Companion Animal Mycobacterial Infections: Background and Clinical Presentation

Mycobacteria are pathogens of global health significance to both human and non-human animals. In recent years the significance of companion animal infections with mycobacteria has become more apparent; it has been demonstrated that approximately 1% of all feline biopsies submitted for histopathological analysis in the UK show changes consistent with mycobacteriosis and a third of these have demonstrable Ziehl-Neelsen (ZN) positive organisms when stained, suggestive of the presence of mycobacteria. Currently equivalent data do not exist with regard to dogs, but canine mycobacteriosis is clinically recognised.

Feline Mycobacteriosis

The myriad of mycobacterial species that have been positively identified in cats can be grouped into three main categories, each with its own clinical significance.

1. **Tuberculosis (TB) complex**

The TB complex consists of nine phylogenetically related species of mycobacteria capable of causing tuberculosis in man. Of these nine, only *Mycobacterium (M.) bovis* and *M. microti* have been frequently detected in cats; successfully cultured samples in one study confirmed that 19% of infections were caused by *M. microti* and a further 15% by *M. bovis*.

M. tuberculosis infection, the leading cause of human TB, is very rare in the cat and it has been demonstrated that cats have natural resistance to this pathogen. The majority of companion animal cases reported have occurred in dogs as a result of reverse zoonotic transmission from an infected human.

There is a strong geographical predisposition to feline infection with members of the TB complex. In the UK, *M. bovis* infections are strongly co-incident with where there are high levels of endemic infection in local bovine and wildlife populations such as the South-West of England. Similarly, *M. microti* infections are much more common in areas with high prevalence of this infection in the wild rodent population, typically South East of London, the North of England and the South of Scotland.

TB is most frequently diagnosed in adult male cats with a history of hunting. The median age of infection is three years for *M. bovis* and eight years for *M. microti*. There is no link between TB complex infection and classical immunosuppression i.e. feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) infection in cats, unlike humans.

Clinical Signs:

The majority of TB cases present with localised nodular cutaneous disease, frequently with a degree ulceration and occasionally with a draining sinus tract. The lesions are typically distributed around the face, extremities and tail base – the so-called "fight and bite sites". Skin lesions may be accompanied by a localised or even generalised lymphadenopathy, or lymphadenopathy may be the only presenting sign (termed an incomplete primary complex).

A predominately gastrointestinal (GI) form of the disease exists where granulomas form in the intestines and there is multicentric addominal lymph node involvement (though almost always mesenteric) causing weight loss, diarrhoea, vomiting and anaemia. This form of the disease is traditionally associated with cats drinking tuberculous cows' milk and therefore, since the introduction of pasteurisation, this form has declined in incidence.

Pulmonary lesions can occur when bacteria are inhaled, resulting in classical tubercle formation in the lungs and hilar lymph nodes. Much more common, however, is pulmonary disease secondary to the haematogenous spread of bacteria from the site of inoculation in the skin. This generates a diffuse interstitial pattern of disease which eventually becomes bronchial and is clinically observable as progressive dyspnoea followed by the development of a soft productive cough. Radiographically this looks different from primary pulmonary infection which more frequently tends to cause cavitating lesions.

Disseminated disease can cause a range of clinical signs including hepato-splenomegaly, pleural and pericardial effusions, generalised lymphadenopathy, weight loss and pyrexia.

There is no breed predisposition but adult males that hunt are most frequently diagnosed. Prevalence is highest in older cats with chronic kidney disease (CKD) and/or FIV infection.

2. Non-tuberculous mycobacteriosis (NTM)

NTM agents are environmental mycobacteria found in numerous biotopes including the soil, water, aerosols, protozoa, deep litter and fresh tropical vegetation. Many species have been identified within this group but the most important clinically are members of the *M. avium-intracellulare* complex (MAC) which are most pathogenic in animals and are also potential zoonoses. This group of opportunistic pathogens infect cats via contamination of open wounds.

Historically the condition of **Feline Leprosy Syndrome** (FLS) was described globally. This was presumed to be caused by *M. lepraemurium* but this could not be confirmed due to the inability to culture this organism within a laboratory setting. More recently, molecular techniques have demonstrated that *M. lepraemurium,* plus a range of other mycobacterial species e.g. *M. visible* can cause this clinical presentation. As a result of these developments there has been a trend in recent years to classify FLS cases as a subset of NTM infections rather than a unique clinical entity.

MAC infections have been seen more frequently in Abyssinian and Siamese cats, but there is no breed predisposition for the other NTM. Adult males that hunt are most frequently diagnosed and some studies have shown that the prevalence is highest in older cats, especially those with chronic kidney disease (CKD) and/or FIV infection.

Clinical Signs:
NTM is more variable in presentation than TB but generally results in; i) (sub)cutaneous nodules (this group contains infections that can be cultured and others that, as yet, cannot and so were previously called FLS), ii) granulomatous panniculitis or iii) disseminated disease. The cutaneous and disseminated forms can have very

similar presentations to TB complex lesions (see above). Granulomatous panniculitis is characterised by multiple punctate drainage tracts and subcutaneous nodules which can coalesce to form large areas of painful, non-healing ulcerated skin. Affected cats are often pyrexic, anorexic and reluctant to move.

Canine Mycobacteriosis

There is little published on the incidence of mycobacterial infections in dogs, and most of the information about disease presentation comes from case reports. Anecdotally, the incidence of disease appears to be much lower in dogs than cats but the clinical severity is much greater. Dogs typically present with extensive GI disease (weight loss, vomiting and diarrhoea) and pulmonary pathology. They also seem more likely to be infected with TB complex pathogens than other mycobacterial species. However, as with cats, the range of clinical signs is wide and has been known to include reticulo-endothelial, musculoskeletal, cutaneous and/or neurological signs.

In 2014, a case of **Canine Leproid Granuloma** (CLG) was diagnosed in Europe (Italy) for the first time. This condition had previously only been seen in Australia, New Zealand, Brazil and the USA. It is characterised by nodular skin lesions, typically seen on the head and dorsal pinnae, which spontaneously resolve over a period of weeks to months. The aetiological agent has yet to be identified but the histological appearance is consistent with granulomatous disease and intracellular ZN-positive bacteria are commonly seen, suggesting a mycobacterial species as the causative agent. Short-coated hunting dogs have been found to be predisposed and active hunting work has been shown to be a risk factor for disease. If GLM is diagnosed, cases require no pharmacological intervention.

Diagnosis of Mycobacterial Diseases

A correct diagnosis of mycobacteriosis in companion animals is challenging to reach for a variety of reasons (discussed below), and it is imperative to remember that several aetiological agents can produce overlapping clinical signs but carry differing prognoses, optimal treatment choice and zoonotic potential.

Cases that would warrant a high index of suspicion for mycobacterial infection would be skin nodules or abscesses that do not heal or are only partially responsive to antibiotic treatment, particularly if the patient resides in the South West or North of England or the South of Scotland.

Non-specific investigations:

During the clinical examination of any case of suspected mycobacterial infection, it is essential to fully establish the extent of any local disease and detect any cases with disseminated disease or systemic involvement.

Full serum biochemistry and haematology typically only reveal non-specific changes e.g. a stress leucogram but some changes such as anaemia and elevated serum calcium levels can indicate more severe disease.

Radiography is useful for detecting systemic involvement, especially pulmonary dissemination, and for monitoring disease progression and treatment response. Whilst radiographic changes are variable, pathology is most frequently seen in the thorax, consisting typically of a diffuse interstitial, alveolar or bronchial pattern with perihilar and sternal lymph node involvement observed with increasing disease severity. It is important to note that no pattern is pathognomonic for mycobacteriosis and that observed lung pathology can be mixed. Similar findings are seen with the use of computed tomography (CT) imaging, though the sensitivity

of detection is increased with this modality, and a diffuse structured interstitial lung pattern is most common, being either nodular or reticulonodular in nature..

Abdominal imaging, either using radiography or ultrasonography, can reveal hepatosplenomegaly, abdominal masses, mineralised or granulomatous mesenteric lymph nodes or ascites.

The FIV and FeLV status of cats should be established as a positive status is a poor prognostic indicator for therapy.

Specific investigations for suspected mycobacteriosis cases:

Histopathology is the first line of diagnostic investigation in these cases. The most typical approach taken is to surgically remove or biopsy a non-healing skin lesion or subcutaneous mass. In some cases, if there is only a single cutaneous lesion, then this may prove curative. When specimens are submitted from cases where mycobacteriosis is a differential diagnosis, this should be clearly stated on the submission form, along with a request for ZN staining of tissue sections; this will ensure that the samples are handled safely by the receiving laboratory. When submitting samples for histopathology it is essential to first section the tissue, ideally into quarters, and only formalin fix one piece whilst keeping the remainder frozen in sterile containers. Histopathology cannot speciate mycobacteria if they are present or suspected and this becomes important to establish the risk to owners and other animals in the household that may have been exposed to these pathogens. Culture can only be attempted on fresh or fresh-frozen tissue samples. The authors recommend that this is the standard approach taken for all cats with skin nodules or lymphadenopathy.

Bacteriological culture is currently the 'gold standard' diagnostic test, although it fails in ~50% of attempts, even when ZN positive organisms are present histopathologically. When it is successful it can take a long time, for example *M. microti* requires a minimum of 12 weeks to culture, during which time treatment is instigated based only on a presumptive diagnosis.

The interferon gamma (IFN-γ) release assay (IGRA) has been validated for use in cats and has anecdotally been useful in dogs; however, test sensitivity depends on interpretation and can therefore range from 70-100%. The IGRA can indicate a likely causal species in cases infected with *M. bovis* and *M. microti*, and can be suggestive of MAC infection. Where ZN positive organisms have been identified histopathologically, but the test is negative, this indicates infection with a NTM (but not MAC) organism.

PCR diagnosis can be performed on fresh tissue, and, occasionally on formalin fixed tissue. However, it is not always successful and is limited to the use of tests usually used in human patients. These tests have a high sensitivity for TB complex mycobacterial organisms i.e. those that are significant human pathogens but not others that are of veterinary importance.

The cost of a PCR to detect TB complex pathogens is ~£200+VAT (Jan 2016) an is performed by Leeds Teaching Hospital, before submitting samples please contact:

Dr Deborah Gascoyne-Binzi, Principal Clinical Scientist, Leeds Teaching Hospital Trust, Department of Microbiology, The General Infirmary, Great George Street, Leeds, LS1 3EX. *Tel: 0113 392 3929*

Tuberculosis Order: The identification of *M. bovis* is notifiable to the AHPA in England, Wales and Scotland.

Management

Treating canine mycobacteriosis is challenging, very little evidence is available with regard to the optimal treatment strategy and the prognosis is generally poor. For advice on treatment options please contact the University of Edinburgh team whose details are below.

For feline mycobacteriosis the prognosis is generally fair with 40% of cases reaching complete remission (it is unclear whether or not this constitutes bacteriological cure) while the remaining 60% show variable responses from temporary or partial remission to no response to treatment. This is probably due to the fact that without accurate speciation of the agent, it is not possible to tailor drug regimes to known inherent antibiotic resistance and sensitivity patterns. It is hoped that this will improve with diagnostic improvements.

Zoonotic Risks:

Before beginning treatment, it is important to ensure that clients are fully informed of and understand the potential zoonotic risks associated with being in contact with an infected animal.

The greatest risk is posed by members of the TB complex of mycobacteria:

- ***M. tuberculosis:*** Though rare, infection of a companion animal with M. tuberculosis would be considered a significant zoonotic risk. Finding an infected companion animal should trigger a search for the infecting human. Infected companion animals should be euthanased.
- ***M. bovis:*** Currently, only ~1% of human TB cases in the UK are caused by *M. bovis* infection. Globally, in the last 150 years, only six cases of human *M. bovis* TB have resulted from exposure to cats, and where infection has occurred the cats have had skin lesions that were draining pus with many ZN-positive bacteria. As a result of this, as of Sept 2015, Public Health England, Public Health Wales and Health Protection Scotland all consider the risks to humans to be "very low". That said the risk is still present and should be considered seriously in the context of humans with specific risk factors for transmission (see below) and the clinical signs present. Extensive and/or purulent lesions pose the greatest risk to human health and are generally less responsive to treatment. By comparison, single non-ulcerated skin lesions and/or regional lymphadenopathy may be very amenable to treatment.
- ***M. microti:*** The risk to humans of *M. microti* is significantly lower than that of *M. bovis*. Fewer than 30 human cases of M. microti infection have been documented in published literature and 11 (~40%) of these had specific risk factors (see below) – none have been shown to have resulted from exposure to an infected cat.
- ***MAC:*** Whilst not members of the TB complex, this group of organisms can infect humans in the presence of specific risk factors (see below) – again, none have been shown to have resulted from exposure to an infected cat.

Specific risk factors for zoonotic transmission:

This list has been compiled from advice published by public health organisations from across the UK and WHO guidelines. Humans are considered at heightened risk if they:

- are under 5 years old (some sources suggest 12 years)
- are pregnant
- are HIV positive
- suffer from substance abuse
- have been diagnosed with diabetes mellitus
- suffer (severe) kidney disease

- have ever received an organ transplant
- are a cancer patient receiving chemotherapy or radiation therapy
- have any medical condition requiring treatment with systemic corticosteroids
- require specialized treatment for rheumatoid arthritis or Crohn's disease

In any of the above situations, the authors would discourage animal treatment. If you would like to discuss these people contact the University of Edinburgh team (see below).

If treatment is to be attempted it requires a prolonged course of antibiotic therapy to achieve successful clinical resolution; owner and patient compliance, drug toxicity, and cost can make this difficult to maintain. For *M. bovis* and *M. microti* the recommended treatment consists of "triple antibiosis" including rifampicin, a fluoroquinolone (ideally pradofloxacin) and a macrolide (typically azithromycin) daily for a minimum of three months and for two months beyond the resolution of clinical signs. Where there is secondary pulmonary involvement, as diagnosed by radiography or CT then treatment is extended to a minimum of 6 months and for 2 months beyond the resolution of clinical signs.