies**
Table 1 Prevalence of feline *Anaplasma phagocytophilum* infections in selected studies (continued)

| Country     | Region                        | n  | Study population                                      | Detection method | Prevalence | Period     | Reference |
|-------------|-------------------------------|----|-------------------------------------------------------|------------------|------------|------------|-----------|
| Spain       | Northeastern regions          | 168| Domestic cats: 70/168 clinically healthy, 60/168 with clinical signs 47/168 additionally examined via PCR (27/47 clinically healthy, 20/47 with clinical signs) | IFAT             | 3/168 (1.8%) | –          | 54        |
|             |                               |    |                                        | PCR              | 0/47       |            |           |
|             | Barcelona and surrounding area| 100| 48/100 clinically healthy, 52/100 with clinical signs (1/52 tested positive) | PCR†             | 1/100 (1%) | 01/2006–12/2006 | 55 |
|             | Madrid and surrounding area   | 52 | Domestic cats: 28/52 clinically healthy, 24/52 with clinical signs 1/4 cats serologically positive with clinical signs | IFAT             | 4/52 (7.7%) | 10/2005–06/2007 | 56 |
|             |                               |    |                                        | PCR + culture    | 0/52       |            |           |
|             | Madrid and surrounding area   | 680| 539/680 domestic cats, 141/680 stray cats, 247/501 with outdoor access, 34/440 with tick infestation, 117/420 with ectoparasitic treatment | IFAT             | 57/680 (8.4%) | 09/2005–08/2008 | 57 |
|             |                               |    |                                        | PCR              | 0/680      |            |           |
| Catalonia   | Animal shelter cats with outdoor access | 116 | Animal shelter cats with outdoor access | IFAT             | 0/116      | 09/2012–11/2012 | 58 |
| USA         | Florida                       | 484| Clinically healthy stray cats            | PCR              | 0/484      | 06/1999–02/2000 | 59 |
|             | Northeastern regions          | 93 | Domestic cats with outdoor access (84/93 clinically healthy, 9/93 with clinical signs) | IFAT             | 28/93 (30.1%) | 1985–1989 | 60 |
|             |                               |    |                                        | ELISA            | 35/93 (37.0%) |            |           |
| Arizona     | Animal shelter cats, 50/112 stray cats, 5/112 cats living in a veterinary clinic | 112 | 57/112 animal shelter cats, 50/112 | PCR†             | 0/112      | 03/2004–07/2004 | 61 |
| USA         | Clinically healthy cats presented for blood donation | 146 | Clinically healthy cats presented for blood donation | PCR              | 0/146      | –          | 62        |
|             | Alabama, Maryland, Texas      | 92 | 54/92 humane shelter cats, 38/92 domestic cats | PCR†             | 0/92       | –          | 63        |
| Florida,    | California, Michigan          | 460| 373/460 stray cats, 65/460 animal shelter cats, 22/460 domestic cats Examination via PCR in 158/460 cats with IFAT ≥1:50 | IFAT             | 20/460 (4.3%) | –          | 64        |
|             |                               |    |                                        | PCR              | 0/158      |            |           |
| Colorado    | Cats with anaemia of unknown origin | 133 | Cats with anaemia of unknown origin | PCR              | 0/133      | 01/2001–11/2004 | 65 |
| Maine       | 159 | 42/159 cats with clinical signs, 117/159 clinically healthy, | SNAP §i          | 10/159 (6.3%) | –          | 66        |
| California, | Illinois, Massachusetts       | 5416| Domestic cats to a commercial laboratory | Specific peptide immunoassay | 9.7%       | 09/2014–02/2015 | 67 |
| Northeastern regions | 4334| 4334 blood samples of cats sent to a commercial laboratory | PCR²             | 40/4334 (0.92%) | 05/2009–05/2011 | 18 |
| Maryland    | 25 | 70 clinically healthy domestic cats (SNAP results from 25/70 cats) | SNAP §i          | 1/25 (4%) | 04/2011–04/2014 | 68 |
| Massachusetts | 175| 175 clinically healthy stray cats (in 175 cats no examination via PCR possible) | SNAP §i          | 17/175 (9.7%) | 06/2015–12/2015 | 69 |
| Other countries | USA, Canada, Caribbean | 858| 827/858 cats from the USA, 28/858 cats from Canada, 3/858 cats from the Caribbean Examination via SNAP test in 715/858 cats, via PCR in 406/858 cats | SNAP §i          | 13/715 (1.8%) | 2008–2013 | 70 |
| Korea Seoul | Animal shelter cats          | 222| Animal shelter cats | PCR              | 2/222 (0.9%) | –          | 71        |

IFAT = immunofluorescence antibody test; morulae = detection of inclusion bodies in blood smears

*No history/anamnesis available

*Anaplasma species/Ehrlichia species PCR without species differentiation

†Multiplex PCR with species differentiation (Ehrlichia species, *Anaplasma phagocytophilum*, *Neorickettsia risticii*, *Mycoplasma haemofelis*, *Candidatus Mycoplasma haemominutum*)

‡SNAP 4Dx Plus Assay (IDEXX)

§Coinfection with *Borrelia burgdorferi*

§§Multiplex PCR with species differentiation (*Anaplasma phagocytophilum*, *Bartonella henselae*, *Bartonella clarridgeiae*, *Bartonella quintana*, *Ehrlichia species*, *Mycoplasma haemofelis*, *Candidatus Mycoplasma haemominutum*, *Candidatus Mycoplasma turicensis*, *Rickettsia rickettsii* and *Rickettsia felis*)

††SNAP Multi-Analyte Test (detection of antibodies against *Anaplasma species*, *Borrelia species*, *Ehrlichia species*); in the case of enough sample material, specific IFAT and SNAP 4Dx Plus Assay (IDEXX)
Infections with *A phagocytophilum* most often produce an acute disease. There are also reports of asymptomatic infections in cats.

Clinical and laboratory findings

Thirty of 34 cats previously reported in the literature to have *A phagocytophilum* infection (see box below) had outdoor access. Twelve of the 34 cats (35%) were infested with ticks; of those cats, outdoor access was available in nine and unknown in three. Clinical signs were described in 33/34 cats; the remaining cat (3%) was clinically asymptomatic. Cats mostly showed non-specific clinical signs such as lethargy (31/33 cats, 94%), increased rectal temperature ranging from 39.1°C to 41.5°C (29/33 cats, 88%), anorexia or reduced appetite (25/33, 76%), conjunctivitis (12/33, 36%) and dehydration (5/33, 15%). Ten of 33 cats (30%) had a painful abdomen or painful limbs. Further clinical signs included pale mucous membranes (3/33, 9%), respiratory signs (3/33, 9%) and tachycardia (3/33, 9%). Neurological signs (2/33, 6%), weight loss (2/66, 6%) and dental calculus (2/33, 6%), with or without gingivitis, were also described in a few cats. Rare clinical signs included recurrent epistaxis, polyuria and polydipsia, and hypothermia, as well as abnormal lung sounds on auscultation.

Clinical signs often occur shortly after tick contact and rapidly improve with antimicrobial therapy.

**Clinical signs often occur shortly after tick contact and rapidly improve with antimicrobial therapy.**

Publications reporting *A phagocytophilum* infections in cats

To the authors’ knowledge, there are 16 publications describing infections with *A phagocytophilum* in 55 cats (Table 2). Eighteen of these 55 cats, from two study populations, were diagnosed based on the detection of morulae in neutrophilic granulocytes. Those cats were not included in the analysis in the ‘Clinical and laboratory findings’ section of this article, because PCR analysis had not been performed in order to confirm *A phagocytophilum* infection. One cat from the UK, as well as one cat from Italy, were also not included in the analysis due to an inadequate description of the clinical signs and laboratory findings. In one cat, a urethral obstruction was the cause for presentation to the clinic; this cat was also not considered for further analysis because the laboratory changes were most likely caused by the underlying urinary disease and not by infection with *A phagocytophilum*. This left 34 cats included in the analysis that had been diagnosed with *A phagocytophilum* infection based on the guidelines of the ABCD.

Mild to severe thrombocytopenia is a common – and the most diagnostically relevant – laboratory finding in *A phagocytophilum* infections in both cats and dogs (Table 2). Mechanisms of induced thrombocytopenia could include reduced production of platelets, increased consumption due to disseminated intravascular coagulopathy, shortened platelet lifespan due to immune-mediated destruction or sequestration of platelets in an enlarged spleen. In humans and dogs, antiplatelet antibodies have been detected, indicating that immune-mediated factors may also play an important role. Antinuclear antibodies, as well as an elevated release of interferon gamma-messenger ribonucleic acid, has been noted in cats, which could indicate an immunological pathogenesis, eventually leading to the development of clinical signs.

In a study from Colorado, USA, wild-caught *I scapularis* ticks were transferred onto four cats, resulting in a subclinical coinfection with *A phagocytophilum* (detection via PCR and antibody ELISA) and *Borrelia burgdorferi* (detection via antibody ELISA). The ticks were collected in a region in which previous examinations had detected *A phagocytophilum* DNA in 15% and *B burgdorferi* DNA in 50% of ticks. The cats showed transient lymphopenia postinfection. In the following 13 weeks, no changes were noted in cats, which could indicate an immunological pathogenesis, eventually leading to the development of clinical signs.

Infections with *A phagocytophilum* most often produce an acute disease (Table 2). To date, there are only a few reports in the literature supporting persistent infections in dogs, sheep and horses. In cats, there are two cases reported where persistent infection was documented, with one cat still PCR positive on day 120 after the initiation of treatment and the other cat being PCR positive until day 37 and negative on day 139 after the initiation of treatment. There are reports of asymptomatic infections with *A phagocytophilum* in cats. Subclinical and self-limiting infections have been described after natural exposure in dogs and have also been experimentally confirmed in studies with sheep and horses. PCR-positive dogs may also be clinically healthy. There is widespread serological detection of the pathogen in naturally infected dogs without the development of clinical signs, especially in endemic areas.
### Table 2: Case reports of feline *Anaplasma phagocytophilum* infections (n = 55, 1989–2019)

| Country | n | Signalment | History | Clinical signs | Laboratory results | Diagnostic methods | Therapy | Outcome | Reference |
|---------|---|------------|---------|---------------|-------------------|-------------------|---------|---------|-----------|
| Sweden  | 1 | ESH, 1 year, MN | Lethargy, anorexia, tachypnoea | Depression, fever (41.3°C), dehydration, tick infestation | Neutrophilia, lymphopenia | Morulae*, PCR positive | Doxycycline | Very good | 16 |
| UK      | 1 | Unknown | Acute pyrexia, weakness, lethargy | Fever | Unknown | PCR positive | Unknown | Unknown | 14 |
| Italy   | 15 | Unknown | Anorexia/poor appetite (13/15); weight loss (5/15); vomiting (4/15); incoordination (3/15); tick infestation, haematuria, polydipsia, dyspnoea, hiding (2/15 each) | Pain (8/15); lethargy, lymphopenomghaly, poor coat condition (6/15 each); gingivitis, periodontitis, conjunctivitis (5/15 each); fever (3/15); pharyngitis, dehydration, pale mucous membranes (2/15 each) | Morulae*, PCR positive | Doxycycline | Very good | 46‡ |
| Austria | 2 | ESH, 3 years, FN | Tick infestation, lethargy, poor appetite, incoordination | Dehydration, conjunctivitis, fever (40.4°C) | Thrombocytopenia*, elevated lactate dehydrogenase, lymphocytosis | Morulae*, PCR positive, IFAT positive | Doxycycline | Very good | 9 |
|         | ELH, 4 years, MN | Tick attachment, anorexia, lethargy, pain | Fever (40.3°C), dehydration, conjunctivitis, serous nasal secretion, tachypnoea | Anaemia, thrombocytopenia*, eosinophilia | Thrombocytopenia*, PCR negative, IFAT positive | Doxycycline | Very good | |
| Italy   | 1 | Unknown | Unknown | Clinical signs indicative of vector-borne infections§ | Unknown | PCR positive, IFAT positive | Unknown | Unknown | 13‡ |
| Switzerland | 1 | ESH, 14 years, MN | Lethargy, anorexia | Fever (40.1°C), minor dehydration, gingivitis | Thrombocytopenia, leukocytosis, hypoalbuminaemia, hypokalaemia, low iron | Morulae*, PCR positive, IFAT positive | Doxycycline | Very good | 12 |
| Finland | 1 | Maine Coon, 3.5 years, FN | Tick infestation, reduced appetite, hiding, lethargy, ocular discharge | Fever (39.5°C), tachypnoea, painful cranial abdomen, bilateral increased lung sounds | Lymphopenia, hyperglicemia | Morulae*, PCR positive, IFAT positive | Doxycycline | Very good | 15 |
| Poland | 3 | ESH, 2.5 years, M | Loss of appetite and thirst, lethargy | Pale mucous membranes, fever (39.8°C), pain | Anaemia, thrombocytopenia, leukopenia | Morulae*, PCR positive | Doxycycline | Very good | 10 |
|         | ESH, 3 years, M | Tick infestation, pain, reduced appetite | Leathargy, pale mucous membranes | Anaemia, thrombocytopenia, leukopenia | Anaemia, thrombocytopenia, leukopenia | Morulae*, PCR positive | Doxycycline | Very good | |
|         | ESH, 6 years, F | Tick infestation, lethargy, reduced thirst and appetite | Fever (39.6°C) | Anaemia, thrombocytopenia, leukopenia | Anaemia, thrombocytopenia, PCR positive | Doxycycline | Very good | |
| Poland | 1 | ESH, 2.5 years, M | Loss of appetite, lethargy, tick attachment | Pale yellow mucous membranes, pain | Anaemia, thrombocytopenia, elevated liver enzymes | PCR positive, IFAT positive | Doxycycline | Very good | 11 |
| Germany | 2 | ESH, FN | Fever, loss of appetite, weight loss, polyuria, polydipsia, oculer lesions | Dehydration, hypoferremia (37.4°C) | Anaemia, neutrophilia with left shift, monocytosis, lymphocytosis renal azotaemia, electrolyte shift | PCR positive | Unknown | Unknown | 5‡ |
|         | ESH, M | Unknown | No clinical signs | Thrombocytopenia, leukocytosis, mononucleosis, lymphocytosis, neutrophilia | PCR positive (coinfection with haemotrophic mycoplasma) | Unknown | Unknown | |

*Note: *Morulae* indicates the presence of morulae in blood smear. PCR positive and IFAT positive indicate positive results for polymerase chain reaction and immunofluorescent antibody test, respectively. Thrombocytopenia† and monoclonal gammopathy‡ are additional findings. Clinical signs indicative of vector-borne infections§ include fever, anorexia, weight loss, polyuria, polydipsia, ocular lesions. Doxycycline therapy results in very good outcomes. Additional details for each case report are provided in the reference column.
### Table 2: Case reports of feline *Anaplasma phagocytophilum* infections (n = 55, 1989–2019) (continued)

| Country | n | Signalement | History | Clinical signs | Laboratory results | Diagnostic methods | Therapy | Outcome | Reference |
|---------|---|-------------|---------|----------------|--------------------|-------------------|---------|---------|-----------|
| Germany | 1 | Persian, 7 years, MN | Tick attachment, ocular discharge | Pain, gingivitis | Thrombocytopenia, leucocytosis, eosinophilia, hyperproteinaemia | PCR positive | Unknown | Unknown | 7‡ |
| Germany | 1 | Unknown | Unknown | Obstructive feline lower tract disease | Azotaemia | PCR positive | Unknown | Unknown | 6‡ |
| Germany | 1 | LaPerm longhair, 7 years, MN | Tick attachment, loss of appetite, lethargy | Fever (40.8°C) | Leukopenia, thrombocytopenia, hyperproteinaemia, hyperglobulinaemia, hyperglycaemia, lymphopenia | Morulae*, PCR positive, IFAT positive | Doxycycline | Very good | 8 |
| USA | 5 | DSH; 9 months to 3 years; 3 MN, 2 FN | Lethargy (5/5), tick attachment (3/5) | Fever (5/5, 39.7–40.9°C) | Thrombocytopenia, 1/5 thrombocytic aggregation, hyperglycaemia 1/5 | PCR positive, IFAT positive (1/5 positive for *Bartonella henselae*, 3/5 positive for *Toxoplasma gondii* IgG) | Doxycycline | Very good | 17 |
| USA | 16 | Median 2 years old (4 months to 13 years); 9 MN, 1 M, 6 FN | Lethargy (16/16), loss of appetite (14/16), ocular signs (7/16), ataxia (1/16) | Fever (15/16, 39.6–41.5°C), pain (4/16), tachycardia (3/16), proteinuria (2/16), hepatosplenomegaly (1/16) | Thrombocytopenia, 7/16 thrombocytic aggregation, hyperglycaemia, anaemia, neutropenia (2/16 each), leukopenia (1/16) | PCR positive (1/16 positive for *Mycoplasma haemominutum* and *Bartonella clarridgeiae*, morulae* (3/16)) | Doxycycline | Very good | 18‡ |
| Kenya | 3 | 10 years, M | Loss of appetite, weight loss, dyspnoea | Tick infestation, fever (40.1°C), splenomegaly | Normocytic, normochromic anaemia, hyperproteinaemia, hyperglobulinaemia | Morulae* | Tetracycline hydrochloride | Very good | 89 |
| Kenya | 4 years, M | Loss of appetite, weight loss | Tick infestation, fever (39.7°C), splenomegaly | Normocytic, normochromic anaemia | Morulae* | Imidocarb-dipropionate | Very good |
| Kenya | 2 years, F | Loss of appetite, weight loss, dyspnoea | Tick attachment, fever (40°C), splenomegaly, lymphadenomegaly | Normocytic, normochromic anaemia, leukopenia, neutropenia | Morulae* | Imidocarb-dipropionate | Very good |

ESH = European shorthair; ELH = European longhair; DSH = domestic shorthair; M = male; MN = male neutered; F = female; FN = female neutered; IFAT = immunofluorescence antibody test  
*Microscopic detection in blood smears  
No manual count of platelets with a haemocytometer  
Prevalence study with additional case report content, providing further description of infected cats  
No further definition of clinical signs  
Confirmed by manual count of platelets with haemocytometer

**Mild to severe thrombocytopenia is a common – and the most diagnostically relevant – laboratory finding in *A phagocytophilum* infections in both cats and dogs.**

In all of the 34 cats with *A phagocytophilum* infections from the literature that are analysed here (see box on page 432), haematological examination was performed (Table 2). Thrombocytopenia was diagnosed in 20/34 cats (59%); however, low platelet counts in cats must be interpreted with caution (see box), and in six of these 20 cats platelet aggregation was present. Nine out of 34 cats (26%) were anaemic.

**Interpreting thrombocytopenia with caution**

Thrombocytopenia is the most diagnostically relevant laboratory finding in *A phagocytophilum* infections in cats. However, in general, low platelet counts must be interpreted with caution, because the impedance measurement is influenced by platelet aggregates, giant platelets or inadequate separation of erythrocytes and platelets, all of which can lead to falsely low values. It is therefore recommended that feline platelets are counted manually with a haemocytometer.
Five out of 34 cats (15%) were leukopenic and 3/34 cats (9%) had leukocytosis. Similarly to cats, in the 63 dogs with granulocytic anaplasmosis investigated by Chirek et al, thrombocytopenia was the most common laboratory abnormality (86%), followed by anaemia (70%) and leukocytosis (27%), as well as leukopenia (14%). Leukopenia occurred more often in cats than leukocytosis. A differential blood count was available in 25/34 cats (74%). Nine of 25 (36%) cats were lymphopenic and 3/25 (12%) had a lymphocytosis or a neutrophilia (2/3 with a left shift). Further abnormalities included neutropenia (2/25, 8%), eosinophilia (2/25, 8%) and monocytosis (2/25, 8%). Again, in Chirek et al’s study of 63 dogs, similar laboratory abnormalities such as lymphopenia (44%), monocytosis (43%), neutrophilia (35%), eosinophilia (10%), lymphocytosis (8%) and neutropenia (2%) were described.

Blood chemistry was performed to varying extents in 27 of the 34 cats (79%) (Table 2). The most common finding was hyperglycaemia, which was found in 6/27 cats (22%). Two out of 27 cats (7%) showed azotaemia, one of them due to an underlying disease (chronic renal insufficiency with a suspected acute component) and one during the course of disease while under intensive care. Electrolyte imbalances and increased liver enzymes were detected in 2/27 cats (7%). Further abnormalities included an increase in lactate dehydrogenase (1/27, 4%) and an abnormal albumin concentration (1/27, 4%), as well as a reduction in serum iron levels (1/27, 4%). Hyperproteinemia with corresponding hyperglobulinaemia was detected in 1/27 cats (4%), and hyperproteinemia without hyperglobulinaemia in another cat. In Chirek et al’s study of 63 dogs, similar laboratory abnormalities such as lymphopenia (44%), monocytosis (43%), neutrophilia (35%), eosinophilia (10%), lymphocytosis (8%) and neutropenia (2%) were described.

Diagnosis

Several direct and indirect methods have been described for diagnosing infections with Anaplasma phagocytophilum. The detection of morulae in neutrophilic granulocytes in a blood or buffy-coat smear is one such method and is highly indicative of an infection with Anaplasma phagocytophilum. However, these morulae cannot be differentiated from those of Ehrlichia ewingii; hence, further tests are necessary for confirmation of an infection with Anaplasma phagocytophilum. In addition, there is always the possibility of falsely interpreting stain residues, nuclei or basophil precipitates in the blood smear as morulae. In experimentally infected cats, morulae were detectable 7–9 days post-infection or within the first 10 weeks after tick infestation. In experimentally infected dogs, morulae were detectable 4 days post-infection and persisted for 4–8 days.

PCR examination detects the pathogen’s DNA in peripheral blood, buffy coat, bone marrow or splenic tissue. Some protocols also include the detection of RNA from other pathogens such as A platys or Pseudomonas species, meaning that further sequencing is necessary for the confirmation of Anaplasma phagocytophilum infection. In dogs, the detection of Pseudomonas sequences has been reported to cause false-positive results, which will not be apparent until further sequencing has been implemented. To the authors’ knowledge, there are no similar experiences in cats. Another study in cats described direct antigen detection via PCR, which has a high sensitivity and specificity in acute cases but can be falsely negative in chronic infections due to the absence of the pathogen in blood.

The detection of antibodies via immunofluorescence antibody test (IFAT) or ELISA also indicates exposure to Anaplasma phagocytophilum. However, an acute infection is only confirmed if the antibody titre increases or decreases four-fold within 4 weeks. In general, IFAT and ELISA have a high sensitivity and specificity, but it is important to give consideration to the limitations of these tests, which include, for example, possible cross reactions with Ehrlichia species and A platys.

SNAP tests, for example the SNAP Multi-Analyte Test and the SNAP 4Dx Plus Assay (IDEXX), are used as rapid in-house ELISAs in veterinary medicine. Both tests have been developed as canine assays, but have also successfully detected antibodies against Anaplasma phagocytophilum in domestic cats. A comparison between the two SNAP tests and a commercial IFAT for the detection of Anaplasma phagocytophilum in cats showed discrepancies between the different assays. Reasons for this could include the lack of specificity of peptides chosen in the design of the assays, the lack of sensitivity of commercial ELISA and/or IFAT and/or an enhanced analytic sensitivity of p16 analytes for testing cat sera. In this study, the IFAT was slightly more sensitive than the ELISA.

Detection of morulae in neutrophilic granulocytes is highly indicative of an infection with Anaplasma phagocytophilum, although further tests are necessary for confirmation.

Acute infection with Anaplasma phagocytophilum is confirmed on immunofluorescence antibody test or ELISA if the antibody titre increases or decreases four-fold within 4 weeks.
The limitations of serological tests extend to the premature implementation of tests postinfection before the beginning of seroconversion, the cross-reactions with other pathogens and the possibility of false-negative results, as seen in young or immunosuppressed dogs. Antigens might not be detectable in acute cases; for example, if tested before seroconversion. In an experimental study, antibodies against Anaplasma phagocytophilum were detected in cats within 14 days postinfection. In experimentally infected cats, antibodies were detectable for a duration of 2–6 weeks post-infection. Under natural conditions, seroconversion can also be seen in cats treated with antibiotics. Antibodies can persist for several months after pathogen contact. A measurable antibody titre may also be due to a cross reaction with A platys or Ehrlichia species. In Europe, A platys and E canis are transmitted by the vector Rhipicephalus sanguineus. Owing to the vector distribution, there are no autochthonous infections in northern and central European areas. Of course, this does not account for animals with a stay abroad; for example, those imported from or travelling to endemic regions. This underlines the importance of a thorough history including information on stays abroad.

It is important to obtain a thorough history; information on periods of time the cat has spent abroad (travelling or before importation) is especially pertinent.

Treatment and management

A phagocytophilum is resistant to several antimicrobial agents. Doxycycline is the antibiotic of choice for treating rickettsial infections in cats, although currently there are only retrospective case reports supporting this recommendation. It is administered at 10 mg/kg PO q24h for 28 days. It is recommended that the tablets be dissolved in water or administered with food in order to prevent oesophagitis.

The ABCD guidelines describe rapid clinical improvement in patients within the first 24–48 h after initiation of antimicrobial treatment with doxycycline. One cat tested negative as soon as 1 day after the initiation of treatment with doxycycline. In contrast, however, some studies have described that the pathogen was no longer detectable in blood via PCR after treatment with doxycycline on day 15, after 3 weeks, on days 25, 27 and 30, after 6 weeks and on day 139. A further case report documented that the pathogen was detectable via PCR 8 days after starting treatment with doxycycline; in another cat it was detectable even 120 days after the initial treatment period of 28–30 days. A further cat tested positive after 37 days and negative on day 139. In dogs there are several studies providing varying information. A study in Germany described complete pathogen elimination in all 18 infected dogs 2–8 weeks after the initiation of doxycycline treatment; however, another study described recurrence of clinical signs after antimicrobial therapy or poor response to treatment.

Doxycycline is the antibiotic of choice for treating rickettsial infections in cats, although currently there are only retrospective case reports supporting this recommendation, and the required duration of treatment in cats is unknown.

All of this confirms that the required duration of treatment in cats is unknown. In comparison, in dogs infected with A phagocytophilum, treatment recommendations are doxycycline 5 mg/kg q12h for 14 days.72

Prevention and public health considerations

Humans are also susceptible to infections with A phagocytophilum, making this pathogen relevant for both human and veterinary medicine. Prevention in animals therefore plays an essential role, especially in order to avoid the development of reservoirs.

It is important to raise awareness of tick prevention in endemic areas. Also, clinicians should consider testing potentially exposed animals, as clinical signs are vague and non-specific. Feline vector-borne infections should be on the list of differential diagnoses in cases with a history of vector contact and clinical signs suspicious of an infection.

If cats are housed indoors and arthropod control (see box on page 437) is maintained, the risk to people should be minimal. In addition to antiparasitic treatment, regular examinations for ticks should be carried out by owners and veterinarians. The ACVIM guidelines recommend direct and indirect methods of detection for A phagocytophilum in blood donor cats. Only seronegative and PCR negative cats should donate blood. If no other blood donors are available in endemic regions, seropositive and PCR negative cats may also be used as blood donors.
Licensed antiparasitic agents with repellent effects against either all ticks, or specifically *Ixodes* ticks, are recommended for both indoor and outdoor cats (Table 3). There are different terms used for the effects of applied compounds:120
tick repellency sensu stricto is characterised by an irritant effect causing the tick to move away and fall off soon after contact with the haircoat of the host. Various other terms are as follows:

- Disruption of attachment: interference with the natural process of tick fixation
- Tick expellency: disruption of the mechanisms of attachment or prevention of attachment of new infesting ticks
- Antifeeding effect: interference with the natural process of tick feeding, avoiding any blood meal
- Killing effect (acaricidal effect sensu stricto): ability to induce death of the ticks

**Future research needs and conclusions**

Feline vector-borne infections are gaining in importance. Further research to investigate the pathogenesis of *A. phagocytophilum* infections in cats is required. The spread of potential vectors and pathogens to currently non-endemic regions due to growing tourism, increasing numbers of imported animals, goods traffic and climatic changes makes prophylaxis for companion animals and biological limitation of the tick population even more relevant. As with other vector-borne infections, *A. phagocytophilum* is of great importance for public health in human and veterinary medicine due to its zoonotic potential.

**The spread of potential vectors and pathogens to currently non-endemic regions makes prophylaxis for companion animals especially more relevant.**
A 7-year-old male neutered LaPerm longhair cat with outdoor access was presented due to lethargy and lack of appetite.

Case work-up On physical examination, the cat had a rectal temperature of 40.8°C, and an I. ricinus tick was observed to be attached. Blood samples were collected for haematological and biochemical analysis and a blood smear was prepared. Laboratory abnormalities at initial presentation included thrombocytopenia and hyperproteinaemia with hyperglobulinaemia (see table). During the course of the disease, the cat developed leukopenia, mild anaemia and azotaemia.

Diagnosis The diagnosis of an infection with *A. phagocytophilum* was established through the microscopic evidence of morulae in the cat’s neutrophilic granulocytes (figure), the detection of pathogenic DNA via PCR in EDTA blood and the detection of antibodies using an IFAT (titre 1:40).

Treatment and outcome The cat was treated with intravenous fluids and antipyretic agents for 3 days. Doxycycline 10 mg/kg PO q24h was given over 3 weeks. The rectal temperature, appetite and laboratory abnormalities normalised during the course of treatment. After 9 days of treatment the PCR test was still positive. We were not able to initiate a further PCR or IFAT.

What this case demonstrates: A *phagocytophilum* infection and granulocytic anaplasmosis should be on the list of differential diagnoses in cats with outdoor access and/or tick infestation when suspicious clinical signs are present. Cats should be treated with antiectoparasitic agents in order to prevent vector-borne infections.

### Haematological and biochemical analysis

| Parameter     | Reference interval* | Day 1 | Day 2 | Day 3 | Day 9 | Day 21* |
|---------------|---------------------|-------|-------|-------|-------|---------|
| WBC (x 10⁹/l)| 6–11                | 5.11  | 3.27  | 3.9   | 8.42  | 6.2     |
| Hct (%)       | 30–44               | 35    | 29    | 35    | 32    | 38      |
| Plt (x 10⁹/l)| 180–550             | 78*   | 88    | 111*  | 180   | 270     |
| Creatinine    | 53–168              | 132   | –     | 144   | 202   | 172     |
| Total protein | 57–78               | 86    | –     | 78    | 82    | –       |
| Albumin (g/l) | 22–40               | 30    | 27    | 28    | –     | –       |

WBC = white blood cell count; Hct = haematocrit; Plt = platelet count
*Reference values of the Clinic for Small Animals, Faculty of Veterinary Medicine, Freie Universität Berlin, Germany
†Reference values of the laboratory IDEXX GmbH, Ludwigsburg, Germany
‡Manual count of platelets: 72,000/µl
§Manual count of platelets: 116,000/µl

Conflict of interest

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