Feline Masterclass Day
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Early diagnosis of kidney disease (KD) in cats has been discussed for many years and a raft of both blood and urine tests have been investigated to look for a simple, inexpensive, achievable option. To date the results have been disappointing against the gold standard of measuring glomerular filtration rate (GFR) in cats. This presentation will review the various tests that have been used, their strengths and weaknesses with a focus on the most recent tests that are in commercial use or development.

Measurement of glomerular filtration rate
A variety of methods have been described in cats, all generally rely on multiple, timed samples which can be challenging in many of our feline patients; at best a minimum of three samples are required but ideally 5-6 samples to produce a reliable curve. Whilst exogenous creatinine clearance remains the most attractive option as it is easily assayed in-house (although assessment at an external laboratory have shown greater consistency) obtaining a source of commercially available creatinine suitable for IV injection is problematic. Other markers that have been used in cats include iohexol, inulin and radiolabelled markers ($^{99m}$Tc-DPTA and $^{51}$Cr-EDTA) by scintigraphy. Scintigraphy has the advantage of allowing each individual kidney to be assessed. Studies trying to relate GFR results to standard biochemical and urinary parameters have been disappointing showing poor correlations.

Urinary markers
N-acetyl-β-D-glucosaminidase (NAG), urinary lysozyme, retinol binding proteins and cauxin are part of a number of urinary markers that have been used to try and establish the presence of tubular dysfunction. NAG-B is released during proximal tubular damage but offers no benefit over urine protein : creatinine ratio in predicting the onset of routinely measurable CKD. NAG is however a useful marker of acute renal damage. Urinary lysozyme also detects renal tubular damage but is also most valuable in acute injury. Retinol binding protein is a small molecular weight protein filtered by the glomerulus and reabsorbed by the proximal tubule. It has been shown to reduce following radioiodine treatment in cats but has not been studied in a general population of KD cats. Cauxin expression has been demonstrated to be reduced in feline kidneys with tubulointerstitial nephritis and azotemia and whilst it may be a useful marker, assay is complex and there is significant overlap between cats with and without renal disease. In terms of urinary markers, a combination would appear to offer most promise. Looking at the urinary proteome as a whole, distinct difference between healthy cats and those with KD are noted in particular increased expression of retinol-binding protein, cystatin M and apolipoprotein-II associated with decreased expression of uromodulin and cauxin confirmed tubular damage in CKD cats suggesting that these proteins are candidate biomarkers.

Serum markers
A number of serum markers have also been studied including cystatin C, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF 23) and symmetric dimethyl arginine (SDMA). Like most single biological parameters some overlap between healthy and affected individuals will always exist. Cystatin C has not been shown to give better diagnostic rates than creatinine. Although PTH does increase earlier in the course of disease, its assessment is complicated by the cost and difficulties in sample handling. FGF-23 is a hormone which acts on the sodium-phosphate co-transporters in the proximal tubules of the kidney to decrease phosphate reabsorption from the urine. Assay is not commercially available and the current results from experimental studies have not shown clear benefit as an early diagnostic tool. SDMA has been recently available as a commercial assay for the early diagnosis of KD in cats. Studies are relatively limited to date but do suggest that, in most but not all cats, SDMA increases outside the reference interval before creatinine (by 1.5-48 months). SDMA is filtered by the kidneys and is less affected by non-renal factors e.g. muscle mass. Theoretically SDMA will increase when >40% of renal mass has been lost (vs. 75% for creatinine). Serum SDMA had higher sensitivity (100%) compared with creatinine (17%), but lower specificity (91% vs. 100%) and positive predictive value (86% vs. 100%).

What about creatinine?
Potentially creatinine assessment may offer greater benefits that currently is evident. Two main issues with creatinine that exist are variation/reliability of assay particularly on in-house machines and the variation in creatinine relative to muscle mass hence many thin old cats will have a creatinine within the reference range.
despite significant CKD. These are not insurmountable problems but require further research input: in particular a way of assessing muscle mass and the correlation this has to creatinine reference intervals.

Why make a diagnosis of early KD?
Medicine is generally predicated on the assumption that early diagnosis of disease has significant clinical advantage in that more limited organ damage has occurred, the primary disease process may still be a driving factor that can be treated and early intervention delays the onset of clinical signs and increases life expectancy. The early diagnosis of KD however raises a number of dilemmas common to many disease states where our ability to make a diagnosis exceeds our knowledge of management strategies.

1. Does early diagnosis lead to better outcome for the cat in terms of morbidity and longevity?
   a. The traditional measure we use in our patients often tends to be survival from time of diagnosis but if we are making that diagnosis early we would expect patients to live longer – showing added value is more problematic.
   b. Currently there is little information about the best management options in early KD in cats.

2. If we make an early diagnosis of KD how should we proceed with management?
   a. There may be no clinical/biochemical signs in early disease
   b. Managing the underlying disease would generally require diagnosis by kidney biopsy a procedure with moderate costs and complications.

3. What is the tipping point in KD?
   a. We do not know at what level of renal dysfunction will inevitably progress so some cases with early KD may remain stable for the very long term or never reach the point of significant compromise of kidney function.

4. How much anxiety will we create in the owner?

Conclusion
As yet we do not have a simple, cost effective test for screening cats to establish a diagnosis of early KD Further, in order for the early diagnosis of KD to benefit cats we need an international consensus on the development of a more standardised definition of early KD along with better evidence of the value of biopsy in these cases and how we manage these early cases (beyond watchful waiting) to maximise quality of life and longevity.

References

INTRODUCTION
The haemotropic mycoplasmas (haemoplasmas) are small bacteria that parasitise red blood cells and can induce haemolysis, causing anaemia. They were formerly classified as Rickettsial organisms (when they were named *Haemobartonella* spp.) but sequencing and resulting phylogenetic analysis showed that they were actually mycoplasmal in nature. Reclassification and renaming of these organisms within the genus *Mycoplasma* occurred, although recent work suggests they should reside in a genus of their own\(^1\). A resumé of currently recognised feline haemoplasma species is shown in Table 1.

<table>
<thead>
<tr>
<th>Species Name</th>
<th>Reported Prevalences</th>
<th>Pathogenicity</th>
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<tbody>
<tr>
<td><em>Mycoplasma haemofelis</em></td>
<td>0 – 46.6% (median 4.8%)</td>
<td>Acute infection often results in haemolytic anaemia</td>
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<tr>
<td>‘<em>Candidatus haemominutum</em>’</td>
<td>0 – 46.7% (median 14.4%)</td>
<td>Acute infection can induce a drop in erythrocyte parameters but not usually severe enough to cause anaemia unless cat has concurrent disease or is immunocompromised e.g. chemotherapy</td>
</tr>
<tr>
<td>‘<em>Candidatus turicensis</em>’</td>
<td>0 – 26% (median 2.0%)</td>
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All three feline haemoplasma species have been identified in Australia, in prevalence studies done on the Eastern coast\(^2-4\).

In most studies, feline haemoplasma infections are more common in male, non-pedigree cats with outdoor access. Infection with ‘*Ca. M. haemominutum*’ is usually more prevalent in older cats, presumably because the chance of acquiring chronic subclinical infection increases with time. Some studies have shown an association between haemoplasma infection and FIV\(^5,6\) whereas others have not\(^7\), and most studies have failed to show an association between haemoplasma infection and FeLV\(^5,7\), but variable results are seen. Recent epidemiology work suggests that the host phenotype may drive these associations rather than infections being simple risk factors for each other\(^8\).

PATHOGENICITY
Different species...different strains
*Mycoplasma haemofelis* is the most pathogenic of the feline haemoplasma species. Acute infection often results in severe haemolytic anaemia although in some cases only mild anaemia results. Chronic infection is not usually associated with significant anaemia. Cats do not need to be immunocompromised or splenectomised to succumb to clinical disease with *M. haemofelis*. In the author’s experience, young cats may be more likely to develop severe clinical disease compared to older cats. Epidemiological studies have, however, only variably demonstrated associations between anaemia and *M. haemofelis* infection. This may be because these studies usually include chronically *M. haemofelis*-infected asymptomatic cats. Persistent autoagglutination or positive Coombs’ testing, indicating the presence of erythrocyte-bound antibodies, have been demonstrated in anaemic cats with acute *M. haemofelis* infection. One detailed study\(^9\) showed that erythrocyte-bound antibodies reactive at 4°C (cold reactive antibodies; both IgM and IgG) appeared a few days earlier than those reactive at 37°C (warm reactive antibodies; primarily IgG). However, in most cats, these antibodies appeared *only after* the development of anaemia had started. The absence of erythrocyte-bound antibodies at the onset of development of anaemia could reflect a problem with the sensitivity of their detection or that erythrocyte-bound antibodies appear as a result of haemoplasma-induced haemolysis rather than initiating it. In line with the latter, we have found that these antibodies disappear with antibiotic and supportive treatment alone, without the need for specific glucocorticoid treatment.

Although ‘*Ca. M. haemominutum*’ infection can cause a *drop* in red blood cell parameters, anaemia is not usually induced except in cats with concurrent problems e.g. FeLV infection. ‘*Ca. M. haemominutum*’ has also been associated with the development of myeloproliferative disease in cats with FeLV infection in one experimental study\(^10\). Although concurrent problems are usually present in ‘*Ca. M. haemominutum*’ infected cats that develop anaemia, cases of so-called primary ‘*Ca. M. haemominutum*’ anaemia (i.e. without any apparent concurrent disease or infection present) have also been reported\(^11\), so infection with this species cannot be ruled out as a cause of anaemia in an individual case. However conflicting data do exist, as one recent US
study actually documented that ‘Ca. M. haemominutum’ infected cats were less likely to be anaemic than non-
‘Ca. M. haemominutum’ infected cats\textsuperscript{12}.

‘Candidatus’ Mycoplasma turicensis’ infection has resulted in anaemia or a small drop in red blood cell parameters in some experimental studies, but generally anaemia is uncommon following infection. Concurrent disease and immunosuppression are both thought to be involved in the pathogenesis of ‘Ca. M. turicensis’ disease, in a similar way to the pathogenesis described for ‘Ca. M. haemominutum’. Determining the pathogenicity of ‘Ca. M. turicensis’ in naturally infected cats has been difficult in epidemiological studies as cats are often co-infected with other haemoplasma species, confounding disease associations.

Different strains of each of the feline haemoplasma species may exist, varying in pathogenicity. This might explain some of the conflicting data in different studies. However, other factors such as the underlying health status of the cat are also likely to play an important role in the outcome of haemoplasma infection. Carrier cats often have subclinical infections, but reactivation of infection can occur and may result in clinical disease\textsuperscript{11}.

**Transmission may influence pathogenicity**

Canine and feline haemoplasma DNA has been found in fleas and ticks\textsuperscript{2,13-18}, however this could reflect their haematophagous activity on infected hosts rather than signifying their role as a vector. The clustered geographical distribution of infection in some studies supports the role of an arthropod vector in haemoplasma transmission\textsuperscript{12}. The cat flea has been implicated in feline haemoplasma transmission, but only very transient \textit{M. haemofelis} infection has been reported via the haematophagous activity of fleas, and clinical and haematological signs of \textit{M. haemofelis} infection were not induced in the recipient cat\textsuperscript{19}. Additionally, a recent study found no evidence of haemoplasma transmission by fleas in an experiment involving the introduction of fleas into groups of cats housed together\textsuperscript{20}.

Some have suggested that cat fights are involved in transmission. Subcutaneous inoculation of ‘Ca. M. turicensis’-containing blood resulted in infection transmission, whereas the same inoculation method using ‘Ca. M. turicensis’-containing saliva, did not\textsuperscript{21}. This suggests that haemoplasma transmission by social contact (saliva via mutual grooming etc.) is less likely than transmission by aggressive interaction (blood transmission during a cat bite incident)\textsuperscript{22}. However, a recent study\textsuperscript{20} found evidence of horizontal transmission of ‘Ca. M. haemominutum’, but not \textit{M. haemofelis}, by direct contact between cats in the absence of aggressive interaction and vectors. Vertical transmission has not been definitively shown using molecular methods with canine or feline haemoplasma infections but has been suggested for other haemoplasma species\textsuperscript{22}. Blood transfusion is another potential route of transmission, and blood donors should be screened for haemoplasma infection\textsuperscript{23}.

**DIAGNOSIS**

**Culture……if only!**

Haemoplasmas are currently unculturable \textit{in vitro} despite numerous attempts in our and other laboratories. Recently a number of haemoplasmas have been subjected to whole genome sequencing, including work performed by our group in sequencing two feline haemoplasma species; \textit{M. haemofelis} strain Langford\textsuperscript{1}\textsuperscript{24} and ‘Ca. M. haemominutum’ strain Birmingham\textsuperscript{1}\textsuperscript{22}. These data have highlighted the limited metabolic capabilities of these important pathogens (glucose is their only energy source), which likely contribute to the haemoplasmas’ current uncultivatable status. Such knowledge of haemoplasma metabolic capabilities has allowed us to direct \textit{in vitro} cultivation attempts but successful growth has not yet been possible.

**Cytology is not reliable**

Cytology of blood smears may show haemoplasmas on the surface of erythrocytes but this is known to be very insensitive for diagnosis, and cytology cannot easily differentiate between haemoplasma species. The untrained eye may also fail to distinguish stain precipitate and Howell-Jolly bodies from true haemoplasma organisms, although those confident in identifying haemoplasma organisms may be able to diagnose infection cat-side by examination of a blood smear as a screening tool, but organism numbers need to be extremely high in the blood to allow visualization on cytology.

**Polymerase chain reaction (PCR) assays are usually great**

PCR is now the diagnostic method of choice for haemoplasma infection. PCR is far more sensitive and specific than cytology. Real-time quantitative PCR (qPCR) assays allow quantification of haemoplasma DNA in the sample being analysed (usually a defined volume of blood, which is subjected to extraction and then PCR) so we can monitor haemoplasma infection and evaluate response to treatment e.g. a decrease in the level of haemoplasma DNA in the blood following institution of effective antibiotic treatment. Quantitative PCRs have enabled us to describe the \textit{in vivo} kinetics of experimental haemoplasma infection. Cats experimentally infected with haemoplasmas initially show a rapid increase in copy number with peak numbers typically being reached.
around 2 to 4 weeks after infection, although *M. haemofelis* copy numbers can fluctuate greatly, especially in the first few weeks post-infection. Some (<1/3) *M. haemofelis*-infected cats continue to show very large fluctuations in *M. haemofelis* copy number for several months following experimental infection; this should be considered when interpreting qPCR results. In contrast, ‘Ca. M. haemominutum’- and ‘Ca. M. turicensis’-infected cats show little fluctuation in copy number over time. The reasons for the marked fluctuations in blood *M. haemofelis* copy number over time is not known. We have not been able to show any evidence of sequestration of *M. haemofelis* organisms in tissues (e.g. spleen, liver) at times of cyclical low copy number. The marked increase in *M. haemofelis* copy number seen in the blood immediately after initial infection confirms that rapid multiplication of organisms is possible in infected cats, so this can explain the marked rapid increases in *M. haemofelis* copy number seen during *M. haemofelis* cycling. The rapid decreases in copy number could then arise due to autolysis of bacteria and subsequent rapid clearance from the blood. Antigenic variation may mediate such fluctuations. Indeed analysis has shown that a very large portion (>70%) of the *M. haemofelis* genome encodes a set of uncharacterized hypothetical proteins arranged in multiple series of paralogous repeats; these could mediate antigenic variation through differing expression of haemoplasma surface proteins over time (we have confirmed in *vivo* expression of some of these proteins), thus enabling *M. haemofelis* to evade the host’s immune response.

**Serology**

The development of haemoplasma protein-based serological assays has been limited by our inability to culture haemoplasmas *in vitro* preventing the easy acquisition of adequate amounts of haemoplasma proteins for use in such assays. Studies in our laboratory have evaluated the feline serological response to haemoplasma infection using antigen preparations obtained both from purified haemoplasma organisms collected at peak parasitaemia and recombinant haemoplasma proteins expressed from haemoplasma genes identified by shotgun cloning. Additionally an ELISA has been developed based on recombinant *M. haemofelis* DnaK, and this has been used to screen the sera from experimentally infected cats. Experimentally infected cats became seropositive following infection, with a greater antibody response recorded in those cats inoculated with *M. haemofelis*, compared to ‘Candidatus M. haemominutum’ and ‘Candidatus M. turicensis’. This could be due to the humoral immune response being directed against conserved, haemoplasma clade-specific, and/or species-specific epitopes on *M. haemofelis* DnaK, or a measure of the degree to which the immune response to DnaK is triggered by the infecting haemoplasma species due to the severity of disease. Antibody levels were maximal in the early (~2–4 weeks) post-infection period, suggesting that antibody levels may help differentiate acute from chronic *M. haemofelis* infection. The cross-reactivity seen between the haemoplasma species limits the usefulness of this particular assay, but since serology can be more sensitive than PCR in detecting haemoplasma exposure (PCR negative seropositive cats have been identified), the development of further serological assays should be investigated.

**TREATMENT**

**Antibiotics**

Tetracyclines (primarily doxycycline) and fluoroquinolones (e.g. marbofloxacin, pradofloxacin) are effective in reducing haemoplasma copy numbers in experimental studies. In most studies these antibiotics have also improved clinical signs and haematological abnormalities. The majority of studies have been for *M. haemofelis*. Doxycycline (10 mg/kg daily PO) is often used and longer treatment courses (<6 weeks) are recommended by some to increase the chance of eliminating infection, although longer antibiotic treatment courses have not been properly evaluated for the clearance of infection. One study suggested that pradofloxacin (at two doses; both the standard 5 mg/kg daily PO, as well as a higher dose of 10 mg/kg daily PO) may be more effective at clearing *M. haemofelis* than doxycycline. Another found that ‘Ca. M. haemominutum’ infection only temporarily responded to marbofloxacin (2 mg/kg daily PO), with no evidence for clearance of infection seen. Variability in response to treatment in different studies may thus arise due to differences between haemoplasma species, isolates, host factors and/or route of administration.

**Corticosteroids**

Corticosteroids have been recommended as adjunct treatment for haemoplasmosis, to treat any immune-mediated component of anaemia, although their efficacy has not yet been proven. In our experience, clinically ill cats, including those that are Coombs’ positive, respond to antibiotic treatment and supportive care alone without the need for corticosteroids. Indeed immunosuppressive doses of corticosteroids have been used experimentally to exacerbate haemoplasma infection, so their routine use is not advised.

**Supportive care**

Supportive care is also required for acute haemoplasmosis treatment. This should include correction of dehydration with fluid therapy, and blood transfusion if the anaemia is severe.
PREVENTION
Blood donors should be screened for haemoplasma infected by PCR to help prevent inadvertent transmission by blood transfusion from asymptomatic carrier cats. Keeping cats indoors is also likely to prevent infection, as outdoor status has been identified as a risk factor and, in view of the potential for vector transmission, preventative flea and tick treatment is recommended. Recent work suggests that protective immunity develops following *M. haemofelis* infection, opening the way for future haemoplasma vaccination.

HAEMOPLASMAS OF MEN…..

PCR methods using generic haemoplasma PCR assays are now used to reliably investigate human haemoplasma infections, although limited human epidemiological studies have failed to detect significant infections. However studies describing human haemoplasma infections have been reported in China, with increased prevalences in children and adolescents and herdsman, *M. haemofelis* and/or *Mycoplasma haemocanis* or *Ca. M. haematoparvum*, and *Mycoplasma ovis*, raising the possibility of zoonotic infections. In one study haemoplasmas were more commonly found by PCR in people with veterinary involvement (e.g. veterinarians, technicians etc) and/or frequent exposure to animals or arthropods. However any association between haemoplasma infection and clinical signs in these reports is difficult to fully ascertain due to either lack of clinical information provided or concurrent *Bartonella henselae* infection. The frequent report of concurrent *B. henselae* and haemoplasma infection in people may reflect a common vector or common environmental source.

We have recently published a human case report documenting acute haemolysis and pyrexia in association with infection with a novel haemoplasma species. The patient responded clinically to doxycycline, but moxifloxacin was subsequently added to aid infection clearance. Quantitative PCR documented a fall in haemoplasma copy number during treatment, with eventual negative qPCR results obtained. The origin of the haemoplasma species, arbitrarily called ‘*Candidatus Mycoplasma haemohominis*’, identified in this patient is not known but it is possible that it represents a zoonotic infection or is a novel haemoplasma species whose primary host is humans. Recently, high haemoplasma prevalences have been reported in bats and *M. haemohominis*; 97% of 31 bats sampled in North eastern Spain (Catalonia) were haemoplasma infected, with 23 harbouring a species with 97% identity to ‘*Ca. M. haemohominis*’. It is possible that ‘*Ca. M. haemohominis*’ infection is zoonotic from bats. Another recent study describe the presence of a novel haemoplasma in a human being, but its sequence was not made available, so it is not known whether it is similar to ‘*Ca. M. haemohominis*’.

Thus zoonotic infections may well be possible with haemoplasma and this should be borne in mind when handling infected animals.

REFERENCES
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sectional data: structural equation models to understand infection and co-infection. *Parasit Vectors*. 2015; 8: 658.


COAGULATION – WHAT’S DIFFERENT ABOUT CATS?
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Cat blood clots easily is a well known ‘fact’ as evidenced by the frequency with which, at least microclots form in cat blood samples and the propensity for cats to develop arterial thromboemboli. This apparent hypercoagulability can be particularly frustrating when trying to measure platelet numbers in some cats. Whilst coagulation failure is a major cause of death in canine critical care cases this does not seem to be the an issue in cats; disseminated intravascular coagulopathy (DIC) being a relatively uncommon presentation.

The general overview of coagulation has changed to reflect much more of a complex cell-based model with multiple events occurring simultaneously rather than the more traditional cascade model. As such it is events that are occurring at the cell surface that seem to be critical and certainly in some cases such as thromboembolic disease in cats, damage to the endothelial surface and exposure of collagen is a major factor in promoting a hypercoagulable state.

Evidence to support cats being a hypercoagulable species is not overwhelming. Whilst standard reference interval for buccal mucosal bleeding time in cats are generally shorter - estimated at 90-150 seconds compared to 84-210 seconds in dogs. Prothrombin time (PT) and activated partial thromboplastin time (APTT) times tend to be similarly to slightly longer in cats; PT 8-13sec (C) vs. 6-12 sec (D); APTT 12-25sec (C) vs. 8-20sec (D). Activated clotting times are also similar between cats and dogs (See et al 2009). Recently published reference intervals for BMBT in sedated cats (ketamine, medetomidine and morphine) (Alatzas et al 2014) showed a mean time of 58.6 seconds and a reference interval of 34-105 seconds. However intra-observer repeatability was up to 87 seconds questioning the true diagnostic utility of this test. The use of sedation in cats (ketamine-diazepam) does not seem to adversely affect clotting times (Dirks et al 2012). Cats appear less likely to bleed following snakebite than dogs (Holloway & Parry 1989).

As with dogs, our routine tests for haemostasis are relatively crude. Although possible, platelet function testing is rarely undertaken and similarly individual factors including anti-FXa are rarely measured. Antithrombin (AT), fibrinogen, fibrinogen degradation products and D-dimers can be measured in cats; D-dimers have a low specificity and sensitivity at 56% and 67% respectively (Tholen et al 2009) for disseminated intravascular coagulopathy (DIC). Similarly the diagnostic utility of AT in diagnosis of DIC is poor in cats. Fibrinolysis is a rare problem in cats with ROTEM figures in cats suggesting slower clot lysis when compared to dogs.

The uncertainties of measuring coagulation status in cats and difficulty of measuring BMBT in many patients has prompted increased interest in viscoelastic testing in cats with reference intervals for thromboelastometry (TEM) (Doderlein and Mischke 2015) and thromboelastography (TEG) (Blois et al 2012) having been published. Review of published literature indicates that the reference intervals are dependent on the test system used and the type of activator. There is also likely to be some institutional variation.

<table>
<thead>
<tr>
<th>Table 1 - Comparison of published medians for various ROTEM parameters</th>
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<tr>
<td>Activator</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Ex-tem – cat</td>
</tr>
<tr>
<td>Ex-tem – dog</td>
</tr>
<tr>
<td>In-tem – cat</td>
</tr>
<tr>
<td>In-tem -dog</td>
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* Alpha – tangential angle between baseline and clotting curve@ 2mm
Doderlein & Mischke 2015; Sturgess et al 2010

DIC is relatively uncommon in cats with only relatively low numbers of cases reported in the literature. DIC seems to be most commonly associated with FIP, a disease that appears to becoming less prevalent in the UK. Other conditions associated with DIC include neoplasia, hepatic disease, systemic infection/sepsis and pancreatitis. Pulmonary thromboembolism also appears relatively uncommon in cats most commonly associated with cardiomyopathy, neoplasia, corticosteroid use, DIC and protein-losing pathologies (Norris et al 1999).

Coagulation deficits may be more common in feline compared to canine liver disease. With markedly elevated alkaline phosphatase being a predictor of coagulation abnormalities usually associated with vitamin K deficiencies (Lisciandro et al 1998) in cats with liver disease. Overall, prolonged APTT seems to be a better
predictor of a tendency to bleed after ultrasound guided biopsy in cats compared to prolonged PT in dogs with the most serious haemorrhaging occurring in thrombocytopenic cases (Bigge et al 2001).

Hypercoagulability, that may be associated with an increased platelet response to collagen in cats (Welles et al 1994), is documented in cats with cardiomyopathy (Stokol et al 2008) including asymptomatic hypertrophic cardiomyopathy (Bedard et al 2007) as well as in cats with FIV (Hart and Nolte 1994). There is limited evidence that obesity in cats also causes a hypercoagulable state (Bjornvad et al 2012).

Conclusion

The difference in perceived coagulability between cats and dogs seems to lie with cats’ platelet activity rather than their clotting factor function. Cat platelets seem to aggregate more easily and more rapidly than dogs reducing the tendency to bleed. The lack of bleeding disorders in cats may also reflect the difference in the types of disease seen in cats for example the relatively low incidence of immune-mediated thromboctopenia. The impression that cats are hypercoagulable is most dramatically seen in the occurrence of feline aortic thromboembolism generally associated with hypertrophic cardiomyopathy but in this case the state may be more of a function of the disease than the species as pulmonary thromboembolism, for example would appear less common in dogs than cats. When comparing the anticoagulant effect of low molecular weight heparin, cats require higher doses than man (Alwood et al 2007).

References and further reading

- Sturgess CP, Dunning M & Larcocia L (2010) Thromboelastometry in dogs presenting with overt haemorrhage or at risk of a coagulopathy. BSAVA Conference (Birmingham)
Inflammatory bowel disease (IBD) (chronic inflammatory enteropathy) is not a diagnosis but a description of a histopathological picture with a variety of different forms that have a multifactorial aetiology. Even the name may be misleading in terms of whether inflammation has a central role in the disease process. Unravelling the picture and understanding the relative contribution of genetics, environment and disease in an individual case is an almost impossible task with current technologies. Around four times as many papers have been published on canine IBD compared to feline IBD yet the condition would have to a similar prevalence in these populations. A pubmed search of “inflammatory bowel disease and feline” identified 127 papers however many of these are review articles and opinion papers none of these are from an epidemiologic aspect and a number (six) focus on distinguishing IBD from small cell lymphoma. The actual number of research-based papers on feline IBD numbers less than fifty. Of these ten are focussed on immunologic aspects of IBD, seven on diet and dietary therapy involving some 160 cats and seven are case series primarily looking at therapy. There is a single paper reporting the feline chronic enteropathy activity index. These numbers are considerably less than dogs and the emphasis is somewhat different. Over the past few years the number of papers looking at feline IBD is increasing.

Feline IBD differs from canine IBD in a number of ways not only in presenting clinical signs where diarrhoea is not such a strong feature but also in inflammation of other organs and what appears to be a greater propensity to undergo neoplastic transformation. The fact that IBD in cats occurs in conjunction with inflammatory disease of the liver and pancreas may speak to aetiology and reflect a more global immune-mediated disease or is truly an expression of the elevated duodenal bacterial numbers reported in cats in conjunction with the unusual anatomy their biliary and pancreatic duct is unclear.

IBD describes a stereotypic response of the gastrointestinal tract (GIT) to a variety of disease processes that result in the presence of increased numbers of inflammatory cells, usually lymphocytes and plasma cells, in the lamina propria that lies below the surface epithelium. IBD denotes a heterogeneous group of idiopathic, chronic, relapsing inflammatory disorders affecting the GIT that are presumed to be immunologically-mediated. Terminology is confusing as a variety of names, including IBD, have been used to describe patients with chronic intestinal signs where a specific diagnosis has not yet been reached including gastroenterocolitis, chronic intestinal inflammation or chronic inflammatory enteropathy (CIE). Various forms of IBD are described (lymphoplasmacytic, neutrophilic, eosinophilic and various combinations) although it is unclear whether these reflect aetiology and therefore should drive treatment decisions.

Although a variety of non-invasive diagnostic tests are available and routinely used such as faecal analysis B12, folate, trypsin-like immunoreactivity, pancreatic specific lipase, abdominal ultrasound, as well as a number of other parameters investigated e.g. faecal α1-proteinase inhibitor (Burke et al 2013) IBD is a cytologic/histologic diagnosis and no surrogate marker has been established. Current literature supports the use of full thickness biopsies in the diagnosis of IBD due to concerns over missing lymphoma when compared to endoscopic biopsies. There is also evidence that inflammation tends to be worse in the distal small intestine which would tend to support performing colonoscopy and obtaining ileal biopsies if an endoscopic approach is used. No studies have been published looking at the risks associated with endoscopic biopsies in cats but the general impression is that perforation is more likely in cats than dogs (Bernardin et al 2015). There are however, no papers trying to assess the cumulative risk of morbidity and mortality of full thickness biopsies compared to failing to diagnose lymphoma endoscopically. Sabattini et al (2016), looking at endoscopic biopsies, has suggested that clonality testing was the significantly better predictor of poor survival compared to cytology, histology and immunohistochemistry suggesting that this should be performed routinely on intestinal biopsies.

Published figures indicate that around half of cats with pancreatitis also have inflammation of the liver/GIT and around 30-50% of cats with cholangitis have inflammation of the pancreas/GIT. These figures would suggest that a complete investigation of IBD should include evaluation of the pancreas (ultrasound/pancreatic-specific lipase) and fine needle aspirate/biopsy of the liver ± cytology and culture of the bile. The clinical value in further characterising IBD in terms of pancreatitis and cholangitis has not been established nor is it clear whether having more widespread inflammation alters outcome or should affect treatment.
Little information exists on monitoring feline IBD and in the authors opinion this is an essential part of any discussion with the owner early on in managing the disease to establish criteria for success. Resolution of clinical signs, weight gain, improvement in the feline chronic enteropathy activity index (FCEAI) can all be used. Repeat biopsy is generally disappointing as improvement in the histological picture particularly in relation to the number of inflammatory cells is frequently minimal. This is likely to reflect the redundant capacity of the gastrointestinal system and a tipping point effect, i.e. a small change in disease severity resulting in subclinical becoming overtly clinical disease and vice versa. What is more challenging for the clinician is making rational decisions about treatment change particularly reducing the level of immunosuppressive therapy. Currently we base these decisions on clinical parameters but they are poorly sensitive only showing that a decision was incorrect when overt disease recurs rather than predicting that recurrence. Unfortunately although and inflammatory disease acute phase proteins (APP) are rarely significantly increased in cats with IBD and if they are, rapidly return to within the reference interval once treatment is commenced. Little attention has been paid to developing a panel of APP how they change over treatment and whether and what level of increase even if remaining within the reference interval would be a predictor of impending treatment failure. With the development of bench top measurement systems this may become a more feasible and useful way of developing better treatment protocols and providing a rationale for treatment changing levels of immunosuppression or relaxing dietary therapy once overt clinical signs have been controlled.

A number of studies have looked at the immune environment associated with IBD in cats (Waly et al 2014, Niguyen Van et al 2006, Waly et al 2004) based on intestinal biopsies. Early work has been published looking at measuring the circulating cytokine environment such as TNF-α (Steiner et al 2014) could have value in monitoring IBD in cats and in particular whether a more tolerant environment is developing.

The microbiota is different in cats with and without IBD, with the development of high throughput genetic chip technology this may also afford a way of looking at how well IBD cats are responding to management.

Feline IBD remains a challenging disease to diagnose and monitor requiring a concerted international effort to develop projects capable of answering the unknowns aimed at improving management of cats living with inflammatory bowel disease

References and further reading


