GUIDELINE for Feline respiratory Mycoplasma infections

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Key points

- *Mycoplasma felis* may be identified in cats with clinical signs or in healthy cats living with infected animals.
- *M. felis* is typically associated with Upper Respiratory Tracy Disease (URTD) but sometimes may be associated with lower respiratory tract infections (LRTIs).
- *M. felis* is transmitted directly from infected cats to in-contacts by aerosol.
- Indirect transmission is not important, because mycoplasmas are not able to survive for a long time outside the host.
- *M. felis* has been associated with other pathologies such as pyothorax, conjunctivitis, keratitis and monoarthritis or polyarthritis.
- The diagnosis of mycoplasma infections requires use of a diagnostic laboratory.
- Antimicrobial therapy is commonly used to treat mycoplasma respiratory infections. Doxycycline is a good first choice.
- As no vaccine is currently available, the prevention of mycoplasma infections is based on the control of concurrent infections and correct management of the cat communities.

Agent properties

Mycoplasmas (M.) are the smallest prokaryotic organisms with the smallest genomes (a total of about 500 to 1000 genes) that can grow in cell-free culture medium (fried-egg-shaped colonies are seen on agar).

The dependence of mycoplasmas on their hosts for many nutrients may explain the great difficulty in cultivating many of these infectious agents in the laboratory. For example, they require cholesterol, a unique property among prokaryotes, for their growth *in vitro*.

The term mycoplasma (from Greek: mykes, fungus; plasma, formed) refers to the filamentous (fungus-like) nature of the organisms of some species and to the plasticity of their outer membrane resulting in pleomorphism (from spherical to filamentous). Mycoplasmas have surface antigens such as membrane proteins, lipoproteins, glycolipids and lipoglycans. Some of the membrane proteins undergo spontaneous antigenic variation (Razin, 1996). As they lack cell walls, mycoplasma cells are easily damaged outside of the host (Maglaras and Koenig, 2015).

In the cat, several species of non-haemotropic mycoplasmas have been described: *M. arginini, M. arthriditis, M. canadense, M. canis, M. cynotis, M. feliminutum, M. felis, M. gallisepticum, M. gatae, M. hyopharyngis, M. lipophilum, M. pulmonic* and *M. spumans.*

Although *Mycoplasma* spp. may be part of the normal flora of the upper respiratory tract of cats (Tan et al., 1977), *M. felis* can be identified in cats with clinical signs or in healthy cats living with infected animals (Holst et al., 2010). Nowadays it is considered a

primary opportunistic pathogen of upper respiratory tract disease (URTD) (Chandler and Lappin, 2002; Holst et al., 2010; Le Boedec, 2017).

Epidemiology

Prevalence

Table 1 shows the prevalences of *M. felis* infections (PCR-positive) in various reports.

Table 1: Prevalence of *M. felis* infections

Country	Prevalence	Type of cat sampled	Reference
Australia	13.4% 21.5%	FCV-positive cats cats with URTD	Nguyen et al. (2018)
Canada	29.2% 20.3%	cats with URTD cats without URTD	Gourkow et al. (2013)
Spain	46.5% 38.3% 37.7% 20.4%	cats with URTD cats with conjunctivitis cats with gingivostomatitis healthy cats	Fernandez et al. (2017)
Switzerland	48% 31%	FCV-positive cats healthy cats	Berger et al. (2015)
USA	50%	shelter cats	Bannasch and Foley (2005)
USA	84% 86%	Long term sanctuaries: cats with URTD cats without URTD	McManus et al. (2014)
USA	58% 38%	Foster care programs: cats with URTD cats without URTD	McManus et al. (2014)

Transmission

As a normal inhabitant of the respiratory mucosae, *M. felis* is transmitted directly from an infected cat to an in-contact one by aerosol, but also by grooming. Indirect transmission is not important, because mycoplasmas are not able to survive for long outside the host (Maglaras and Koenig, 2015).

Stressors, such as overcrowding, concurrent respiratory viral infections and poor hygienic situations, may promote proliferation of mycoplasmas and their transmission between cats (Sykes, 2014). The risk of being infected with *M. felis* increased from 21% to 32% within 10 days of a cat entering a Canadian shelter (Gourkow et al., 2013).

Pathogenesis

The primary habitat of mycoplasmas in general and, in particular, of *M. felis*, is the mucosae of the upper respiratory tract, where it adheres to the epithelial lining. The intimate association between the adhering mycoplasmas and their host cells provides an environment in which local concentration of toxic metabolites, (i.e. H_2O_2) excreted by the bacteria, build up and cause tissue damage. Furthermore, as mycoplasmas lack cell walls, fusion between the membrane of the bacteria and host cells may occur causing changes in cell membrane composition and increased permeability to the mycoplasma's hydrolytic enzymes. These events are able to exacerbate the damage to the host tissues. Finally, the spontaneous genetic mutations are responsible for rapid changes at major surface protein antigenic levels helping the bacteria to escape the recognition by the immune system of the host (Razin, 1996).

Mycoplasmas may also invade the lower respiratory tract as secondary opportunistic pathogens in animals with impaired mucociliary functions, as a consequence of primary bacterial or viral infection and of ciliary dyskinesia (Bernis, 1992).

Clinical signs

Mycoplasma *felis* is typically associated with URTD but sometimes it may be associated with lower respiratory tract infections (LRTIs).

The upper respiratory tract includes the nasal passages, sinuses, pharynx and the larynx. Signs of upper respiratory tract infections include clear or coloured discharge from the eyes or nose, coughing, sneezing, conjunctivitis, with swelling of the conjunctival mucous membranes (chemosis), lethargy and anorexia. Rarely, cats may have trouble breathing. Very young, very old and immunosuppressed cats are more likely to develop severe disease and possibly die as a result of their URTD, usually due to secondary infections (e.g. causing pneumonia), consequence of anorexia (hepatic lipidosis) and dehydration (Cohn, 2011).

LRTIs may cause coughing, lethargy, anorexia, tachypnoea or dyspnoea, nasal discharge and pyrexia in the lower respiratory tract, which includes the portion of the larynx below the vocal folds, the trachea, bronchi and bronchioles (MacDonald et al., 2003; Foster et al., 2004). Cats showing coughing, dyspnoea or tachypnoea should be investigated for LRTIs (Foster and Martin, 2011).

After the first isolation and identification of *M. felis* by Cole et al. (1967) from cat saliva and ocular discharges, several authors have described syndromes in which *M. felis* may be involved (Aroch et al., 2008).

Switzer (1967) and Pedersen (1988) reported mycoplasmal pneumonia in kittens and Tan (1974) described subclinical pneumonitis in young cats experimentally infected with *M. felis*.

Glucocorticoid immunosuppressed cats may also develop mycoplasmal pneumonia (Pedersen, 1988) and a mycoplasma species has been isolated from a pulmonary abscess in a mature cat (Crisp et al., 1987).

Mycoplasma purulent pleurisy (pyothorax) was described for the first time by Malik et al. (1991). Trow et al. (2008) reported a clinical case of an adult cat with primary mycoplasma pneumonia associated with reversible respiratory failure

M. felis may be associated with chronic rhinosinusitis in cats (Johnson et al., 2005). Schulz et al. (2014) described *Mycoplasma* spp. in cats with lower respiratory disease (asthma and chronic bronchitis).

Hofmann-Lehmann reported an association between *M. felis* infection and nasal discharge and conjunctivitis in an epidemiological study (personal communication) and recently Pazzini et al. (2018) described a clinical case of upper respiratory disease in a cat showing chronic purulent nasal discharge and co-infection with *M. felis* and *Tritrichomonas foetus*.

Lastly, *M. felis* was identified in cats with ulcerative keratitis (Gray et al., 2005; Ledbetter and Scarlett, 2008), with conjunctivitis (Hartmann et al., 2010) and with polyarthritis (Hooper et al., 1985) or monoarthritis (Liehmann et al., 2006).

Diagnosis

Mycoplasma infection may be clinically suspected in cats with URTD and has to be evaluated in cats with chronic respiratory disease, such as asthma (Fig. 1, 2) and chronic bronchitis, as well as in unresponsive patients being treated with antimicrobial drugs targeting cell wall synthesis, which are not effective against mycoplasmas as they do not have cell walls.

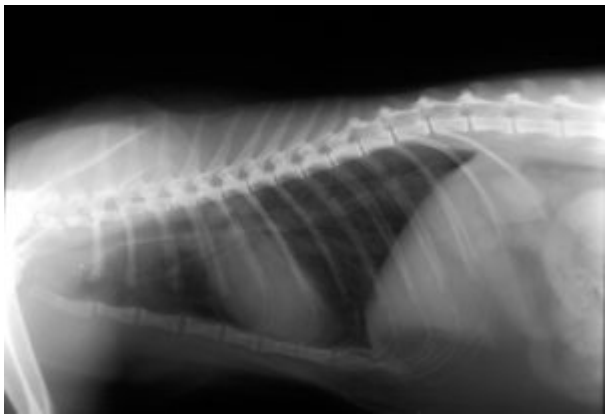

Fig. 1: Chest radiograph from a cat showing a diffuse bronchial and interstitial pattern – the cat had feline asthma and a secondary mycoplasmal infection diagnosed by PCR on a BAL. Courtesy of Prof. S. Tasker

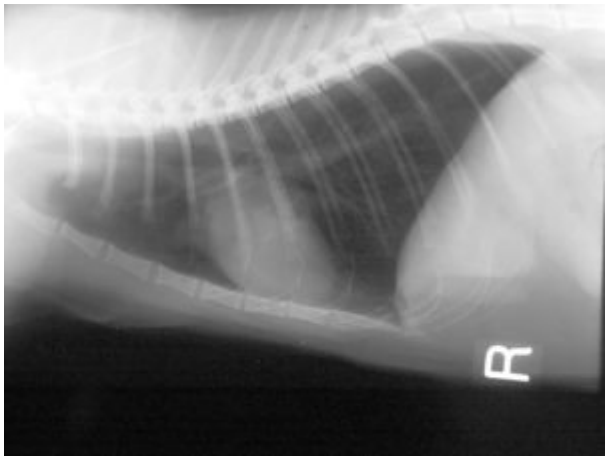

Fig. 2. Chest radiograph from the same cat as in Fig. 1 after 6 weeks of doxycycline treatment – only a fine bronchial pattern was evident after antibiotic treatment. Courtesy of Prof. S. Tasker

In order to collect the right diagnostic samples (depending on the location of the infection), contacting the diagnostic laboratory is useful to ensure the appropriate collection, handling and transportation of specimens (Maglaras and Koenig, 2015). Veir et al. (2008) suggested collection of both samples from nasal and pharyngeal sites from cats with URTD, while Lee-Fowler and Reinero (2012) recommended endotracheal washes or bronchoalveolar lavages (BAL) for sampling of the lower feline airways. Samples should be collected and placed into a solid transport medium for isolation (Amies is the best choice) or a sterile tube for biomolecular tests (Fig. 3). They have to be kept cool (not frozen) during the transportation (Chandler and Lappin, 2002).

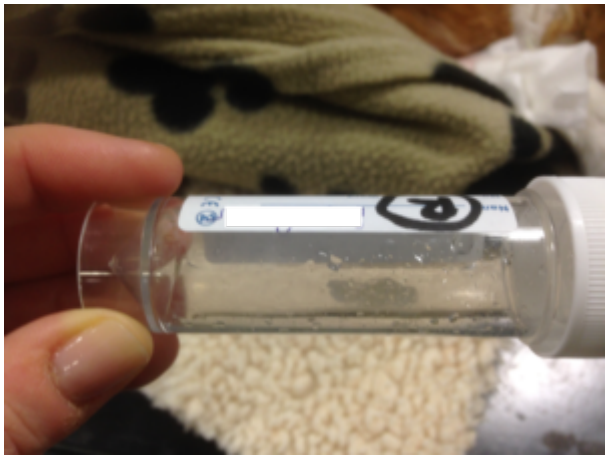

Fig. 3. BAL sample in a vial from the same cat as in Fig. 1 – this sample was used to identify M. felis lower respiratory tract infection by PCR. Courtesy of Prof. S. Tasker

At the laboratory, the samples are tested for mycoplasmal DNA by Polymerase Chain Reaction (PCR). PCR, mainly real time (quantitative) PCR, is widely used for its rapidity, sensitivity and ability to identify non-viable bacteria (Söderlund et al., 2011; Litster et al., 2015), as well as allowing identification of non-culturable species. Isolation is not used routinely because the mycoplasmas do not survive outside the host and so culture may be negative as a result of improper handling, prolonged transport time or collection errors.

As reported by Reed et al. (2012), with PCR and culture, if the organism is not cultured and only DNA is detected, the possibility of commensal contamination has to be considered due to the higher sensitivity of PCR over culture. However, quantitative PCR is useful to interpret positive results in clinical scenario, mainly when conjunctival cells from cats with conjunctivitis, or BALs from cats with lower respiratory tract signs, or lung samples from dead cats, are collected. In cats with no clinical signs, *M. felis* may be detected in oropharyngeal cells, and less often in conjunctival cells.

In order to improve the characterization of fastidious respiratory mycoplasma Framst et al. (2022) developed a long-read next generations sequencing workflow. As stated by these authors, the complete classification of a mycoplasma species involved in pathology can be achieved within 5 days.

Treatment

Antimicrobial therapy is commonly used to treat mycoplasma respiratory infections. Doxycycline is a good first line agent because it is well tolerated by cats and relatively narrow in spectrum. The recommended dose is 5 mg/kg, PO, q12h or 10 mg/kg, PO, q24 (Lappin et al., 2017). Oxytetracycline or chlortetracycline ophthalmic ointment can be used q6h in addition to topical treatment.

Macrolides (azithromycin), lincosamides (clindamycin) and fluoroquinolones (marbofloxacin or pradofloxacin) could be used as second line agents (Hartmann et al., 2008; Maglaras and Koenig, 2015).

The duration of treatment required is not clear. Clinical signs disappear within one week, but chronic intracellular infections may prevent complete elimination of the mycoplasmal infection (Reed, 2016). Greene and Chalker (2012) suggested a treatment period of longer than one week. Hartmann et al. (2008) recommended a treatment period of 42 days, with doxycycline or pradofloxacin, to achieve PCR negative results (Table 2).

Table 2: Oral antibiotic therapy against respiratory mycoplasma infections in cats (Lappin et al., 2017, mod.; Reed, 2016, mod.)

Drug	Dose
Doxycycline	10 mg/kg every 24 h 5 mg/kg every 12 h
Azithromycin	5-10 mg/kg, every 24 h for 5 days, then every 48 h
Clindamycin	10-15 mg/kg, every 12 h
Marbofloxacin	2 mg/kg every 24 h
Pradofloxacin	5-10 mg/kg every 24 h

As mycoplasmas lack of a cell wall, ß-lactam antibiotics (i.e. penicillin) are not effective (Lee-Fowler, 2014).

The antimicrobial susceptibility test results from nasal discharges are difficult to interpret because mycoplasmas cannot be cultured on standard laboratory media and, sometimes, positive cultures might not be associated with bacterial infection due to growth of commensal organisms (Lappin et al., 2017).

Disease control

As no vaccine is currently available, the prevention of mycoplasma infections is based on the control of concurrent infections and the correct management of cat communities. For example, in shelters, efforts are required to avoid overcrowding and to reduce stressors and concurrent infections (Lappin et al., 2017). Washing hands and wearing gloves, as part of normal good infection control, when handling a cat with respiratory clinical signs is required to reduce the spread of pathogens between animals (Lee-Fowler, 2014). Furthermore, it is good practice to isolate cats with respiratory signs and the routine use of effective disinfectants (Addie et al., 2015).

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