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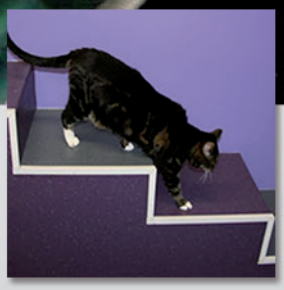
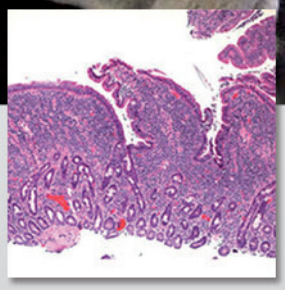
Osteoarthritis
Environmental enrichment for cats with OA

Chronic enteropathies
A diagnostic challenge

MEOW!
Increased vocalisation in elderly cats

The elderly feline patient

SPECIAL ISSUE
Geriatric feline medicine


Also in this volume:
Role of retroviruses in feline lymphoma, Home monitoring of the feline diabetic, Endocrine hypertension in cats, Early recognition of chronic kidney disease in cats, veterinary app & book reviews, FECAVA news... and more

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special issue on geriatric feline medicine

Contents

Icons

Each scientific article is classified with one or more icons.

These refer to the species (in green) of animal or the veterinary discipline (in blue) relevant for the article.


Dogs


Cats


Dogs and Cats/
Small animals


Rabbits


Less common pets


Anaesthesia


Bacterial Diseases


Behaviour


Cardiovascular


Dental


Dermatology


Diagnostic imaging


Digestive System


Ear Nose Throat


Genetics


Internal Medicine


Neurology


Oncology


Opthalmology


Orthopaedics


Practice Management


Surgery


Urogenital

Commissioned paper*

Management of the elderly cat

Sarah M. A. Caney[1]

SUMMARY

Over recent decades, the lifespan of cats has increased dramatically and where it was once considered normal for a domestic shorthair cat to have an expected lifespan of 12-14 years, now 18-20 years seems more appropriate. This improved longevity is likely to be due to a variety of factors including improved diet and healthcare of cats and it is certainly true that much current research is focused on old cat illnesses, such as those discussed elsewhere in this issue. Effective preventive healthcare, as discussed in this article, facilitates prompt diagnosis and appropriate interventions benefitting the cat's quality (and potentially length) of life as well as the human-pet bond.

* *Eur J Comp An Pract* (2015), Autumn 25(3); p4-19
Go to http://www.ejcap.org to see the online presentation of this paper.

Introduction

Given that the title of this article is 'Management of the elderly cat' it is first appropriate to consider at what age we consider a cat to be elderly. The charity, International Cat Care (www.icatcare.org), have produced feline lifestage guidelines which also incorporate a human equivalent age (Table 1) and these are the lifestages the author shall refer to through this article. Of especial interest when considering elderly cats are those in the Mature, Senior and Geriatric lifestages. Whilst clinical disease is most common in the Senior and Geriatric lifestages ('elderly' cats), early disease may be detectable in the Mature lifestage. Reference to the human equivalent age is helpful when encouraging age-related preventive healthcare as many owners are familiar with the concept of more frequent medical assessment in themselves as they grow older.

What are the common health issues affecting the older cat?

The common conditions affecting the older cat are presented in Table 2. The older the cat, the more likely it is to suffer from one or more of these possibilities. Attention to detail is important in order to accurately document all of the cat's problems and ensure that the optimum treatment plan is designed.

Importance of subclinical illness

Cats are notoriously good at hiding all signs of illness and many older cats are not presented for assessment unless perceived to be unwell. Unfortunately this can mean that the cat is only presented when in advanced stages of disease. Detailed history taking and physical examination often reveals subclinical problems in apparently healthy Senior and Geriatric cats and is vital to ensure that appropriate healthcare is provided. For example, one study in which the author was involved reported that a third of apparently healthy cats aged 10-18 years had a urine specific gravity lower than 1.035, a commonly used cut-off for this parameter (Mitchell, 2011). In this same study around a third of the cats were found to be suffering from significant disease including hyperthyroidism, systemic hypertension and chronic kidney disease.

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Table 1: Lifestages of cats and their human equivalent age (courtesy of International Cat Care, www.icatcare.org)

Lifestage	Age of cat	Human equivalent
Kitten: birth to 6 months	0 – 1 month 2 – 3 months 4 months 6 months	0 – 1 year 2 – 4 years 6 – 8 years 10 years
Junior: 7 months to 2 years	7 months 12 months 18 months 2 years	12 years 15 years 21 years 24 years
Prime: 3 years to 6 years	3 4 5 6	28 32 36 40
Mature: 7 years to 10 years	7 8 9 10	44 48 52 56
Senior: 11 years to 14 years	11 12 13 14	60 64 68 72
Geriatric: 15 years+	15 16 17 18 19 20 21 22 23 24 25	76 80 84 88 92 96 100 104 108 112 116

A more recent and larger study revealed that 21% of cats aged ten or older were found to have a urine specific gravity lower than 1.035 although the proportion of cats ultimately diagnosed with significant subclinical disease was lower than this (Paepe et al, 2013). It is of prime importance that clinicians make maximum use of any vet visits involving an older cat to ensure that subclinical illness is detected at the earliest possible opportunity. Regular preventive healthcare checks should be encouraged in all apparently healthy older cats, as discussed later in this article. Many common health problems are very treatable and outcome is improved by early diagnosis and intervention.

Table 2. Health problems affecting the older cat and their approximate prevalence, where known

Illness	Comment
Bacterial UTI	Reported to affect around 12% of hyperthyroid and diabetic cats and 22% to 30% of cats with chronic kidney disease (Mayer-Roenne et al, 2007; White et al, 2013)
Cognitive dysfunction	The age-related deterioration in brain function which results in behavioural changes such as toileting accidents, increased vocalisation, confusion, forgetfulness and altered sleep patterns. This is estimated to affect more than 50% of cats over the age of 15 (Moffat and Landsberg 2003, reviewed in Gunn-Moore and others 2007).
Constipation	
Deafness	
Dental disease	
Diabetes mellitus	Estimated to affect up to 0.4% of cats (McCann et al, 2007)
Hyperthyroidism	Estimated to affect about 9% of cats aged 10 years or older (Stephens et al, 2014)
Chronic kidney disease (CKD)	Estimated to affect about 30% of cats over the age of 15 (Lulich et al, 1992)
Neoplasia	
Osteoarthritis	One study estimated that this affected more than 90% of cats over the age of 12 (Hardie et al, 2002)
Systemic hypertension	Estimated to affect more than 20% of cats with chronic kidney disease (Syme et al, 2002)

What check-ups are recommended and how often should these be done?

The American Association of Feline Practitioners and International Cat Care have both provided guidelines on care of Senior cats. The author follows the 'Wellcat' guidelines initially devised by the charity International Cat Care. iCatCare advocate that:

- Cats of all ages should be assessed at a veterinary practice at least once a year and their weight and

body condition score recorded in addition to a general physical examination and discussion of appropriate preventative health care

- In addition to this:
  - o 'Mature' cats – those aged ≥ 7 years - should have their blood pressure (BP) checked once a year (Fig 1) and a urinalysis performed.
    Urine collection and specific gravity interpretation is discussed in more detail later in this article.
  - o 'Senior' cats – those aged ≥ 11 years - should have blood tests done (haematology, serum biochemistry, total thyroxine) once a year in addition to the recommendations already made for mature cats. Consideration should be given to increasing the frequency of BP and urinalysis check-ups to every 6 months in these cats.
  - o 'Geriatric' cats – those aged ≥ 15 years - should be assessed at a veterinary practice every 6 months at which time a clinical examination, weight check, body condition score, BP and urinalysis should be performed. Blood tests should continue to be done annually unless there is any clinical indication to increase the frequency of these.

The author prefers to see Senior patients every 6 months and Geriatric patients every 3 months.

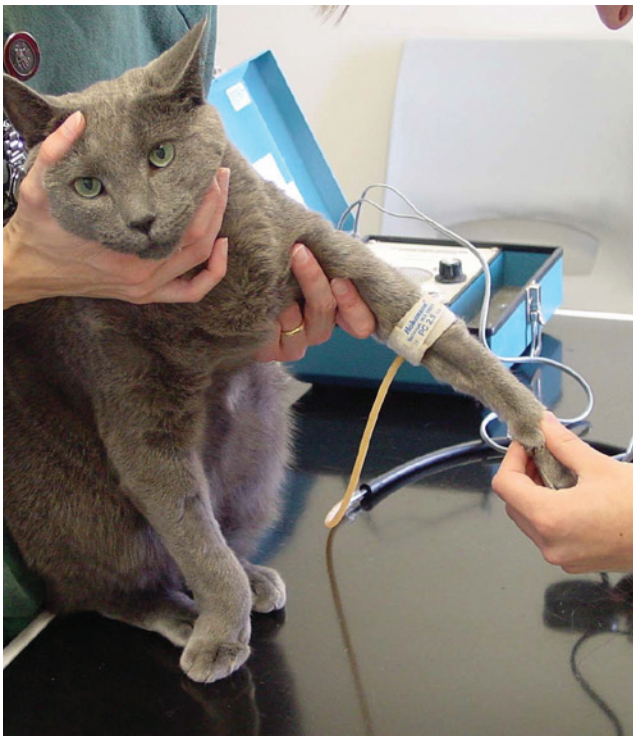

Fig. 1. Blood pressure measurement is a vital component of the elderly cat check. The author recommends Doppler blood pressure measurement, as shown in this patient.

History taking – tips for older cats

A thorough history looking to identify potential clues of any problems is a vital component of the assessment. Open-ended and closed questions are important to establish owner concerns and ensure that nothing is missed. The author has provided an Appendix document 'Elderly cat health check form' which can be used as a pro-forma for history and physical examination of the older cat. In a busy clinic, use of health questionnaires can be very helpful in saving time and ensuring that nothing is missed. Questionnaires can be completed by an owner in the waiting room prior to their appointment. The aim of the questionnaire is to quickly establish whether there are issues requiring further attention in the history and/or physical examination.

Particular attention should be paid to:

- The cat's weight and body condition – has the owner noticed any changes?
- Appetite – any increase or decrease? What is the cat's current diet and food consumption?
- Thirst – any increase?
- Litter tray or toileting behaviour - for example inappropriate urination may be seen in cats unable to use a cat flap due to pain associated with osteoarthritis (OA)
- Mental status – any evidence of cognitive dysfunction or behavioural changes? For example has the owner noticed any changes in the cats interaction with people or other animals in the home?
- Mobility issues – any stiffness or reduced jumping? Mobility questionnaires such as those included in the 'Elderly cat health check form' can be helpful in identifying subtle signs of OA
- Energy levels – any hyperactivity or restlessness that could be compatible with hyperthyroidism?
- Gastrointestinal signs – any vomiting or diarrhoea?
- Urination/defecation problems – for example missing the litter tray due to pain when posturing to eliminate?
- Eyesight – any evidence of visual problems, which could indicate systemic hypertension?

Physical examination in older cats

Elderly cats are often very set in their ways and easily stressed when taken out of their home environment and normal routines. Stress can have significant negative impacts on a number of clinical and laboratory parameters

as well as potentially hindering examination of the cat. For example, stimulation of the sympathetic nervous system may result in an increased heart rate, respiratory rate and blood pressure. Abdominal palpation is more challenging in cats that are tense and distressed.

Laboratory consequences of stress in cats most commonly include hyperglycaemia (which can be dramatic enough to exceed the renal threshold in some cases), lymphopenia and other evidence of a stress leukogram. A calmer and happier cat will be more straightforward to examine, provide more accurate clinical and laboratory results and should allow a more rapid and accurate clinical diagnosis.

A 'cat friendly' approach is important to minimise the effects of stress on patients. The iCatCare website contains a large number of helpful articles and other resources which deal with this topic in more detail. General recommendations include:

- Where possible, provide advice regarding the type of cat carrier a client uses: a top-loading basket is preferred where possible. Covering the cat carrier with a towel can be helpful in cats prone to stress. If using a basket with a detachable lid, the cat may feel more secure when examined in the lower part (Fig 2) rather than on the consulting room table
- Use of synthetic F3 pheromone preparations (e.g. Feliway, Ceva) in the consulting room and cat basket (prior to adding the cat) help to provide some reassurance. Install synthetic F3 pheromone diffusers throughout the practice.

Fig. 2. Some cats feel more secure when examined in the lower portion of their basket.

- Use of dog appeasement pheromone (DAP, Ceva) can help to calm dogs visiting or staying in the clinic and therefore make the environment more peaceful for feline patients
- Before examining the cat, allow them some time to 'unwind', preferably in a calm and quiet environment. A consulting room, with the owner present, is often ideal for this. Open the basket and give the cat the opportunity to come out in its own time, if possible (Fig 3).

Fig. 3. If possible, allow the cat to come out of their basket voluntarily.

- Talk to the cat using a calm level tone, moving slowly and quietly and without making sudden movements while taking the history or let it wander around for a few minutes
- Be calm and gentle when examining and sampling elderly cats. Many have significant OA which can result in chronic pain. This may make the elderly cat grumpy and especially reluctant to leave their basket and be examined or restrained
- A soft, padded bed is helpful when examining patients in the consulting room
- Consider that many elderly cats may be suffering from hearing and/or visual deficits which may make them more anxious/concerned
- Cats are very sensitive to smell - wearing strong perfumes or using strong smelling disinfectants and cleaning products can be unpleasant for the cat. Where possible, ventilate rooms and rinse off disinfectants thoroughly

- Be willing to use chemical restraint to avoid/decrease stress which may be caused by using physical restraint on the patient

Physical examination should aim to identify as many of the common problems as possible. In elderly cats, particular attention should be paid to:

- Observation of posture and gait – e.g. any evidence of pain or stiffness? If possible, assess jumping and or use of steps (Fig 4)
- Systolic blood pressure measurement – ideally using Doppler equipment with the cat in a calm state (best performed at the beginning of the physical examination)
- Oral examination – e.g. any evidence of dental disease, pallor, etc
- Thyroid palpation – any evidence of a goitre (Fig 5)?
- Cardiac auscultation – e.g. any evidence of tachycardia which could be consistent with hyperthyroidism?
- Abdominal palpation – e.g. any evidence of masses or constipation?
- Ocular examination – e.g. any evidence of hypertensive damage? Fundus examination is discussed in more detail below.
- Bodyweight and body condition score – any change since last recorded? Percentage changes are useful in evaluating the significance of any weight changes (Table 3).

Fig.4. Gait and mobility assessment is helpful, if possible. In this consultation room, steps have been built into the side of the wall so that cats can be observed coming up/down these.

Fig. 5. A goitre should not be present in a healthy cat. Where present, goitre may indicate presence of hyperthyroidism. To palpate for a goitre the clinician can stand behind the cat (as in this photo) or in front of it. Using a thumb and forefinger the larynx is palpated before sliding the thumb and forefinger down the neck to the thoracic inlet and back up again. A goitre often feels like a small pea-sized swelling which slips under the clinician's finger/s. In some cases it can help to turn the cat's head to each side when palpating the neck.

Fundus examination in older cats

Fundus examination is a valuable component of the clinical examination and is specifically helpful in identifying elderly patients with systemic hypertension. The patient should be examined in a dark room. If the room cannot be adequately darkened then it may be necessary to dilate the pupils using one drop of 0.5% tropicamide to facilitate thorough examination.

Distant indirect ophthalmoscopy is a fantastic technique for quick but thorough examination of the fundus. To perform this technique the clinician needs a light source and 20-30 dioptre condensing hand lens. The cat should be minimally restrained with their head in a neutral position or with their chin slightly tilted up. The light source is held by the clinician's eye with the lens held in their other hand, just in front of the cat's eye and perpendicular to the light beam. The arm of the hand holding the lens should be straight. The clinician alters the angle at which they are looking at the eye until an inverted view of the fundus is visible. When first learning this technique, the author recommends that the lens is not placed in front of the eye until a tapetal reflection is

Table 3. Calculation of percentage weight changes in cats

Gandalf is a 15 year old male neutered domestic shorthair cat. When healthy, he weighed 5.17 kg; today he weighs 4.77 kg. Gandalf is reported to have an increased thirst, reduced appetite, lethargy and some vomiting which have been present for the last few months.

Calculation of percentage weight loss:

Step 1: Calculate the amount of weight lost by subtracting today's weight from the previous weight:
5.17 - 4.67 = 0.5 kg
Step 2: Divide the number obtained in Step 1 by the original weight. 0.5 ÷ 5.2 = 0.0967
Step 3: Multiply the number obtained in Step 2 by 100%:
0.0967 x 100% = 9.7%

Assessment:
Gandalf has lost 9.7% bodyweight. This is the equivalent of a 63-kg (10 stone) person losing over 6 kg (6.1 kg, nearly one stone).

Interpretation of percentage weight loss figures – author's recommendations:

> 10% weight loss	Severe weight loss, immediate action justified. Further investigations (blood and urine tests to look for common causes of weight loss) are recommended.
5 – 10% weight loss	Significant weight loss, further investigations (blood and urine tests to look for common causes of weight loss) are justified.
2.5 - 5% weight loss	Mild weight loss. Consider further investigations (blood and urine tests to look for common causes of weight loss) and/or reassess weight in 2-4 weeks. In cats known to have underlying disease, even as small a change in weight as 2.5% is likely to be significant and should not be ignored
< 2.5% weight loss	Unknown significance. Could represent normal weight fluctuation or the beginning of more significant weight loss. Re-check, for example, in 2-4 weeks if concerned.

Outcome

Further investigations revealed IRIS Stage 3 chronic kidney disease. In Gandalf's case, a change to a renal diet with antacids and appetite stimulants was successful in improving his clinical condition and he gained 0.3 kg over the following two months' treatment.

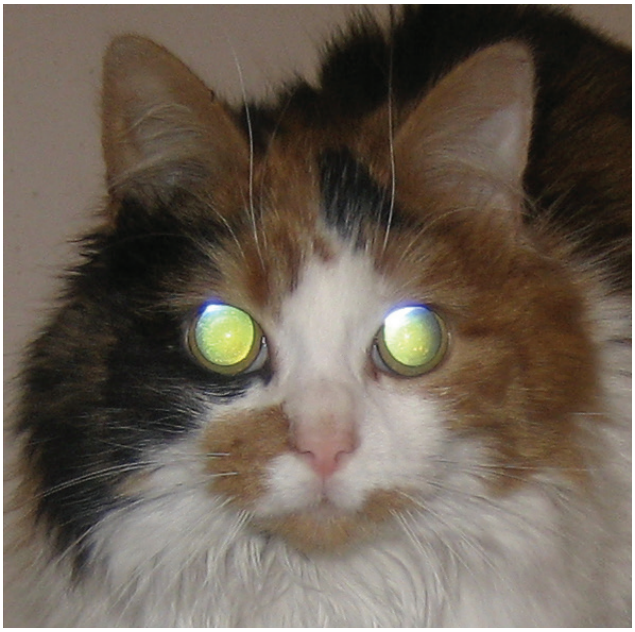

Fig. 6. The tapetal reflection is the bright 'cat's eye' reflection seen when shining a light into the cat's eyes. In this example, the tapetal reflection is exaggerated due to bilateral retinal degeneration. Photo courtesy of Natasha Mitchell MRCVS.

Fig. 7. Distant indirect ophthalmoscopy is a helpful technique for fundus examination. This procedure is performed in a dark room.

obtained (Fig 6). Once the tapetal reflection is visible, the hand lens is inserted 2-4 cm in front of the cat's eye (Fig 7). Indirect ophthalmoscopy has advantages of allowing a large area of fundus to be visualised quickly. Pupil constriction is less of an issue compared to direct ophthalmoscopy since the light source is relatively far from the eye. This technique is well tolerated by the cat and there is less of a risk of the clinician being bitten or scratched, if examining a difficult cat, since their head is 40-50 cm away from the cat's face. A video illustrating the technique can be found on the author's website as can an annotated guide to lesions seen in cats with systemic hypertension.

Any lesions seen can be examined at a higher magnification using a direct ophthalmoscope or PanOptic™ ophthalmoscope. Direct ophthalmoscopy produces a magnified and upright image of the fundus but pupil construction can restrict the field of view.

Urine collection in older cats

A free-catch urine sample brought in by an owner is an adequate starting point for urine specific gravity (USG) and dipstick evaluation. Guides on cystocentesis and free-catch urine collection by owners are available on the author's website. A USG < 1.035 is generally considered abnormal in cats. If the USG is less than 1.035 then a detailed history should be taken to rule out non-renal and physiological causes of producing poorly concentrated urine such as receiving a liquid diet, enjoying drinking 'tasty' liquids such as 'cat milk', receiving diuretics or parenteral fluid therapy. Dipstick testing to check for presence of glucose (diabetes mellitus) is also recommended. Further tests, ideally using cystocentesis collected urine, should be considered if an abnormal dipstick or USG is identified. For example, urine sediment examination, culture and a urine protein to creatinine ratio are indicated in cats with kidney disease.

Blood sampling older cats

Blood samples are often required for preventive healthcare and monitoring of illness. In most cases, jugular puncture is desirable to facilitate collection of a suitable volume in a reasonable timescale. Cephalic puncture is possible but the generally slower blood flow means that the blood may clot preventing haematological analysis and reducing the amount of blood it is possible to collect. Medial saphenous blood sampling is popular with some clinicians, especially with fractious cats, and can be successful for collection of appropriate samples. Restraint should be as gentle as possible, especially showing consideration for likely OA affecting the limbs and spine.

The author prefers to clip fur using scissors rather than clippers. Use of clippers on the neck is often poorly tolerated by cats due to the proximity of the noise and vibrations to their ear. In sensitive cats, use of topical local anaesthetic cream (e.g. EMLA) is of some help although this requires 20-40 minutes to be effective. Clients may wish to apply this themselves with the cat at home (some of my clients also prefer to clip their cat's neck with curved scissors).

Use of small blood tubes (e.g. 0.5 ml EDTA tubes for haematology) helps to maximise usefulness of the blood sample and minimise iatrogenic anaemia.

What challenges are there associated with optimum care of elderly cats?

Providing 'Gold Standard' care for elderly cats, for example through following iCatCare's Wellcat guidelines, is challenging for all veterinary clinics. Taking a detailed history and performing a physical examination incorporating BP checks is time-consuming. Clinicians are often very short of time and the older, apparently healthy cat coming in for a routine appointment may not appear to be a high priority. As already discussed, subclinical illness is common and successful identification of this requires attention to detail in both the history and physical examination. It can be difficult to persuade colleagues that the Wellcat approach is justified and unless everyone in the practice is 'on board' the initiative may fail.

If colleagues need persuading of the benefit of the Wellcat checks then a staged approach can be considered. For example:

- Initially only introduce health checks for Geriatric cats (15 years and over). Almost all of these cats will be suffering from one/more problems that would benefit from further diagnosis and treatment proving the value of performing health checks. Once confident in performing health checks for Geriatric cats, these can be introduced for Senior cats (11-14 year olds), finally including Mature cats (7-10 years).
- Initially focus on urinalysis screening rather than BP assessment which is more time-consuming. Free-catch urine samples brought in by an owner take less than five minutes to analyse. Once colleagues can see the benefit of urine screening it should be possible to persuade them to invest more time in BP assessment.

Time-saving tactics such as use of health questionnaires and involving veterinary nurses are vital to ensure success. Where possible, the author believes that nurses should be empowered to carry out as much of the elderly cat health checks as possible. For example, patient history, physical examination (including examination of the eyes for evidence of systemic hypertension), blood pressure measurement and analysis of a urine sample brought in by an owner can all be performed by a vet nurse.

As clinicians we also face challenges from the cat's owner who may be reluctant for preventive healthcare checks for a number of reasons. Common examples and ideas for how to tackle these are presented in Table 4.

Finally cats provide us with a range of challenges, as already discussed, including their ability to hide illness by adjusting lifestyle rather than displaying obvious clinical signs. Presence of multiple problems simultaneously can confuse diagnosis and complicate management. For example, an owner may be concerned that periuria represents incontinence when in fact chronic pain associated with OA may be responsible.

Strategies for encouraging owners of elderly cats to maintain contact with their vet clinic

Strategies to establish better contact with our older patients are not always straightforward to design. Efforts should be made to ensure that older, 'at risk', patients are seen more frequently, as per the Wellcat guidelines, and that sufficient time is allowed in appointments to facilitate a thorough history and physical examination.

A variety of strategies can be considered but not all of these will suit all practices and their staff/building set-ups. Whichever strategies are chosen should be agreed and accepted by all staff to ensure maximum success. Receptionists are often the first point of contact for owners, are responsible for booking most appointments and therefore need to be trained and 'on board' with any changes introduced. Options which can be considered:

1. Introduce the iCatCare 'Wellcat' recommendations into your clinic.
2. Train and empower nurses to perform 'elderly cat consultations' which can be either 'stand alone' (i.e. advertised to owners as an opportunity for a health check) and/or done in combination with veterinary appointments (e.g. booster vaccination). Given the relative infrequency with which most elderly cats visit the vet practice, all opportunities to assess the cat should be taken, where at all possible.

There is justification for offering these checks free of charge or as part of your normal fees for health checks or vaccinations. Many cats over the age of 11 years will have at least one health problem which will benefit from treatment and/or closer monitoring which can

Table 4: Common owner concerns and advice on tackling these

Owner concern	Potential solution
If I believe my cat's health is 'normal', why should I bring my older cat in for preventive health checks?	Explain how common subclinical illness is and how many diseases start quite insidiously with subtle clinical signs. 'Sell' the importance of preventative healthcare in the same way that breast and prostate cancer screening is standard practice in human medicine.
I don't want my older cat to be distressed by tests	Free-catch urine sample testing, history taking and physical examination are not painful or stressful tests for a cat to have and yet can reveal much valuable information. Reassure your clients that you will be gentle with their precious elderly cat.
Tests are expensive and unnecessary – they won't improve my cat's quality or length of life	Medicine has advanced hugely and there are enormous gains to be had from treating affected cats. Even if the disease cannot be 'cured', quality and even length of life can be greatly enhanced with modern treatments.
I know my cat is thin/has a poor coat/etc but he/she is old and it's normal for an old cat to look like this	Explain that whilst it is common for elderly cats with medical problems to develop clinical signs such as weight loss/poor coat/etc this is not normal! It is a sign of illness that probably can be helped with modern medicine.
If I bring my older cat in to see you, you will probably recommend euthanasia	Many owners fear that their vet will recommend euthanasia if their elderly cat looks unwell. This often is far from the truth but we need to reassure owners that our prime aim is to restore health and quality of life.

then be charged for. Check-ups can also be a good way of discussing routine healthcare (e.g. flea and worm treatments) and providing dietary advice.

A 20-30 minute appointment with a nurse should be sufficient to:

- Collect a detailed patient history including information on behavioural and mobility changes.
- Measure blood pressure
- Examine the eyes for evidence of damage associated with systemic hypertension.
- Complete a general physical examination
- Weigh the patient, calculate percentage weight changes and record a body condition score
- Perform a urinalysis on an owner brought in sample

If required (e.g. booster vaccination cases), this appointment can then be followed by a 10 minute appointment with the veterinarian who can assimilate the data collected, timetable further tests/treatments and advise the client as necessary as well as giving the booster vaccination. Further advice might include planning a check-up sooner than 12 months time to assess specific areas of concern such as any weight loss documented.

3. If there is insufficient consulting room space to allow nurses to conduct their own 'elderly cat consultations' then extended booster consultations with the veterinarian are recommended for cats aged 7 years and over. For example 30 minutes should be sufficient for all of the procedures itemised above.
4. Offer 'free' annual urinalysis and blood pressure checks in older cats to encourage uptake. For the majority of cats, several normal results will be received (e.g. from the ages of 7-11 years) before abnormal results become more likely. Receipt of normal results help to 'bond' clients to the practice and allow education regarding the value and importance of preventive healthcare checks. Owners exposed to this sort of programme are more likely to appreciate abnormal results and elect for further investigations when recommended by the clinician. It is still important to 'sell' this concept even if it is being offered free of charge.
5. Encourage receptionists to promote the elderly cat health checks to any clients phoning or visiting the practice. Receptionists can also help by posting out urine collection kits and encouraging urine sample collection prior to appointments.
6. Run dedicated elderly cat clinics. These can be nurse-driven concentrating on evaluating history and clinical examination of the elderly cat as discussed earlier. Cats identified with clinical signs such as weight loss, systemic hypertension, reduced urine specific gravity can be referred on for further evaluation by the veterinary surgeon.

The author is keen for practices not to rely solely on elderly cat clinics to identify health problems – not all owners will 'sign up' for these, even if they are free of charge. Therefore, as stated earlier, all opportunities for assessment of older cats visiting the practice should be pursued as far as practically possible – at the very least not missing the chance to record a bodyweight and invite the owner to come back for a more detailed check on another day.

7. Have educational literature available for owners: provide information which supports lifestage appropriate checks for cats, such as that produced by iCatCare.
8. Provide supportive material in the clinic and on the practice website: For example case reports to illustrate the benefits of early diagnosis and successful treatment.
9. Run open days or evening events to inform clients about common health problems of older cats. Many owners do not realise how treatable elderly cat conditions are.

General maintenance advice for owners

A consultation with an elderly cat is a good opportunity to discuss general healthcare of the older cat. Items not already covered in this article which are relevant here include:

- Claw maintenance: older cats are very vulnerable to overgrown claws since they are less able to retract their claws and the claws are shed less easily. The claws often become thickened and may require regular trimming to prevent them catching in carpet or soft furnishings or overgrowing into the pads (Fig 8).
- Grooming assistance: older cats are often less able to groom due to painful OA and may benefit from gentle grooming from their owners. Care should be taken to be gentle, especially in thin elderly cats with little fat over bony prominences.
- Close monitoring for changes in behaviour and health, as discussed in the history section. Owners should be encouraged to report any change in their cat's behaviour or health to their veterinary clinic, however trivial they feel that this may be. Prompt diagnosis

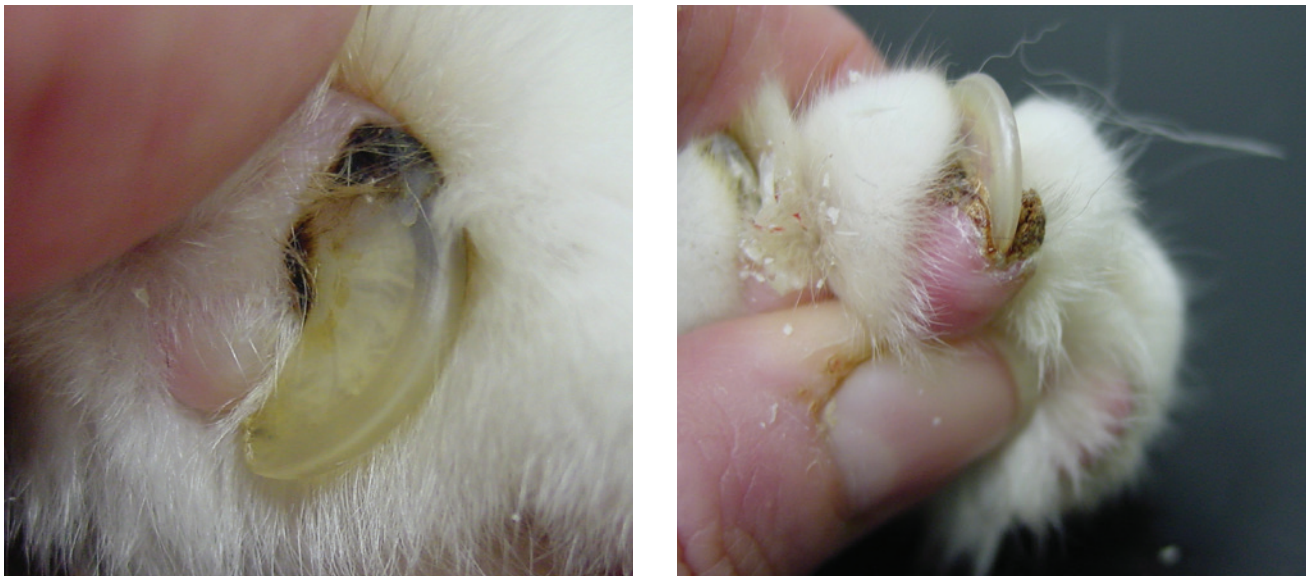

Fig. 8. (i) Claws of elderly cats often become thickened and overgrown. Regular trimming is recommended to prevent overgrowth into the pads (ii).

facilitates appropriate treatment and may enhance the treatment outcome.

Dietary advice for elderly cats

Dietary advice should be individualised to each cat and will depend on a variety of factors. Whilst many Mature cats are vulnerable to weight gain, many elderly cats will be vulnerable to weight loss. Senior and Geriatric cats are more vulnerable to losing weight since they have a reduced sense of smell and taste, and less efficient digestive system. Increasing the amount of food offered, preferably in the form of multiple small meals, may be all that is needed to maintain bodyweight. Offering very palatable diets may also help. Monitoring of body weight and general condition is of enormous value in determining the most appropriate diet for an older cat – the ideal being to find a regime which maintains a healthy bodyweight and good health. The dietary options available to older cats include standard commercial cat food, lifestage diets, prescription diets and home-prepared diets.

In elderly cats reduced appetite is common and it can be helpful for owners to be provided with some tips for encouraging food intake, such as:

- Offer food little and often
- The food should be easy to access at all times. For cats with mobility problems this might entail having multiple 'feeding stations'
- Food should not be placed close to the water bowl or litter tray
- Cats usually prefer wide, shallow bowls and those made of stainless steel, glass or china
- Offer food at room temperature or just below body temperature
- Experiment with the consistency of the food offered. Some elderly cats, especially those with dental problems, prefer soft food to lumps or dry biscuits.
- Raise the food bowl: this may offer more comfortable eating to a cat with OA affecting the neck. Try placing the food bowl on a box or other raised surface
- Avoid leaving uneaten wet food out for more than a couple of hours depending on the ambient temperature.
- Sit with the cat whilst talking to it (and possibly grooming it). Many cats appreciate being hand fed.
- Choose a quiet area for offering food
- Smear a small amount of food onto the paws or face to stimulate eating
- Avoid leaving a range of different foods out for prolonged periods as this can be overwhelming and off-putting to the cat. If not eaten after an hour or so, this is usually a good indication to take the food away and try again later
- Tempting treats can be helpful in triggering an interest in food. Examples include cooked chicken or fish, cooked prawns, cheese and some proprietary 'cat treats'.
- For cats receiving medication: try not to associate timing of medication with mealtimes. Some cats can subsequently start to associate food with unpleasant events and this can put them off eating. For cats that

dislike their medication, it can be helpful finding someone less involved with other aspects of their daily care to dose them

Managing specific conditions

Other articles in this issue cover selected elderly cat health problems in more detail and should be consulted for specific advice on treatment.

Conclusion

Providing 'Gold Standard' care for elderly cats is challenging for everyone involved. A successful approach requires attention to detail which can be time consuming but is worthwhile in terms of ensuring an accurate diagnosis and optimal management. Management of elderly cats can be very rewarding to clinicians, cats and their owners.

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Websites

International Cat Care: www.icatcare.org for resources dealing with cat-friendly tips, owner advice sheets and more

The author's website is www.vetprofessionals.com with many useful resources located on the Free Downloads page: http://www.vetprofessionals.com/catprofessional/free_downloads.html

Elderly cat health check form

1. Cat and Owner name

2. Date of assessment

3. Age

4. Breed

5. Gender and neuter status (circle as appropriate)

F FN MM N

6. Clinical history – does the owner have any concerns?

7. If owner has not already completed the health questionnaire sent out to them, run through it with them in the consulting room

Have you noticed any change in your cat's....	Yes	No	Not sure	Comments
.... thirst?				
.... appetite?				
.... eating?				
.... breath?				
.... weight?				
.... behaviour?				
.... mobility or agility?				
.... energy levels?				
.... urination or defecation?				
.... grooming?				
.... coat condition?				
.... breathing?				
.... body condition?				
.... eyes, ears and nose?				
.... claws?				
..... anything else?				

8. **Mobility questionnaire – please tick the relevant boxes below:**

Question	Yes	No	Not sure	Comments
Have there been any changes in the cat's ability or enthusiasm to:				
1. go up and/or down stairs				
2. use the cat flap				
3. jump onto or off the bed/sofa/ your lap/work surfaces etc.				
4. jump or climb into/onto its favourite bed				
5. play				
6. climb trees/fences etc.				
7. use scratching posts (or other substrates)				
Have any of the following been noticed:				
1. a stiff or stilted gait (i.e. less fluid – less 'feline' - motions)				
2. a limp				
3. vocalising or hissing in response to moving around or being stroked over joints				
Have any of the following changes in your cat's behaviour been detected?				
1. Grumpy or less happy with people and other animals in the house				
2. More withdrawn – interacting less with others in the house				
3. Less active				
4. Sleeping in different locations e.g. on the floor				
5. Not coming upstairs/into the house any more				
6. Passing urine or faeces in abnormal locations, e.g. beside the litter tray, other locations inside the house				
7. Purring less				
8. A reduced appetite				
9. Changes in coat condition *(e.g. matted, scurfy) and/or grooming behaviour – e.g. grooming less overall, neglecting certain areas, overgrooming certain areas (e.g. due to pain over a joint)*				

Question	Yes	No	Not sure	Comments
Has the cat had any musculoskeletal injuries in the past (to the owner's knowledge)?				
Any knowledge concerning affected relatives? *(e.g. hip dysplasia is more common in certain breeds such as the Maine Coon and possibly Siamese, Burmese, Tonkinese, Oriental, Balinese)*				

9. Patient assessment

Assessment	Comment/result
General mobility in the consulting room	
General demeanour and attitude – normal/subdued/?	
Blood pressure measurement (average of 3 readings) Please record cuff size and location (e.g. tail) here:	*Do this procedure first, preferably after the cat has had a 5-10 minute period of acclimatisation whilst you have been taking the patient history - insert the result here:*
Eye examination with a hand lens and ophthalmoscope	*Assessment for ocular manifestations of systemic hypertension. Insert any comments here:*
Bodyweight in kg	
% weight change *(difference in today and last time's weight) divided by (last time's weight) x 100 e.g. 5kg at last check, 4.7kg today.* *% weight change = (0.3÷5) x 100 = 6% weight loss*	
Body condition score	Record using a 5 or 9 point scale – insert BCS here
Examination of the oral cavity e.g. dental disease, pale gums	
Examination of the ears e.g. wax/discharge	
Examination of the eyes and nostrils e.g. discharge	
Palpation for a thyroid nodule (normal cats should not have a goitre)	
Auscultation of the chest e.g. murmur, gallop, arrhythmia	

Assessment (cont.)	Comment/result
Palpation of the abdomen e.g. constipation, mass	
Examination of the skin and coat e.g. poor coat, matts	
Run your hands over the cat's body e.g. lumps, bumps	
Skin tenting (dehydration)	
Other abnormalities?	

10. Urinalysis results

Test	Result/s	Comment/interpretation
Specific gravity (refractometer)		
Dipstick		

11. Blood test results

Test	Result/s	Comment/interpretation
Haematology		
Serum biochemistry		
T4 test		

12. Patient summary

13. Action required?

All OK – book next health check in

☐ **6 months (cats aged 7-14 years)** ☐ **3 months (cats aged 15y and over)**

Further veterinary assessment required

Commissioned paper*

Increased vocalisation in elderly cats

Danièlle Gunn-Moore[1]

SUMMARY

- With evermore cats living to become elderly, age-associated behavioural changes are being seen with increasing frequency.
- The behavioural changes reported most commonly are increased vocalisation (especially at night), and inappropriate elimination.
- The most common causes of increased vocalisation are cognitive dysfunction syndrome, hyperthyroidism (with or without systemic hypertension), systemic hypertension (most commonly associated with chronic kidney disease, hyperthyroidism or hyperaldosteronism), deafness, osteoarthritis (or other causes of chronic pain) and brain tumours.
- Approximately 30% of pet cats aged 11-14 years develop at least one age-associated behavioural problem; this increases to over 50% for cats aged ≥15 years.
- The diseases most frequently associated with increased vocalisation occur most commonly in elderly cats, and elderly cats often suffer from a number of concurrent interacting conditions.
- Owners often think increased vocalisation is a normal (if distressing) aging change so they fail to mention it to their veterinarian, hence manageable conditions are neglected and the cat's quality of life is poorer than it needs to.

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Go to http://www.ejcap.org to see the online presentation of this paper.

Introduction

The life expectancy of pet cats is increasing, such that >10% are now over 12 years of age [35]. Unfortunately, accompanying this growing population of elderly cats, are many cats with age-associated behavioural changes (Figure 1; Box 1). Two unpublished studies from the UK, each looking at >1000 elderly cats, found that increased vocalisation occurred in 54-66% of cats, with 30-37% of them vocalising most at night (V. Hall, unpublished data

Figure 1: Behavioural changes seen commonly in elderly cats.

- Inappropriate vocalisation, especially at night
- Spatial disorientation, e.g. forgetting where their litter box is (inappropriate elimination is the most common reason for the referral of elderly cats to behavioural specialists)
- Altered interaction with the family (people or other pets) e.g. attention-seeking behaviour
- Altered sleep/wake patterns
- Altered behavioural responses e.g. increased anxiety, or decreased response to stimuli
- Altered activity e.g. aimless wandering, or reduced activity
- Altered interest in food e.g. increased or, more typically, decreased
- Altered grooming, e.g. decreased or stereotypical
- Temporal disorientation e.g. forgetting that they have just been fed

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Box 1: Behavioural changes seen commonly in elderly cats (questionnaire studies of cats of ≥12 years of age (median 15 years) as observed in two studies from the UK, 15 years apart)[a]:

1995; 1134 owners		2010; 1016 owners	
Increased affection to owner	81%	Increased affection to owner	30%
More vocal [b]	66%	More vocal [b]	54%
More vocal at night [b]	30%	More vocal at night [b]	37%
Less tolerant of other animals in the house	26%	Less tolerant of other animals in the house	21%
More tolerant of other animals in the house	24%	More tolerant of other animals in the house	12%

[a] V. Halls, unpublished data, 2002; author unpublished data, 2012.
[b] "Cries out loudly for no apparent reason and/or to try to gain my attention".

2002; author, unpublished data 2012, see Box 1). Interestingly, these studies both showed that with age, cats often become more affectionate towards their owners, and more demanding of their attention (30-81% of the cats); the increased vocalisation is often aimed at trying to gain their owners attention. However, at other times the cats appear to be vocalising excessively and frantically about something quite mundane e.g. being fed, or using the litter box. Sometimes they appear to be meowing for no apparent reason at all. Many owners report that this behaviour is, at times, quite frustrating. Unfortunately, having an elderly cat crying loudly at night can be particularly distressing as it results in broken sleep that can significantly damage the owner-cat bond and test family loyalties.

While increased vocalisation (Figure 2) is not a disease in itself, it is a sign that an elderly cat is stressed and/or ill. It is important that we find out what is wrong and treat them appropriately, so we can give them the best quality of life, for as long as possible. Excessive vocalisation (and other age-associated behavioural changes) can result from a number of

Figure 2: The author's elderly cat vocalising to gain her attention.

Figure 3: Potential causes of increased vocalisation in elderly cats.

- Cognitive dysfunction syndrome (CDS e.g. resulting in senility, disorientation and confusion)
- Hyperthyroidism (with or without systemic hypertension e.g. resulting in irritability, disorientation, confusion and possible headache)
- Systemic hypertension (either primary, or secondary to hyperthyroidism, chronic kidney disease or possibly, hyperaldosteronism, diabetes mellitus, acromegaly, hyperadrenocorticism, or chronic anaemia e.g. resulting in irritability, disorientation, confusion and possible headache)
- Deafness (deaf cats, like deaf people, often vocalise loudly, probably because they cannot hear how loudly they are meowing)
- Osteoarthritis (OA e.g. resulting in pain on moving)
- Brain tumours (e.g. meningioma or lymphoma, resulting in headache, confusion, and seizures)
- Infectious disease causing neurological dysfunction (e.g. FIV, FeLV, toxoplasmosis, FIP, certain urinary tract infections)
- Chronic kidney disease (CKD e.g. uraemia encephalopathy)
- Acute blindness (often resulting from systemic hypertension e.g. resulting in confusion and disorientation)
- Liver disease (e.g. hepatic encephalopathy)
- Gastrointestinal disease (e.g. diarrhoea and intestinal spasm causing pain, or constipation causing pain leading up to and/or during defaecation)
- Other neurological diseases
- Other causes of pain (e.g. periodontal disease, ureteroliths, pancreatitis)
- True behavioural problems (e.g. separation anxiety)

different disorders (Figure 3), including systemic illness (e.g. hyperthyroidism and/or systemic hypertension), organic brain disease (e.g. brain tumours, especially meningioma), true behavioural problems (e.g. separation anxiety) or, when everything else has been excluded, cognitive dysfunction syndrome (CDS). Determining the cause(s) involves a detailed investigation looking for physical (Figure 4) and/or behavioural problems.

Potential causes of increased vocalisation in elderly cats

Perhaps the most common causes of increased vocalisation in elderly cats are CDS, hyperthyroidism (with or without systemic hypertension), systemic hypertension (typically secondary to chronic kidney disease (CKD), hyperthyroidism or, possibly, hyperaldosteronism or diabetes mellitus (DM), deafness, osteoarthritis (OA, or other causes of chronic pain), and brain tumours (most commonly meningioma) (Figure 3). Since many of these conditions are discussed elsewhere in this journal, this paper will concentrate on the recognition and treatment of CDS, with only brief comments on the other conditions.

Cognitive dysfunction syndrome describes an age-related deterioration of cognitive abilities, characterised by behavioural changes (Figure 1; Box 1), where no medical cause can be found [10, 64, 39, 21]. A survey of older cats revealed that 28% of owners reported at least one age-related behavioural problem that appeared to relate to CDS in their cats aged 11-14 years, and this increased to over 50% in cats of ≥15 years: excessive vocalisation and aimless activity were the most common problems in these older cats [47, 21]. Another study found that 36% of cats aged 7-11 years developed age-related behaviour problems, and this increased to 88% for cats of aged 16-19 years [37].

The cause of CDS is still unknown, but compromised cerebral blood flow and chronic free radical damage because of poor antioxidant defences (e.g. lack of vitamins A, C and E) are believed to be important [21]. Ultimately, chronic damage leads to disease similar to Alzheimer's disease in humans.

Hyperthyroidism is a common treatable cause of increased vocalisation, which can occur as a direct effect of thyroxin on the brain (typically seen as agitation, restlessness and aggression), and/or be associated with systemic hypertension causing cerebral vascular compromise. Other factors may also be involved e.g. polyuria without adequate access to water can cause

Figure 4: Investigation of increased vocalisation in elderly cats

Investigation of increased vocalisation in elderly cats should include:

- Full history, including previous trauma (which may have lead to OA), potential exposure to toxins or drugs (recreational or prescription), and any recent changes to the cat's environment (e.g. family members, other pets, the house itself, diet, etc.). Asking specific questions about alternations in the cat's behaviour can help in determining just how significantly the cat has changed (Elderly Cat Cognitive Dysfunction and Mobility Survey – see box on following page)
- Full physical examination (including assessment of body weight, calculation of percentage weight change since last seen and in the last year, body condition score, body muscle score, and retinal examination)
- Assess systemic blood pressure (this is essential as systemic hypertension is common in elderly cats and often presents as increased vocalisation)
- Mobility assessment; neurological and orthopaedic examinations - these can be challenging to perform in elderly cats as they need time to relax in a consultation room and then move about on their own volition, preferably on a floor that gives them sufficient grip without catching their nails. Setting up an obstacle course in the consultation room can be useful at assessing vision, plus neuromuscular and orthopaedic fitness. Asking the owner to bring in videos of their cat walking, climbing up and down the stairs, and navigating obstacles at home can be very helpful.
- Assess routine haematology and serum biochemistry, including total thyroxin and cobalamin (B12) concentrations.
- Urine analysis (including urine protein to creatinine ratio and bacterial culture [even if the urine sediment appears non-reactive as many elderly cats can have apparently silent urinary tract infections that can actually be causing problems, and their weak immune systems can result in apyruric infections where there is failure of migration of neutrophils into the urine [44])

Depending on the initial findings, further investigation may include:

- Serological testing for FeLV, FIV, Toxoplasmosis, FIP or other infectious diseases
- Thoracic, abdominal or skeletal radiography or CT, abdominal ultrasound examination, ECG, echocardiography, intestinal endoscopy / exploratory laparotomy and biopsy collection
- Head or spine CT or MRI

Elderly Cat Cognitive Dysfunction and Mobility Survey

Is your cat ...	Yes	Maybe	No
Crying out loudly for no apparent reason	☐	☐	☐
Crying out loudly to gain your attention	☐	☐	☐
Crying out loudly at night	☐	☐	☐
Increasingly wanting to interact with you	☐	☐	☐
More reluctant to interact with you	☐	☐	☐
Playing less with other pets or toys	☐	☐	☐
Sleeping more and/or is less active	☐	☐	☐
Appearing forgetful	☐	☐	☐
Appearing anxious	☐	☐	☐
Wandering aimlessly around the house or garden	☐	☐	☐
Spending less time grooming	☐	☐	☐
Spending more time grooming	☐	☐	☐
More interested in food	☐	☐	☐
Less interested in food	☐	☐	☐
Urinating inappropriately in the house	☐	☐	☐
Defecating inappropriately in the house	☐	☐	☐
Crying when being lifted up	☐	☐	☐
Less willing to jump up or down	☐	☐	☐
Only willing to jump up or down from lower heights	☐	☐	☐
Showing signs of stiff limbs and/or spine	☐	☐	☐
Less agile than previously	☐	☐	☐
Showing signs of lameness or limping	☐	☐	☐
Having difficulty getting in or out of its cat flap	☐	☐	☐
Having difficulty going up or down stairs	☐	☐	☐

It is important to ask if there that been any changes to the cat's environment that may be causing anxiety or distress as this can result in significant changes in the cat's apparent cognitive function and/or its willingness to be mobile.

It can be difficult to differentiate between many of the behavioural changes caused by CDS and/or other behavioural/neurological diseases in old cats, and those caused by OA. In addition, it is not unusual for an individual cat to have multiple interacting conditions.

cerebral dehydration resulting in confusion and depression, and polyuria may also be associated with secondary urinary tract infections (see UTI). Poorly controlled hyperthyroidism can occasionally present with disorientation and signs of bilateral central vestibular disease (dilated pupils, lack of menace response, neck ventroflexion and, sometimes, vocalisation); this is thought to result from secondary thiamine deficiency (similar to thyrotoxicosis-associated Wernicke's encephalopathy in humans [67]).

Systemic hypertension is a common cause of behavioural changes in elderly cats. It can result in increased vocalisation (especially night-crying), disorientation, altered consciousness, circling and even seizures. It is most commonly associated with CKD, and hyperthyroidism. Systemic hypertension has a reported prevalence of ~25% in cats with CKD in general practice, increasing to 60-65% in referral practice [75, 61], and between 10 and 90% in hyperthyroid cats [33, 73]. Hypertension in cats can also be associated with hyperaldosteronism, hyperadrenocorticism, DM, acromegaly, chronic anaemia, and erythropoietin therapy plus, potentially, glucocorticoid administration, phaeochromocytoma, and obesity [30]. Since many of these diseases occur mainly in elderly cats this explains why hypertension is most common in this age group. In addition, a study of apparently healthy cats of ≥9 years of age (median 13 years) found 13% to be hypertensive [32].

Deafness can cause cats to meow more loudly [69]. The lack of familiar noises at night may cause a deaf cat to vocalise loudly when it wakes up disorientated, and so tries to attract its owner's attention looking for reassurance.

Osteoarthritis occurs in 60-90% of cats over 12 years of age [23, 12, 20, 42, 5], with changes being found most frequently in elbows, hips, stifles, tarsus and shoulders [23, 12, 11, 42, 71]. However, it can be easy to overlook OA in cats because it develops slowly, is typically symmetrical and cats are good at hiding their pain. The signs of OA in cats typically include a hesitance to jump, a stilted gait, more resting or sleeping, inappropriate elimination, poor grooming, aggressive behaviour, and/or a reluctance to use the cat flap [12, 20, 11, 71]. Increased vocalisation may occur in response to pain when being picked up and/or when changing position after resting or sleeping.

Brain tumours occur most commonly in older cats (mean age 11 years), with 70% being primary tumours, e.g. meningioma (58%), lymphoma (14%), pituitary tumours (14%) and gliomas (7.5%) [77]. The most common clinical signs are altered consciousness, circling, and seizures; increased vocalization can occur as a result of disorientation and confusion [49, 77, 76].

Chronic kidney disease can result in increased vocalisation when associated systemic hypertension causes cerebral vascular compromise (as in CDS). It can also occur when polyuria without adequate access to water cause cerebral dehydration, when polydipsia/polyuria predisposes to a secondary UTI (see UTI), or when severe uraemia results in uraemic encephalopathy.

Diabetes mellitus can result in increased vocalisation for many of the same reasons as CKD. In addition, unstable diabetes may cause sensory neuropathies, resulting in irritability, sensitivity to touch, and/or muscle pain; irritability may result in increased vocalisation.

Infectious disease e.g. FIV, FeLV, FIP and, particularly, toxoplasmosis, can all cause increased vocalisation associated with other behavioural changes when disease recrudesces in elderly cats undergoing immune senescence.

Urinary tract infections (UTIs) most commonly cause increased vocalisation as a result of bladder and/or kidney pain, typically associated with dysuria, periuria, pollakiuria, hiding, aggression, and/or pain on being lifted. *E. coli* UTIs can sometimes present with confusion and disorientation, similar to that seen in elderly humans with quinolone-resistant *E. coli* UTIs, where the bacteria produce systemic toxins [13].
In elderly cats, UTIs are usually associated with CKD, hyperthyroidism or DM, where less concentrated urine is associated with local and/or systemic immunosuppression: 12% of cats with DM or hyperthyroidism have a UTI at some point in their illness, compared with 22-35% with CKD [18, 44].

Separation anxiety can occur in cats that are very bonded to their owner, when that person is absent. It affects indoor-only cats most frequently, and cats that are less than five years of age. However, it can still be seen in elderly cats, especially females. The most commonly clinical signs are inappropriate urination (70%), inappropriate defecation (35%), excessive vocalization (12%), destructiveness (9%), and psychogenic grooming (6%) [65].

Diagnosis of elderly cats with increased vocalisation

Veterinarians must ask about increased vocalisation in elderly cat consultations as owners rarely volunteer this information. This can be for a number of reasons: some owners do not realise that vocalisation is a sign of ill-health, some think it is just a sign of ageing, others feel that nothing can be done to help so there is no point in mentioning it, while others are embarrassed as they are not coping with the broken sleep that night-crying can cause. Veterinarians need to educate owners to realise that increased vocalisation is a sign of ill health or stress, and that ignoring it is to ignore a potentially treatable/manageable condition, and so leave the cat in a poorer quality of life that it deserves.

Determining why a cat has started to vocalise excessively involves a thorough investigation (Figure 4). Unfortunately, the diagnosis and management of disease in elderly cats is often complicated by concurrent interacting disorders. For example, hyperthyroidism and DM can cause very similar clinical signs, including increased vocalisation, and each can affect the diagnosis of the other; DM may suppress the serum thyroxin concentration to within the reference range [19, 15], while the increased protein turnover associated with hyperthyroidism can reduce the serum fructosamine concentration to much lower than would be expected with untreated DM [27, 60].

Figure 5: The author's elderly cat with marked elbow OA seen as elbow thickening and outward bowing of the front legs.

Much information can be gained from a careful, gentle and thorough physical examination. Pay particular attention to indicators of diseases that are associated with increased vocalisation, notably the rate and strength of the heartbeat, and the size of the kidneys and thyroid glands. Ophthalmic examination is mandatory, looking for signs of systemic hypertension (e.g. intraocular haemorrhage and/or hypertensive retinopathy), and/or signs of infectious disease (e.g. toxoplasma retinopathy), intracranial neoplasia (e.g. papilloedema – which can be subtle in cats), or malnutrition (e.g. taurine retinopathy). Let the cat walk around the consultation room: this can give insight to its vision, and enable some assessment of its nervous and musculoskeletal systems. Performing a careful orthopaedic examination, and watching a cat walk, are often all that is needed to diagnose OA. For example, feeling thickened elbows and seeing the cat walk with obviously bowed front legs is typical of elbow OA (Figure 5). While it is not necessary to confirm this with radiographs, it is always sensible to look for signs of OA when taking radiographs for other reasons.

Systemic blood pressure (BP) should be evaluated in all elderly cats. The Doppler method is currently considered the most appropriate indirect method for assessing BP. Unfortunately, oscillometric methods tend to underestimate the BP and fail in a significant number of conscious cats, and the Doppler method does not always allow the diastolic BP to be measured [3, 9, 31].

Further investigations should be tailored to the individual; starting with haematology and serum biochemistry, including thyroxin and cobalamin (B12) concentrations. The latter is recommended as many elderly cats may be hypocobalaminaemic because of pancreatic and/or intestinal disease [58], lack of intake (chronic hyporexia), hyper-metabolism associated with hyperthyroidism [14], and/or increased loss associated with CKD or other causes of polydipsia/polyuria [54]. Hypocobalaminaemia (in both cats and humans) can result in anorexia, anaemia, weakness, and neurological signs, including confusion and disorientation [70, 24, 78].

Urine should undergo routine analysis, protein to creatinine ratio, and bacterial culture. Since UTIs do not always result in clinical signs referable to the urinary tract, it is essential that elderly cats have regular urine cultures – if left untreated a UTI can cause deterioration of renal function, renal and/or bladder pain, urinary urgency and, in some cases, dementia and confusion. Pyuria and an active urine sediment are not always present with CKD, hyperthyroidism or DM [44], so the presence of a UTI can only be confirmed with bacterial culture. To reduce the need for repeated cystocentesis, primary screening can be performed on urine collected by the owner using a clean litter box with non-absorbent litter; even when collected like this a pure heavy growth of bacteria is highly suggestive of a UTI [17].

As indicated by the cat's history and clinical signs, serological and/or molecular testing may be undertaken to investigate the possibility of infectious disease(s).

Initially, most cats will only need to attend a clinic once or twice a year. However, those cats showing significant disease and/or more significant ageing changes will need to attend more frequently for repeated reassessment, monitoring and treatment.

Management of elderly cats with increased vocalisation

Successful management depends of making a full diagnosis of all potential causes of the cat's vocalisation (plus its other clinical signs), then addressing these disorders in a sensible stepwise manner. It is important to remember that elderly cats typically have a number of concurrent and interacting disorders, so the treatment of

one disease may affect another, sometimes improving it (e.g. treatment of hyperthyroidism can reduce concurrent hypertension), sometimes worsening it (e.g. treatment of hyperthyroidism can unmask CKD [19]).

While we may be able to offer complex therapeutic options (environmental, nutritional, medical and/or surgical), it is important to remember that older cats are often poorly tolerant of the stress of change, handling, medicating and/or hospitalisation. It is essential that each cat is assessed and treated as an individual, and the veterinarian needs to consider each cat's ability to cope with intervention(s) before undertaking them. Some investigations and interventions may have to be adapted or even abandoned if the cat is poorly tolerant of them for either medical or temperamental reasons. In addition, it is important that euthanasia be discussed at an early stage so that the cat's quality of life is always precedent: with chronic disease, it can be difficult for owners to decide when it is the best time to let their cat go, so having some form of record of the cat's time partitioning to different activities can help to bring objective data to this painful decision making process.

This EJCAP issue contains wonderful articles discussing DM, CKD, OA, hypertension and GI disease in elderly cats. There are also many reviews available for the treatment of hypertension [73], hyperthyroidism [66, 16, 55], DM [7, 55, 72], CKD [4, 34, 56], OA [43, 6], UTI [50], and brain neoplasia [77, 68, 48], and for the nutrition of aging cats [36].

Management of cats with CDS can involve environmental changes, dietary modifications and supplements, nutraceuticals, and/or drugs [22]. Unfortunately, there are few feline studies, and advice is largely extrapolated from dogs with CDS.

Environmental management, dietary modifications and supplements

Environmental factors can be positive or negative. Environmental enrichment can give mental stimulation, increase activity, and improve cognitive function, especially when combined with dietary modification [45,46]. Lack of environmental stimulation can exacerbate CDS, as can negative factors that cause frustration, e.g. inconsistent feeding times add stress and can lead to intense vocalisation. Older cats often have concurrent diseases, which can lead to further frustrations, e.g. giving a high-sided litter box to a cat with CDS and OA can lead to more vocalisation around the time of elimination. Environmental application of synthetic feline appeasement pheromone (Feliway®; Ceva) may help to alleviate anxiety and so reduce vocalisation.

There are a number of studies in dogs that show that nutraceuticals (enriched with antioxidants and essential fatty acids to reduce oxidative damage; alpha-lipoic acid and l-carnitine to enhance mitochondrial function; and omega-3 fatty acids promote cell membrane health) can significantly reduce signs of CDS in elderly dogs [8, 29, 63, 25, 51, 1, 59, 52, 2], as can enhanced diets, although they take longer to have an effect [29, 45].

In contrast, there is only one, rather poor, study looking at giving a nutraceutical (S-adenosyl-l-methionine; SAMe) to cats with CDS [2], and very few studies looking at changing their diet (Hill's data 2008 [53]). Unfortunately, alpha-lipoic acid is toxic in cats [26] so products containing it should not be given. There is now a growing list of compounds suggested to be beneficial for cats with CDS, either as single ingredients or in potentially synergistic combinations [41]; however, placebo-controlled studies are needed to see which are truly effective.

Unfortunately, once a cat develops significant CDS, instigating change can have a negative effect as the stress of change (whether in environment, routine, diet, or family members) can exacerbate the signs of CDS [28]. Change should therefore be kept to a minimum, and when it must be made, introduce it gradually (where possible) and give the cat plenty of reassurance. Cats with severe CDS may feel less stressed if they are confined to a single room which contains all their essential needs (food, water, litter box, resting places, somewhere to hide, and companionship [if it makes then less anxious]); this core territory should then be kept constant [22].

Potential drug therapies

While there are a number of drugs to treat CDS in dogs, there are no drugs licensed to treat CDS in cats. However, selegiline (Selgian®; Ceva: Anipryl®; Zoetis: suggested dose 0.25-1.0 mg/kg PO q24h), propentofylline (Vivitonin®; MSD Animal Health: suggested dose 12.5 mg/cat PO q24h) and nicergoline (Fitergol®; Merial: when available, suggested dose 0.25 to 0.5 mg/kg) have all been used 'off label' in cats with varying success [40, 39, 74, 41]. A small open trial using selegiline showed a positive effect [38] and the American Association of Feline

Practitioners support its use for the treatment of CDS. Other drugs have been used to treat particular signs of CDS in cats, including anxiolytic drugs/nutraceuticals (e.g. Zylkène®; MSD Animal Health), buspirone and benzodiazepines (e.g. diazepam – care – hepatotoxicity), or antidepressants (that lack anticholinergic effects) such as fluoxetine.

Useful resources:

Cornell Feline Health Center: The Special Needs of the Senior Cat:
http://www.vet.cornell.edu/FHC/health_information/brochure_seniorcat.cfm

Pet Advisor: Why Does My Older Cat Yowl All the Time? (I'm Trying to Sleep!):
http://www.petsadviser.com/pethealth/my-old-cat-meows-all-the-time/

AAPCA Pet Care: Behavior Problems in Older Cats:
https://www.aspca.org/pet-care/virtual-pet-behaviorist/cat-behavior/behavior-problems-older-cats

Healthy Pets: Cognitive Dysfunction: Does Your Cat Prowl the House at Night and Vocalize? This May Be Why:
http://healthypets.mercola.com/sites/healthypets/archive/2014/03/12/cat-cognitive-dysfunction.aspx

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Commissioned paper*

Role of Retroviruses in Feline Lymphoma

Katrin Hartmann[1]

Lymphoma is the most common haematopoietic tumour of cats [1-6], and feline retrovirus infection is a known risk factor for the development of lymphoma [7-11]. Three retroviruses have been identified in domestic cats: Feline immunodeficiency virus (FIV), feline leukaemia virus (FeLV) and feline foamy virus (FeFV), which was previously known as feline syncytium-forming virus (FeSFV). All have a globally widespread distribution but differ in their potential to cause disease [12-15]. Feline foamy virus is a spumavirus and not associated with clinical disease, including tumour development [16].

Clinical signs in FIV and FeLV infections vary, and infection with either virus can lead to the development of tumours, haematopoietic and neurological disorders, immunodeficiency, immune-mediated diseases and stomatitis, after a long asymptomatic period [17,18]. The pathomechanism of these diseases syndroms, however, differs depending on the retrovirus involved (Table 1).

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Feline immunodeficiency virus

FIV, a lentivirus, shares many properties with human immunodeficiency virus (HIV). Cats infected with FIV can develop an acquired immune deficiency syndrome, which increases the risk of tumours, secondary infections, stomatitis, immune-mediated diseases and neurological disorders [19]. In most naturally infected cats, FIV infection does not cause severe clinical syndromes, and with proper care FIV-infected cats can live many years. In fact, many FIV-infected cats die at an older age from causes unrelated to their FIV infection [17,18]. In a follow-up study in naturally FIV-infected cats, the rate of progression was variable, with death occurring in about 18% of infected cats within the first two years of observation (i.e. about five years after the estimated time of infection). An additional 18% developed increasingly severe disease, but more than 50% remained asymptomatic during the first two years [20]. FIV infection has little impact on a cat population and does not reduce the number of cats in a household [21]. Thus, overall survival time in FIV-infected cats is not shorter than in uninfected cats [21,22], and quality of life is usually fairly high over an extended period of time [23].

Pathogenesis and clinical signs

Clinical signs in naturally FIV-infected cats usually reflect secondary diseases, such as tumours and infections, to which FIV-infected cats are considered more susceptible. Rarely, some clinical signs (e.g. neurological disorders) attributable to abnormal function or inflammation of affected organs are directly caused by FIV. In experimental FIV infection, an initial stage is described, which is characterised by transient and mild clinical signs that include fever, lethargy, enteritis, stomatitis, dermatitis, conjunctivitis, respiratory tract disease and generalised lymph node enlargement [24]. However, in naturally infected cats, the acute stage is often not present or not noticed by the owners. The acute stage can

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Table 1. Comparison of clinical syndromes and their main pathomechanism in feline leukaemia virus- (FeLV-) infected and feline immunodeficiency virus- (FIV-) infected cats

Clinical syndrome	FeLV	FIV
Tumours	62 times as likely as in non-infected cats, direct role of FeLV, mainly T-cell lymphoma	5 times as likely as in non-infected cats, indirect role of FIV, mainly B-cell lymphoma
Bone marrow suppression	common, anaemia, thrombocytopenia, neutropenia or pancytopenia, primary infection of bone marrow precursor cells and stroma cells	rare, mainly neutropenia, soluble factors inhibiting bone marrow function
Neurological disorders	rare, direct influence of the virus, lymphoma and neurotoxic effects (of FeLV envelope glycoprotein)	rare, direct influence of the virus (specific FIV strains), impairment of astrocyte function
Immunodeficiency	common, several mechanisms, e.g. replication of virus in all bone marrow cells (including neutrophils), changes in cytokine pattern	common, several mechanisms, e.g. decrease in CD4+ cells, changes in cytokine pattern
Immune-mediated diseases	rare, e.g. immune-mediated haemolytic anaemia	occasional, hyperglobulinaemia common with immune complex deposition leading to e.g. glomerulo-nephritis and uveitis
Stomatitis	common, multi-factorial disease	very common, multi-factorial disease

last several days to a few weeks and is followed by an asymptomatic period that usually lasts many years. The duration of the asymptomatic stage depends on the pathogenicity of the infecting FIV strain and subtype, exposure to secondary infectious agents and the age of the cat at the time of infection [25]. In the final symptomatic stage ('AIDS phase') of infection, the clinical signs are a reflection of secondary infections, neoplasia, stomatitis, immune-mediated diseases and neurological disorders. Although secondary infections are common, specific opportunistic infections or acquired immunodeficiency virus- (AIDS-) defining infections, such as those that occur in HIV, are not commonly reported in FIV-infected cats [17,18], and staging in FIV infection is not as clear-cut as it is in humans with HIV infection.

Lymphoma

FIV-infected cats are about five times more likely to develop lymphoma or leukaemia than non-infected cats [26, 27]. In addition to lymphoma and leukaemia [26-29], other tumours such as squamous cell carcinoma, fibrosarcoma and mast cell tumour have been described in association with FIV infection [20, 26, 30-34].

In most cases, the role of FIV in lymphoma formation is suspected to be indirect rather than direct because FIV provirus is only occasionally detected in tumour cells [35-38]. While FeLV-infected cats usually have T-cell lymphomas, FIV-infected cats most commonly have B-cell lymphomas [26,27]. Indirect mechanisms leading to lymphoma development include decreased cell-mediated immune surveillance or chronic B-cell hyperplasia [37,39]. Clonally integrated FIV DNA was found in lymphoma cells from one cat that had been experimentally infected six years earlier, indicating the possibility of an occasional direct oncogenic role for FIV [35,36,40]. The prevalence of FIV infection in one cohort of cats with lymphoma was 50% [41] and thus much higher than the FIV prevalence in a population of cats without lymphoma, which is also supportive of a cause-and-effect relationship.

Feline Leukaemia Virus

FeLV, an oncornavirus, is more pathogenic than FIV. Historically, FeLV was thought to account for more disease related deaths and clinical syndromes than any other infectious agent. It was proposed that approximately one third of all tumour-related deaths in cats were caused by FeLV, and an even greater number of cats died of FeLV-related anaemia and infections secondary to bone marrow suppression and immunosuppression [42]. The prevalence and importance

of FeLV have decreased, mainly because of testing and eradication programs and the use of FeLV vaccines [43]. However, if present in closed households with other viruses, such as feline coronavirus (FCoV) or FIV, progressive FeLV infection has the greatest impact on survival [21]. The death rate of progressively FeLV-infected cats in multi-cat households has been estimated at approximately 50% in two years and 80% in three years [44,45], but survival time is considered higher today, at least for cats that are well taken care of and that are kept strictly indoors. A survey in the United States compared the survival of more than 1,000 progressively FeLV-infected cats with that of more than 8,000 age- and sex-matched uninfected control cats and found that in progressively FeLV-infected cats, median survival was 2.4 years compared with 6.0 years for control cats [46]. In a long-term follow-up study of cats experimentally infected with FeLV, progressively infected cats lived an average (median) of 3.1 years (range 0.6 to 6.5 years) [47]. Thus, progressive FeLV infection leads to a decrease in life expectancy [21, 22]; however, with appropriate care, many FeLV-infected cats can live for many years with a fairly good quality of life [23].

Pathogenesis and clinical signs

There are three major outcomes of FeLV infection: Progressive infection (antigen-positive, provirus-positive cats), regressive infection (antigen-negative, provirus-positive cats) and abortive infection (antigen-negative, provirus-negative, but antibody-positive cats) [12,23,48]. Differentiation of these three outcomes is done through testing for antigen, proviral DNA and antibodies (Table 1). The outcome of infection depends on the immune function of the cat and the amount of infecting virus. In addition to these three outcomes, so-called focal infections have been described as rare events in which FeLV infection is restricted to certain tissues, such as spleen, lymph nodes, small intestines or mammary glands [49,50]. However, these focal infections probably do not play an important role in naturally infected cats.

In the past, it was assumed that most cats would clear the virus from the body after a period of transient viraemia. However, the development of more sensitive PCR assays has revealed that most (or even all) cats remain infected for life [47].

In most cats, antigenaemia (presence of viral proteins in the blood) correlates with viraemia (presence of infectious virus that can be cultured from the blood) [51]. Infected cats can remain viraemic and antigenaemic (progressive infection) or revert to an aviraemic state (regressive infection) in which neither antigen nor culturable virus is detected but in which FeLV proviral DNA can still be identified by PCR [48,52].
A third possibility is that cats test negative in all direct virus detection methods (such as tests detecting antigen and proviral DNA), but remain antibody-positive (abortive infection). Regressive and progressive infections can be distinguished by repeated testing for FeLV antigen in serum because progressor cats remain antigen-positive, while regressor cats revert to an antigen-negative status[52]. They can also be distinguished by their provirus load [47]; during early infection, all cats have similar provirus loads [53], but after a few weeks, the provirus load drops in regressively FeLV-infected cats, while it remains high in progressively FeLV-infected cats [48].

Table 2. Feline leukaemia virus infection status possibilities [23,48]

	Soluble FeLV p27 antigen in blood	Proviral DNA in blood	Antibodies in blood	Replicating virus in blood	Viral RNA in blood	Viral shedding	FeLV-associated diseases	Vaccination useful
Test	**ELISA or other immuno-chromatography test**	**PCR**	**Different tests available**	**Viral Culture**	**RT-PCR**			
Progressive infection	Positive	Positive	Low or negative	Positive	Positive	Yes	Common	No
Regressive infection	Negative	Positive	High	Negative	Negative	No	Uncommon, reactivation possible	No
Abortive infection	Negative	Negative	High	Negative	Negative	No	None	No
Not FeLV-infected	Negative	Negative	Negative	Negative	Negative	No	None	Yes

Progressive infection

In progressive infection, insufficient FeLV-specific immunity results in extensive virus replication that occurs first in the lymphoid tissues and then in the bone marrow. Spread to mucosal and glandular tissues and excretion of infectious virus occurs simultaneously with bone marrow infection [54]. The number of cats that will develop progressive FeLV infection depends mainly on infection pressure and varies from 3% (after single contact with an FeLV-shedding cat) to 30% (when living together for several weeks with a shedding cat) [55]. Progressively infected cats are persistently antigenaemic, continuously shed the virus, frequently succumb to FeLV-associated diseases within a few years and have a decreased life expectancy [47].

Regressive infection

In regressive infection, an effective immune response limits virus replication prior to or at the time of bone marrow infection. In recent studies, 2 to 10% of FeLV-antigen-negative cats were found to be positive for FeLV provirus by PCR and thus were characterised as regressively infected [48,56,57]. In these cats, FeLV antigen is sometimes detectable in peripheral blood within two to three weeks after virus exposure but then disappears two to eight weeks later or, in rare cases, even after several months. Some infected cats fail to ever develop detectable antigenaemia. Cats with regressive infection have persistent integration of FeLV DNA in their genome [58]. In a recent study, complete clearance of FeLV viral RNA or provirus was not detected in cats with regressive infection, even up to 12 years after exposure [47]. Regressively infected cats only rarely develop FeLV-associated diseases [43,57,59,60], such as lymphoma [61] or bone marrow disorders[62]. Even though viral shedding does not occur, it is possible that cats with regressive infection transmit FeLV via blood and tissue donation because provirus is infectious [63,64]. It is also possible that the regressive state can convert to a progressive state (reactivation). This is more likely to occur soon after exposure to FeLV, but has been described in cats that were antigen-negative for many years [65]. In a long-term follow-up study on experimentally infected cats, five of 10 regressively infected cats had reactivation of infection and became antigen-positive at different time points over a period of up to 8.5 years after infection [47].

Abortive infection

In abortive infection, cats are negative for culturable virus, antigen, viral RNA and proviral DNA [52,66], but remain antibody-positive. Recent studies suggest that abortive infection is more common than previously estimated [56]. These cats are assumed to have life-long protection against new infection.

The outcome of FeLV infection and the clinical course are determined by a combination of viral and host factors. Some of the differences in outcome can be traced to properties of the virus itself, such as the subgroup that determines differences in the clinical picture (e.g. FeLV-B is primarily associated with tumours, whereas FeLV-C is primarily associated with non-regenerative anaemia). One study found that high levels of circulating FeLV-specific effector cytotoxic T-lymphocytes (CTL) appear before virus-neutralizing antibodies in cats that have recovered FeLV viraemia. In contrast, progressive infection with persistent viraemia has been associated with a silencing of virus-specific humoral and cell-mediated immunity host effector mechanisms [59]. Probably the most important host factor that determines the clinical outcome is the age of the cat at the time of infection[25]. Neonatal kittens develop marked thymic atrophy after infection ("fading kitten syndrome"), resulting in severe immunosuppression, wasting and early death. As cats mature, they acquire progressive resistance. Older cats that become infected tend to have abortive or regressive infections or if progressive infection occurs, they have milder signs and a more protracted period without clinical signs [45].

Clinical syndromes associated with FeLV infection can be classified as tumours, immunosuppression, haematologic disorders and other syndromes including neuropathy, reproductive disorders and fading kitten syndrome [17,18]. Most FeLV-infected cats are taken to the veterinarian for anaemia or immunosuppression rather than tumours [67]. Of 8,642 FeLV-infected cats presented to North American veterinary teaching hospitals, various co-infections (including FIV infection, feline infectious peritonitis (FIP), upper respiratory infection, haemotropic mycoplasmosis and stomatitis) were the most frequent findings (15%), followed by anaemia (11%), lymphoma (6%), leukopenia or thrombocytopenia (5%) and leukaemia or myeloproliferative diseases (4%) [67]. The most common FeLV-associated tumours are lymphoma and leukaemia, while other haematopoietic tumours and other malignancies (including neuroblastoma, osteochondroma and others) are much rarer [68-72]. The exact role of FeLV in the genesis of these other tumours is unclear.

Virus-induced fibrosarcomas are very unique neoplasms caused by feline sarcoma virus (FeSV), a recombinant of FeLV that develops de novo in FeLV-infected cats by recombination of the infective FeLV genome with cellular oncogenes. Through a process of genetic recombination, FeSV acquires one of several oncogenes, such as *fes, fms* or *fgr*. As a result, FeSV is an acute transforming (tumour-causing) virus, leading to polyclonal malignancy with multifocal tumours arising simultaneously after a short incubation period. Strains of FeSV identified from naturally occurring tumours are defective and unable to replicate without the presence of FeLV-A as a helper virus that supplies proteins (such as those coded by the env gene) to FeSV. With the decrease in FeLV prevalence, FeSV has also become less common. FeSV-induced fibrosarcomas are multicentric, usually occur in young cats and tend to grow rapidly, often with multiple cutaneous or subcutaneous nodules that are locally invasive and metastasize to the lung and other sites. Fibrosarcomas caused by FeSV are different tumours and should not be mixed up with solitary fibrosarcomas that are classified as feline injection site sarcomas (FISS) caused by the granulomatous inflammatory reaction at the injection site, commonly occurring after inoculation of adjuvant-containing vaccines. Neither FeSV nor FeLV play a role in the development of FISS [73].

Lymphoma

FeLV can act as a major oncogene in cats [6-11,23,74-76] and progressively FeLV-infected cats have a 62-fold increased risk of developing lymphoma [11]. Lymphoma can affect up to 25% of cats with progressive FeLV infection, usually within two years after diagnosis of the infection. FeLV-induced lymphomas are mainly T-cell lymphomas [73]. Multicentric and mediastinal lymphoma are the most common forms, although spinal, renal, ocular and other forms of lymphoma are occasionally reported in FeLV-infected cats.

In the past, young to middle-aged cats (median 7 years) were commonly diagnosed with lymphoma, but more recent data show that lymphoma is currently a disease of mostly older cats with a median age of 11 years [77]. This is likely a result of the decreasing prevalence of progressive FeLV infection as a contributing factor for lymphoma, as cats with FeLV-associated lymphoma are usually younger than cats with lymphoma without FeLV infection [22]. In addition, improvement in veterinary medical diagnostics, access to veterinary specialists and increased owner commitment have led to an increase in the average age of the cat population presented to veterinarians and the likelihood of diagnosing lymphoma in older cats, which also increases the median age of feline lymphoma patients. One study in North America demonstrated an approximately 20% increase in the incidence of FeLV antigen-negative lymphoma compared with the general feline caseload [78].

The association between FeLV and lymphoma has been clearly established: Lymphoma can be induced in kittens through experimental FeLV infection [68,69,71]; cats naturally infected with FeLV have a higher risk of developing lymphoma than uninfected cats [68,79]; and in the past, when the prevalence of FeLV was higher, most cats with lymphoma had progressive FeLV infection. These old studies showed that up to 80% of feline lymphomas and leukaemias were FeLV-related [7,8,74,80], and from the 1970s to the early 1990s, more than 80% of cats with lymphoid malignancies had progressive FeLV infection [7-11]. However, the prevalence of progressive FeLV infection in the general cat population is decreasing and has been recently determined to be only 1 to 5% e.g. in cats in Germany [22,81-83]. The prevalence of progressive FeLV infection is also decreasing in cats with lymphoma worldwide and is now reported to be not more than 21% [62,78,84,85]. The decrease in the prevalence of FeLV has led to a decrease in the incidence of FeLV-associated lymphoma [22,77,78,86-89], and the decrease in prevalence of FeLV infection in cats with lymphoma or leukaemia also indicates a shift in tumour causation. A study conducted at a veterinary teaching hospital in Germany showed that from 1980 to 1995, 59% of all cats with lymphoma were FeLV antigen-positive, but from 1996 to 1999, only 20% were FeLV antigen-positive [77]. This finding confirms results of other recent studies worldwide, in which progressive FeLV infection in cats with lymphoma is far less common than reported in earlier studies and occurs in only 0 to 21% of feline lymphoma cases [28,62,78,84,85,90]. In a recent study in the Netherlands, only four of 71 cats with lymphoma were FeLV-positive, although 22 of these cats had mediastinal lymphoma, which previously was reported to be strongly associated with FeLV infection [85].

FeLV infection can cause tumours indirectly by immunosuppression or more importantly by directly by activating proto-oncogenes or disrupting tumour suppressor genes at or near the sites of feline leukaemia proviral DNA integration (insertional mutagenesis [23,41,91]).

This leads to disruption of the molecular regulatory circuits of cell physiology, the basic principle of tumour development. The most important mechanism for the development of malignancy is insertion of the FeLV genome into the cellular genome near a cellular oncogene (most commonly *myc*). This results in activation and over-expression of that gene and uncontrolled proliferation of these cells (clone). FeLV can also incorporate the oncogene to form a recombinant virus (e.g. FeLV-B, FeSV) containing cellular oncogene sequences that are then rearranged and activated. When they enter a new cell, these recombinant viruses are oncogenic. Thus, FeLV-induced neoplasms are caused, at least in part, by somatically acquired insertional mutagenesis. In a study of 119 cats with lymphoma, transduction or insertion of the *myc* locus had occurred in 38 cats (32%) [92]. Another study suggested that the U3-LTR region of FeLV transactivates cancer-related signalling pathways through production of a non-coding 104 base RNA transcript that activates NF kappaB [93]. Twelve common integration sites for FeLV associated with lymphoma development have been identified in six loci: *c-myc, flvi-1, flvi-2* (contains *bmi-1*), *fit-1*, *pim-1* and *flit-1* [41]. Oncogenic association of the loci is based on the fact that *c-myc* is known as a proto-oncogene, *bmi-1* and *pim-1* have been recognized as *myc*-collaborators, *fit-1* appears to be closely linked to *myb* and *flit-1* insertion was shown to be associated with over-expression of cellular genes, e.g., activin-A receptor type II-like 1 (ACVRL1) [41]. *Flit-1* seems to play an important role in the development of lymphoma and appears to represent a common novel FeLV proviral integration domain that can promote lymphomagenesis by insertional mutagenesis. Of 35 FeLV-related tumours, 5 of 25 thymic lymphomas demonstrated proviral insertion within *flit-1* locus, whereas 0 of 4 alimentary lymphomas, 5 of 5 multicentric lymphomas and 1 of 1 T-lymphoid leukaemia had rearrangements in this region. Expression of ACVRL1 mRNA was detected in the two thymic lymphomas with *flit-1* rearrangement, whereas normal thymuses and seven lymphoid tumours without *flit-1* rearrangement had no detectable ACVRL1 mRNA expression [94]. Some studies also show that variations in the FeLV surface glycoprotein can determine the development of tumours [95].

When lymphoma is caused by FeLV, it is usually because of progressive infection. However, regressive FeLV infection also can be involved in tumour formation, and the prevalence of lymphoma caused by FeLV might be higher than indicated by conventional antigen testing of blood [96]. Cats from FeLV cluster households have a 40-fold increase in FeLV-negative lymphoma compared with cats from the general population. FeLV proviral DNA was detected in lymphomas of FeLV antigen-negative cats [96], and lymphomas have occurred in FeLV antigen-negative laboratory cats known to have been infected previously with FeLV [76]. This suggests that the virus might be associated with a larger proportion of lymphomas than previously thought. FeLV has been shown to incorporate cellular genes, and several such transducted genes, that have been implicated in viral oncogenesis, are also present in regressively infected cells [76,91,97]. The incidence of lymphoma caused by regressive FeLV infection under natural conditions is highly controversial. Two studies reported that regressive FeLV infections occurred in 50 to 52% of antigen-negative lymphomas in older cats (> 7 years) [96,98], while other groups found evidence of provirus in only 1 of 22[97], in 1 of 10 [99] and in 0 of 50 FeLV antigen-negative lymphomas [61] suggesting that regressive infection is only rarely involved in tumour development.

Several studies have compared differences in presentation and outcome of lymphoma in FeLV antigen-negative and FeLV antigen-positive (progressively infected) cats, and the results of a recently published large cohort study are shown in table 3 [77]. In that study, no breed predisposition was found, which is in contrast to the results of other studies in which there was a relatively high incidence of mediastinal lymphoma in young, FeLV antigen-negative Siamese-type cat breeds [78,85,100,101]. These breeds have a predisposition for intestinal lymphoma [102], which suggests that breed predisposition or genetic factors play a role in lymphoma pathogenesis.

The predominant anatomical locations of lymphoma in cats are alimentary (approximately 50%) and extranodal (approximately 25%), mainly kidney and nasopharyngeal [77,78,85,90,103]. The majority of cats with alimentary and extranodal lymphoma are FeLV antigen-negative (96% and 89%, respectively) [77], which indicates a shift from progressive FeLV infection as causative agent to other multifactorial aetiologies, such as chronic inflammation or environmental and genetic factors. The feline gastrointestinal tract, kidneys and nasopharyngeal region are sites where chronic lymphocytic or lymphoplasmacytic inflammation occurs frequently (e.g. inflammatory bowel disease (IBD), dietary allergy, tubulointerstitial nephritis,

Table 3. Comparison of FeLV antigen-positive (progressively infected) cats with lymphoma and FeLV antigen-negative cats with lymphoma in a study including 156 cats with lymphoma (percentages in parentheses indicate percentages of all cats (%) and percentages of cats within the FeLV antigen-positive and -negative group [%], respectively).[77]

Variable and category	All cats evaluated	FeLV antigen-positive cats	FeLV antigen-negative cats	p
n = number of cats	156	20 (13%) [100%]	136 (87%) [100%]	
Median age (years) [range]		3.7 [0.8–13.5]	11.3 [0.7–18]	< 0.001
Sex				0.642
Male	94	13 (14%) [65%]	81 (86%) [60%]	
Female	62	7 (11%) [35%]	55 (89%) [40%]	
Breed				0.379
Domestic shorthair	127	17 (13%) [85%]	110 (87%) [80.9%]	
Mix	7	1 (14%) [5%]	6 (86%) [4.4%]	
Persian	5	0 (0%) [0%]	5 (100%) [3.7%]	
Norwegian Forest	3	1 (33%) [5%]	2 (67%) [1.5%]	
Half Angora	3	0 (0%) [0%]	3 (100%) [2.2%]	
Maine Coon	2	0 (0%) [0%]	2 (100%) [1.5%]	
Domestic longhair	2	1 (50%) [5%]	1 (50%) [0.7%]	
Balinese	2	0 (0%) [0%]	2 (100%) [1.5%]	
Russian Blue	2	0 (0%) [0%]	2 (100%) [1.5%]	
Siamese	1	0 (0%) [0%]	1 (100%) [0.7%]	
Somali	1	0 (0%) [0%]	1 (100%) [0.7%]	
Ragdoll	1	0 (0%) [0%]	1 (100%) [0.7%]	
Anatomical location				< 0.001
Multicentric	15 (10%)	2 (13%) [10%]	13 (87%) [10%]	
Gastrointestinal	80 (51%)	3 (4%) [15%]	77 (96%) [57%]	
Mediastinal	16 (10%)	8 (50%) [40%]	8 (50%) [6%]	
Extranodal	36 (23%)	4 (11%) [20%]	32 (89%) [23%]	
CNS	*4*	*1 (25%) [5%]*	*3 (75%) [2%]*	
Renal	*16*	*1 (6%) [5%]*	*15 (94%) [11%]*	
Nasopharyngeal	*7*	*0 (0%) [0%]*	*7 (100%) [5%]*	
Skin	*6*	*0 (0%) [0%]*	*6 (100%) [4%]*	
Lung	*2*	*2 (100%) [10%]*	*0 (0%) [0%]*	
Retrobulbar	*1*	*0 (0%) [0%]*	*1 (100%) [1%]*	
Lymphoid leukaemia	9 (6%)	3 (33%) [15%]	6 (67%) [4%]	
Overall response to therapy	23/72 (32%)	6/7 [86%]	17/65 [26%]	
CR (complete remission)	14/72 (19%)	0/7 [0%]	14/65 [22%]	
PR (partial remission)	9/72 (13%)	6/7 [86%]	3/65 [4%]	
Median response duration days [range]		25 [17 – 61]	472 [78 – 1156]	< 0.001
Median survival time				
All cats: days [range]		2 [1 – 77]	5 [1 – 1156]	0.131
Treated cats: days [range]		25 [2 – 61]	27 [2 – 1156]	0.271

chronic rhinitis). In cats, chronic inflammation, such as IBD or dietary allergy, is thought to be a precursor of intestinal low-grade lymphoma [104,105] and progression of IBD to lymphoma is reported [106]. This suggests that cats might be predisposed to the development of cancer at or near sites of chronic inflammation. In the past, renal and multicentric lymphomas were frequently associated with progressive FeLV infection; several decades ago, 25 to 31% of renal lymphoma cases were associated with FeLV infection [8,103,107] compared with 0 to 6% in more recent studies [28,77,85,108]. A similar situation is seen in cats with multicentric lymphoma; in the 1980s and 1990s, up to 69% of all lymphomas were multicentric, and 31 to 65% of the cats had progressive FeLV infection [8,96,103] compared with 0 to 13% of cats in more recent studies [28,77,85,90]. Mediastinal lymphoma is uncommon today (10%) [77], but many affected cats have progressive FeLV infection with a prevalence ranging from 19 to 73%

[4,77,96,100,103]. In a study from the Netherlands, only 19% of cats with mediastinal lymphoma were progressively FeLV-infected, but of the cats with lymphoma, all progressively infected cats had mediastinal lymphoma. This most likely reflects the very low prevalence of FeLV (0.3%) among cats in this country [85]. Thus, if a cat is progressively infected with FeLV and develops lymphoma, the tumour will most likely be in the mediastinum.

The results of studies on FeLV as a negative prognostic factor with regard to remission and survival times in lymphoma patients are contradictory [84,85,103,107]. However, in a recent study, FeLV antigen-negative cats with lymphoma had significantly longer remission times (472 days) than FeLV antigen-positive cats (25 days) following treatment [77]. In another study, the median remission and survival times for FeLV antigen-positive cats were 27 and 37 days and for FeLV antigen-negative cats, 146 and 170 days [103]. The prognosis for lymphoma in cats with progressive FeLV infection is poor because of bone marrow suppression, which is usually exacerbated by chemotherapy and can frequently delay treatment. Immunosuppression caused by FeLV infection is also aggravated by chemotherapy, leading to secondary infections that can cause overt clinical signs and impair quality of life. Furthermore, FeLV-associated lymphomas are associated with a higher rate of mitoses [109], possibly indicating a more aggressive biological behaviour that negatively affects outcome. The prognosis is also guarded because of the theoretical risk of the development of additional lymphoid malignancies in cats with FeLV-associated lymphoma. During virus replication, FeLV is integrated into the host genome and recombination with endogenous FeLV-related sequences could form new and more pathogenic variants, such as FeLV-B, with the potential for new lymphoma formation at any time. Finally, owners of cats with progressive FeLV infection and concurrent lymphoma commonly do not comply with treatment and often elect euthanasia.

Conclusions

Lymphoma is a very common tumour in cats, but is only rarely caused by retrovirus infection. There are three retroviruses that have been identified in domestic cats: FeFV, which is common but not pathogenic; FIV, which is associated with an approximately five-fold increase in the risk of lymphoma; and FeLV, which can act as a major pathogen and increases the tumour risk by 62 times. However, because the prevalence of FeLV is low, so is the prevalence of progressive infection in cats with lymphoma. In addition, regressive FeLV infection is not commonly found in cats with lymphoma. Therefore, today, other factors play a much more important role in the development of lymphoma in cats than retrovirus infections.

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Commissioned paper*

Home monitoring of the feline diabetic

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SUMMARY

The home monitoring of diabetic cats is an extremely useful tool with significant benefits for patients, owners and veterinary surgeons. The veterinary surgeon should have a flexible approach towards the tools that are employed to obtain the most satisfactory results for each cat and owner combination. In general, no one single management recipe will be appropriate or successful for all cases; however, the veterinary surgeon should always combine the information obtained from the blood glucose curves with that of the clinical signs displayed by the cat, prior to making any changes or adjustments to the insulin dose. In most cases, performing home monitoring of diabetic cats will result in improved quality of life for the cat and an improved professional relationship between the veterinary surgeon and the owner.

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Introduction

Diabetes mellitus (DM) is one of the most common feline endocrinopathies and its prevalence amongst the mature and geriatric pet cat population seems to be increasing [1]. In around 80% of diabetic cats, the disease is considered to result from similar pathophysiological mechanisms as human type 2 diabetes, which include insulin resistance and β-cell dysfunction [2, 3]. DM tends to affect middle-aged to mature cats, with a peak onset between 10 to 13 years of age [4]. Male cats seem to have a higher risk of developing the disease. The increase in prevalence is likely due to the greater prominence of environmental risk factors of DM, such as: obesity, physical inactivity and the administration of drugs including corticosteroids and progesterone-like drugs [1, 2, 5-7]. DM is most commonly seen in domestic shorthair (DSH) and domestic longhair (DLH) cats. Studies from Australia, the UK and New Zealand have shown that Burmese cats are over-represented in the diabetic population [5, 8].

A diagnosis of DM is usually made when cats present with clinical signs such as polyuria (PU) and polydipsia (PD), which coincide with a blood glucose concentration exceeding the renal threshold (variable, though usually 14-16 mmol/l or 230-280 mg/dl). Cats additionally often present with polyphagia (PP) and in many cases, weight loss.

Historically, the main aims of treatment of feline DM have been to minimise the presence of clinical signs, to provide a satisfactory quality of life and to maintain blood glucose concentrations within an acceptable range (although the definition of "acceptable" has been a variable and arbitrary one). In recent years, the goals for management of feline DM have been expanded, largely due to the increasing realisation that a proportion of cats can achieve diabetic remission [9, 10]. There is no widely accepted definition of diabetic remission in cats, although the one that seems to be most appropriate is, "the presence of normoglycaemia without anti-hyperglycaemic treatment for a minimum of 4 weeks." Remission is thought to occur through the reversal of β-cell dysfunction, mainly via the resolution of glucotoxicity [11]. Although the optimal protocol to achieve remission has not yet been determined, it seems clear that

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the administration of insulin alongside a low carbohydrate diet, to achieve early glycaemic control, seems to improve the chances of remission in cats. Adequate blood glucose monitoring therefore can play a crucial role in this process, assisting the veterinarian to achieve optimal glycaemic control, and in some cases remission. Blood glucose monitoring can also be relevant in those cats that have already entered diabetic remission, even after treatment with insulin is discontinued, as the risk of relapse is high.

Monitoring of diabetic cats

The basic aims of diabetic monitoring are the determination of the right diabetic management strategy and thus establish a good quality of life. This is achieved by reducing blood glucose to a level where there is minimal or absent polyuria, polydipsia, polyphagia, weight loss or risk of diabetic keto-acidosis, whilst preventing dangerous hypoglycaemia. The starting dose of insulin therapy is recommended to err on the conservative side, followed by gradual, infrequent increments, guided by the effect of the chosen insulin dose. Additionally, insulin requirements can, and often do, change even after an ideal dose has been arrived at. After treatment with insulin and diet modification, adequate monitoring is therefore essential to guide the therapy, and most specifically the insulin dose, and ultimately the wellbeing of all diabetic cats.

Various tools are available to the veterinarian and indeed the owner dealing with diabetic pets. Most of those tools until recent years involved regular visits to the veterinary clinic. More recently, the ability to perform home monitoring of diabetic cats is becoming more and more popular as it has multiple advantages for the patient, the owners and the veterinary surgeon (Table 1).

From the owner's perspective, performing home monitoring can represent substantial financial advantages which should not be underestimated, especially in the case of a chronic disease, potentially requiring life-long treatment such as DM. Additionally, in a recent study that investigated the effect that DM has on the quality of life of both cats and their owners, a large proportion of owners mentioned that they wanted to have more control over their cat's disease; additionally, many owners were also concerned about their cat developing hypoglycaemia [12]. Home blood glucose monitoring can help owners feel more involved in managing their cat's disease and being able to measure blood glucose from home can assist with early detection and treatment of hypoglycaemia before it becomes life-threatening. From the point of view of the cat's quality of life, avoiding the stressful effects that frequent visits to the veterinary surgeon can have will always be an advantage. Furthermore, being able to monitor the blood glucose concentration while at home will allow the clinician-owner team to tailor the insulin dose according to the cat's needs, especially during a period in which the cat is showing rapidly changing insulin requirements, such as when entering diabetic remission. From the veterinary point of view, having the owners perform home glucose monitoring can have beneficial effects on their professional relationship with the owners, as they will feel more involved in managing the disease; this can significantly improve compliance. Additionally, performing in-clinic tests such as blood glucose curves will not be fully representative of the cat's daily routine and therefore home-testing may be more representative of the true daily blood glucose fluctuations [13]. In addition to a home blood glucose curve being more representative of the daily routine, one of the potential major advantages of performing home blood glucose monitoring is that stress hyperglycaemia

Table 1: Some suggested advantages of home blood glucose monitoring for owners of diabetic cats, the cats and their veterinary surgeons.

Advantages for the owner	Advantages for the cat	Advantages for the veterinary surgeon
Reduction of veterinary visits & costs	Reduced travel & stress	Improved relationship with clients/improved owner compliance
Greater involvement in the management of the disease	Improved quality of life	Glucose curve performed according to daily routine
Blood glucose curves can be done at any/ convenient time	Early detection of hypoglycaemia	Clinician can request immediate testing +/- curve at any time when concerned
Reduced worry about whether there could be hypoglycaemia		Reduction of stress hyperglycaemia

is less likely to occur in the home environment. Stress hyperglycaemia is a physiological increase in blood glucose which is likely generated by the output of stress hormones (cortisol, glucagon, growth hormone, norepinephrine and epinephrine) and the transformation of lactate generated by muscle contraction (something rapidly achieved during holding for venipuncture). A small study at the author's institution looking at 583 cats, showed that it occurs frequently even when best cat handling practice is adopted and although stress hyperglycaemia might tend to be modest (<270 mg/dl; 15 mmol/l), a broad range of fasting blood glucose values in non-diabetic cats was documented, ranging from 8.2 mmol (148 mg/dl) to 24.8 mmol/l (446 mg/dl).

Home monitoring tools for diabetic cats

There are several tools that the owners of diabetic cats can make use of for monitoring the disease. It is important to remember that in order to get the most out of home glucose monitoring, there has to be a close collaboration between the owner and the veterinary surgeon. On the one hand, owners have the advantage of seeing the cat in the home environment while on the other, the veterinary surgeon will have the clinical training and experience to interpret the information obtained from the owners. The owners should be explicitly instructed not to make any changes to the treatment without discussing it with the veterinary surgeon. Monitoring of diabetic cats should always be multi-dimensional and especially should always involve complete information about clinical signs. Clinical signs will never lie; all glycaemic parameters can and on occasion will do so, especially if clinicians and owners focus only on the numbers of the glycaemic tests and ignore what the clinical picture is telling them. The clinical picture should then be combined with one or more glycaemic parameters such as blood glucose, fructosamine, urinary glucose and/or ketone concentration. Since combining the clinical picture with the glycaemic test(s) of choice is essential, close collaboration between the owner and the veterinary surgeon is key. In addition, each patient-owner combination should be taken into account before identifying which is the best way to monitor a diabetic cat; what is optimal for one household may become a burden in another. In the end, it should be up to the veterinary surgeon and the owner to decide which is the most appropriate in their situation.

The main tools that owners can use to monitor their diabetic cat at home are:

Using the clinical picture

This represents the only monitoring tool all clinicians should be dogmatic about; no glycaemic parameter should ever be interpreted without considering the context of the clinical signs displayed by the cat. The reliability of history and physical examination findings has been well documented [7]. The focus should be on the key clinical signs associated with pathological hyperglycaemia, particularly polyuria, polydipsia, polyphagia and weight loss. Evaluation of the clinical signs of diabetes is also essential when interpreting results obtained in other monitoring tests such as glucose curves, fructosamine concentration, etc. In fact, if these signs are not present or only present in a subtle way, glycaemic parameters suggesting poor control should be mistrusted, unless the owner fails to provide an accurate account of the clinical signs. The author asks the owners to keep a diary of clinical signs including water and food intake and any other clinical signs that may be present, such as vomiting, diarrhoea, etc. They are also asked to monitor their cat's weight (especially during the initial stages of management) as weight changes can be an important indicator of poor glycaemic control. Additionally, the dose and time at which insulin is administered are recorded. This diary is then used to interpret the results of any blood glucose curves performed at home and prior to making decisions about changes in insulin dose; again, the clinical signs are always the starting point. Although it constitutes the key part of monitoring diabetic cats, evaluation of clinical signs as the only monitoring method has significant limitations. For example, a patient who is receiving too much insulin, since he or she is going into remission, will show a perfect clinical picture. However, iatrogenic hypoglycaemia might be just around the corner.

Additionally, a patient whose insulin provides a short duration of action will still show clinical signs; increasing the insulin dose can lead to an excessively low nadir, despite continuing signs suggesting a lack of control. More rarely, an insulin overdose could cause "Somogyi overswing" (or hypoglycaemia-induced hyperglycaemia), which would result in rebound hyperglycaemia and signs of polyuria and polydipsia and, potentially even weight

loss. These signs mirror those seen in cats that are not receiving enough insulin. In summary, adjusting the insulin dose solely on the basis of clinical signs can lead to erroneous and potentially life-threatening decisions.

For those cases in which financial or other reasons prevent further information being collected, such as through the performance of blood glucose curves, the clinician might be forced to solely use the clinical signs as a guide to adjust insulin therapy. In such cases, the owner should be informed of the limitations of this approach and the author recommends a very conservative starting dose and only slow increases in insulin dose (of 0.5 IU/cat/week) until the clinical signs improve. If the clinical signs worsen or if no improvement is obtained when the cat is receiving a dose greater than 1-1.5 IU/kg/injection, further monitoring tools should be used, as these cases are at risk of iatrogenic hypoglycaemia (e.g. in case of short duration of insulin action) or may be showing significant insulin resistance.

Morning urine testing

Morning urine checks for glucose might represent an attractive non-invasive monitoring tool which can easily be practised by a majority of owners at home. This can be achieved by using non-absorbable litter (such as Katkor ®) or using the urine-soaked litter directly on the urine sticks. If urine is negative for glucose, this should trigger further evaluation, as it may represent possible over-dosage or the onset of remission; this finding should therefore be followed by blood glucose determination at home or at the veterinary clinic. It remains true however that, on its own, urine glucose measurements should not be used to trigger an increase in insulin dose, given the potential for stress hyperglycaemia to induce glucosuria, as well as for Somogyi overswing (hypoglycaemia-induced hyperglycaemia) to do the same. Although evaluation of urine glucose is an accessible tool for many owners of diabetic cats, it has limitations, as the concentration of glucose in the urine depends on the renal threshold of the individual, the absolute amount of glucose excreted as well as the overall urine output, which therefore can result in small amounts of glucose causing a high reading on a urine dipstick assessment, despite only mild hyperglycaemia or even euglycaemia. For these reasons, the author never ascribes any importance to the actual concentration of glucose in the urine. Additionally, evaluation of urine glucose concentration can be challenging in multi-cat households as multiple cats may urinate in the same tray. Evaluation of urine for the presence of ketones can also be helpful as it may be suggestive of poor control or impending diabetic keto-acidosis.

The author provides the owners with urine sticks (usually capable of detecting both glucose and ketones, such as Keto-diastix ®) and asks the owners of newly diagnosed cats to test the first urine of the morning once daily for the first week of treatment. The owners are asked to contact the practice if the cat has no blood glucose for three days in a row (or less if the cat is showing signs compatible with hypoglycaemia) or if there are ketones for three days in a row (or less if the cat is unwell). Urine glucose and ketone evaluation can be performed less frequently when the cat is clinically stable; once a week testing is acceptable for stable cats, alternatively, owners can be told to test at their discretion if they have any concerns about their cat or after changes to the insulin dose.

Spot blood glucose testing

Checking a single blood glucose at the time of a previously detected nadir (on the basis of a previous blood glucose curve) is still relatively popular and some veterinary surgeons recommend that this is done at home by the owners in order to help assess the insulin dose that should be administered. However, this is explicitly not recommended, as the timing and magnitude of the daily nadir will vary significantly due to documented inter-day variability of blood glucose curves (see below).

Additionally, stress hyperglycaemia occurs relatively frequently in cats and although this effect might be reduced when checking blood glucose at home, a spot blood glucose test cannot be fully relied upon, as there may be other stressors in the cat's environment at the time when the cat is tested. For all these reasons, spot blood glucose testing at a set time point (e.g. at the time a previous nadir was documented) is regarded as unhelpful, unless it happens to reveal hypoglycaemia; following the same reasoning, this author does not support or use diabetic management protocols that employ daily or within-day insulin dose changes on the basis of single glucose measurements.

Spot blood glucose testing can however be temporarily useful to monitor an animal in or about to enter diabetic remission, or cats that happen to be inappetant due to concurrent illness. In such cases both a pre- and post-

Table 2: example of the insulin dosing guidelines provided to the owner of a diabetic cat on the basis of pre-injection spot home blood glucose testing in anorexic cats or those about to enter diabetic remission

Blood glucose concentration (before food and insulin)	**Recommended insulin dose**
>15 mmol/l (270 mg/dl)	Full dose of insulin (minimum of 1 IU)
10-15 mmol/l (180-270 mg/dl)	½ dose of insulin (minimum of 0.5 IU)
8-10 mmol/l (144-180 mg/dl)	¼ dose of insulin (minimum of 0.5 IU)
<8 mmol/l (144 mg/dl)	No insulin

prandial sample might be of interest. In these cases, the insulin dose that the cat receives can be calculated depending on the spot blood glucose concentration. The author does not have standard recommendations for these patients and recommends that the decision is made on the basis of the insulin sensitivity previously documented in each individual cat; however, an example of the recommendations that the author makes in the clinic can be seen in Table 2.

Home blood glucose curves

The glucose curve is still the only glycaemic tool that at least has the potential to give clinicians useful detail concerning how effective the diabetic treatment is and what insulin dose, insulin type or diet changes should be implemented. Having the potential to look at glucose nadir and insulin duration of action makes this tool unique compared to other glycaemic indices. Home blood glucose monitoring has become very popular in recent years and more and more veterinarians and owners are starting to make use of this powerful tool. However, quality of life investigations suggest that clinicians should not force home blood glucose monitoring upon ALL pet-owner combinations. In fact, home blood glucose monitoring could prove to be an unwanted extra burden for some, on top of the daily necessity of insulin injections. In a modern veterinary practice this option should however be at least offered, also since it might reduce the costs involved in the monitoring process and it may ease some of the concerns and anxiety that some owners have in relation to their cat's diabetes [12]. Some owners may not be prepared to perform home glucose monitoring at the time when the diagnosis is made, as coping with the injections may already seem overwhelming; however, a large proportion of owners can become quite proficient at testing their cat's blood glucose [13, 14]. It is important that owners receive appropriate training by the veterinary surgeon or nurse in charge of the case; they can also be directed to some online resources (Table 3) that will help them learn to perform the task. Overall, the ear or metacarpal/metatarsal accessory pads are considered appropriate places to obtain the small amount of blood needed for this purpose.

Several handheld glucometer devices are currently available, although clinicians should be aware of significant under- and over-estimation of blood glucose values when using particular brands and particularly when using glucometers made for humans. Recent validation of veterinary handheld devices for blood glucose monitoring of cats and dogs such as the Alphatrak® device (Abbot Animal Health, Illinois, USA) [15] has greatly reduced these concerns. If finances prohibit the purchase of these specific devices, it might be wise to run an initial blood glucose curve using both the handheld human glucometer the cat owner will be using at home and the in-clinic biochemistry analyser. This will help to get a feel of the difference in obtained values for that particular hand-held device. Recent research has emphasised that

Table 3. Online learning resources for owners performing home blood glucose testing

Website	**URL**
International cat care	http://www.icatcare.org/news/diabetes-awareness-week
Royal Veterinary College Feline Diabetic Remission Clinic	https://www.facebook.com/RVC.Diabetic.Remission.Clinic/videos
Veterinary partner Diabetes Mellitus Center	http://www.veterinarypartner.com/Content.plx?A=631

clinicians should guard against over-interpretation of one single blood glucose curve, especially if the curve contrasts with the clinical picture. The latter is likely explained by observed significant day-to-day variation in serial blood glucose determinations [16, 17]. Therefore, if the clinical picture does not fit (steady body weight, only subtle polyuria and polydipsia), a "bad curve" should not elicit a dose change. Repeating a curve on a second occasion might then be the best next step, or adding an alternative glycaemic parameter such as the measurement of fructosamine concentration may be indicated.

Stress hyperglycaemia might explain the discrepancy between the clinical picture and a curve; if this happens repeatedly, blood glucose curves, might not be suitable for that particular patient and alternative monitoring tools should be employed.

Various 'curve-recipes' exist, each with advantages and disadvantages; the author prefers to ask the owners to perform glucose estimations every two hours from the first insulin injection until the second (the curve should always include blood glucose measurements performed just before food and insulin administration). On some occasions, an increase in the sampling frequency (to every hour) can be recommended when the blood glucose ventures below 10 mmol/l (180 mg/dl) in an attempt to quantify the lowest blood glucose value (nadir). This nadir value will determine the scope for further insulin dose increases and therefore is a very useful parameter. Occasionally, if the information obtained in the blood glucose curve and clinical signs raise any concerns such as the presence of insulin resistance, the owner will be asked to bring the cat to the clinic and further investigations will be performed as necessary.

In general, the author does not recommend performing home blood glucose curves more often than once every 7-10 days as the effect of any change to the insulin dose will not be fully appreciated until then. Additionally, over-zealous testing of blood glucose (even if this is done at home) can offset some of the advantages of home testing, as it can become stressful for the cat to have blood samples taken too often. In general, the author suggests more frequent monitoring at the time of diagnosis until stabilisation is achieved; after this, the focus is on the evaluation of clinical signs and performance of blood glucose curves if the owners have specific concerns or if there are signs that suggest that the cat may be entering diabetic remission. Additional in-clinic investigations may need to be performed in those cats that have poorly controlled diabetes (Table 4).

Modification of insulin dose after a blood glucose curve

Practice protocols dictating the glycaemic targets and the insulin dose changes depending on set specific blood glucose (or other glycaemic) values can help to provide certainty to those that feel out of their depth in the field of diabetes management. Studying the recommendations from various experts in the field, a multitude of differing protocols could be (and have been) designed for this purpose, undoubtedly leading to owners (and veterinarians) being confused when comparing the different recommendations from practices and hospitals. Some examples include those that advocate relatively intensive insulin dosing and monitoring protocols aimed at obtaining diabetic remission. However, the current available evidence [11] is far from robust enough to justify these protocols, especially, since they come with a greater hypoglycaemia potential than more conservative, traditional protocols. Therefore the author does not routinely recommend or support protocols suggesting daily dose changes (apart from the specific exceptions mentioned above) or those that aim for blood glucose concentrations too close to the hypoglycaemic range. When considering developing or following already established protocols for insulin dosing, it should be remembered that no two patients are alike: each patient will have a different insulin sensitivity (which will also vary over time) and therefore will respond differently to a dose change (compared to the next patient, often also when compared to the same patient a month ago). The author therefore does not follow a set detailed hospital protocol for the management of diabetes. Whether to design a protocol for one's own practice is an individual choice and can certainly be justified despite the above concerns. Overall, a few aspects should be borne in mind during their design. Firstly, clinicians should always ensure the clinical picture is being incorporated in any assessment. All too often, having a practice protocol attempts to make diabetes a mathematical disease with management by numbers, which, given the accuracy concerns inherent in all of the above-mentioned glycaemic parameters and the dynamic nature of the disease, will lead to problems. Secondly, no two pets are the same, and no two owners are the same, therefore some changes may be acceptable for some pet-owner

Table 4. Suggested path of diabetic monitoring after the diagnosis of DM

Newly diagnosed
Baseline haematology, biochemistry, urinalysis and culture
+/- Fructosamine concentration
Record baseline body weight
Initiation of insulin treatment: 0.25-0.5 IU/cat/12h
In-clinic blood glucose curve (to exclude hypoglycaemia, NOT to aim for optimal control)

Owner support
• Demonstration/instruction of how to inject insulin
• Explanation of treatment
  o Dietary changes (start introducing low carbohydrate diet)
  o Insulin
  o Other treatments if necessary (if concurrent disease)
• Explanation of clinical signs to monitor for (including hypoglycaemia)
• Suggest/discuss the option of home glucose monitoring
• Demonstrate how to perform blood glucose testing for motivated owners

Home monitoring
• Urine sticks for glucose and ketones to be used every morning initially
  o Veterinary surgeon to be contacted if ketonuria or no glycosuria (see notes)
• Diary of clinical signs
  o Veterinary surgeon to be contacted if signs of hypoglycaemia or if other concerns exist

7-10 days after diagnosis and 7-10 days after each dose change
Review at the clinic: full clinical examination and record of body weight
Discuss diary of clinical signs and urine glucose/ketone records
Blood glucose curve (in-clinic or at home) • Adjust insulin dose (see table 5) AFTER also reviewing clinical signs
Owner support • Discuss challenges • If not yet being practised: discuss home monitoring options   o Discuss home blood glucose monitoring if appropriate
Long term diabetic cats
Clinically stable • Intermittent urine glucose/ketone check • Diary of clinical signs • Regular weight checks • Blood glucose (BG) curves when concerned • Spot BG if concerned about hypo (remission possible, see Table 3) • Fructosamine (if concerned) **Clinically unstable** • Clinic visit • Evaluation of diary of signs • Further investigations (Blood tests, including fructosamine, urinalysis) if indicated • BG curve (at home or in clinic) • Consider changes to insulin dose or type (Table 5)

combinations and not for others, e.g. insulin dose increases should be done in a slower fashion in those cases in which the cat spends large periods of time alone at home, as the owners may not be present if the cat develops hypoglycaemia; in such cases, those changes may need to be implemented during weekends or holiday periods when the owners can monitor the cat more closely.

In summary, it seems appropriate to have 'guidelines' and 'principles', though we have to be aware that a 'protocol' may cause us to deal with these patients in a simplified and incorrect way, because they more often than not they do not fit with the protocol or their glycaemic parameters might be deceiving us.

An example of potential guidelines for adjusting insulin dose on the basis of home blood glucose curves can be seen in table 5.

Table 5. Example guidelines for adjusting insulin dose based on blood glucose curves (blood glucose measured ideally every 2h).

Blood glucose concentration	Suggested insulin adjustment
Nadir <5 mmol/l (90 mg/dl)	Reduce insulin dose by 50% or by 0.5-1iu/cat/12h
Nadir 5-10 mmol/l (90-180 mg/dl) and rest of the curve <15 mmol/l (270 mg/dl) for most measurements	Maintain current dose of insulin
Nadir >10 mmol/l	Increase insulin dose by 0.5-1iu/cat/12h
Nadir 5-10 mmol/l but rest of the curve >15 mmol/l (270 mg/dl) for most measurements	Consider switching insulin type/change in feeding regime
Pre-insulin blood glucose <5 mmol/l (90 mg/dl)	Withhold insulin
Pre-insulin blood glucose 5-10 mmol/l (90-180 mg/dl)	Reduce insulin by 50 % (minimum of 0.5 IU)

* All blood glucose curves should always be interpreted together with the clinical signs displayed by the cat. If there is any discrepancy, preference should be given to the clinical picture and not to the blood glucose curve values. The exception is when hypoglycaemia is detected, which should always prompt a reduction of insulin dose, even in the absence of clinical signs*

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Commissioned paper*

Feline Endocrine Hypertension

Beate Egner[1]

SUMMARY

Endocrine hypertension in cats is more prevalent than previously thought. Predominant causes are primary hyperaldosteronism (Conn's disease), hyperthyroidism and diabetes mellitus. Other endocrine disorders with an impact on blood pressure rarely occur in the cat. Reliable measurement of both systolic and diastolic blood pressure is vital in identifying hypertension associated with these disorders. An understanding of blood pressure regulation and of the pathophysiology of hypertension development facilitates appropriate diagnostic and therapeutic efforts. Even if other causes of hypertension in a patient are found such as chronic kidney disease, it is important to realize that an underlying endocrine disorder may have been precipitating the renal damage.

Key words: cats, hypertension, hyperaldosteronism, hyperthyroidism, diabetes mellitus, blood pressure Doppler flow meter, High Definition Oscillometry

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Go to http://www.ejcap.org to see the online presentation of this paper.

Introduction

With the advent of easier to use and more reliable non-invasive blood pressure monitors more routine screening of cats has been carried out and feline hypertension is increasingly recognized. Elevated blood pressure can be referred to as secondary hypertension if an underlying disease is present that is known to cause high blood pressure. Hypertension with no evident underlying disease should be termed idiopathic. As in human medicine, systemic hypertension can be subdivided into isolated systolic, isolated diastolic and combined hypertension and all three can cause target organ damage. Underlying causes of feline hypertension are mainly chronic kidney disease (CKD) and endocrine diseases such as hyperthyroidism, hyperaldosteronism, hyperadrenocorticism and diabetes mellitus.[8] With CKD hypertension is common and therefore is frequently screened for. When searching for endocrine causes of hypertension, hyperthyroidism is often the only disease considered. This leads to missed diagnoses such as hyperaldosteronism (Conn's disease) but also hyperadrenocorticism and diabetes mellitus.
Endocrine hypertension is also under-diagnosed as a result of the choice of diagnostic tools used. With the Doppler flow meter (Doppler), diastolic blood pressure usually cannot be reliably diagnosed. For this reason, and because systolic measurements often underestimate systolic pressure (closer to mean), studies performed with that technology may not reflect the true blood pressure situation. Understanding basic blood pressure regulation but also understanding the features and limitations of the technology in use, are as important as knowledge of symptoms of the possibly underlying disease and its diagnosis.

Regulation of blood pressure

Blood pressure is regulated by many mechanisms, including the central nervous system, the baro- and chemoreceptors, the sympathetic and parasympathetic nervous system, circulating hormones and local metabolites acting on vasodilation and vasoconstriction (see Table 1). This complex situation explains the variances in measurement even in a completely relaxed animal and supports the

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Table 1: Main influences on systemic vascular resistance (SVR) affecting blood pressure[26]

Source	Increase of SVR	Decrease of SVR
Neurohormonal	Increased activation of the sympathetic NS	Decreased activation of the sympathetic NS
Endothelium	Endothelin I, Thromboxane A2	Prostacyclin, nitric oxide
Circulating hormones	Epinephrine (adrenalin), norepinephrine (noradrenalin), angiotensin II, antidiuretic hormone	Atrial natriuretic peptide, kinins, histamine
Other factors	Decreased temperature	Increased temperature/K+/ lactate/ PaCO2/pH

need for a stress-free environment and procedure when measuring blood pressure.

Blood pressure (mean arterial pressure – MAP) is determined from cardiac output (CO) and total peripheral resistance (TPR):

MAP = CO x TPR

CO = stroke volume (SV) x heart rate (HR)

SV = diastolic filling x contractility

TPR is mainly affected by vascular status (systemic vascular resistance /SVR - vasolilation vs. vasoconstriction). Blood viscosity can further contribute but plays a minor role.

Hypertension occurs when the regulation of blood pressure lacks negative feedback after a compensatory up-regulation, initiated by direct or indirect hypovolaemia.

One of the most important mechanisms involved in the development of hypertension is the renin-angiotensin-aldosterone system (RAAS). Decreased arterial pressure, decreased tubular sodium/chloride and activation of the sympathetic nervous system lead to renin secretion, transforming angiotensinogen into angiotensin I and then via the angiotensin converting enzyme (ACE) activating angiotensin I to angiotensin II.

Angiotensin II effects are manifold, such as increasing sympathetic activity, tubular sodium and chloride reabsorption and consequently water retention accompanied by potassium excretion. It has an effect on the adrenal gland, leading to aldosterone secretion, further contributing to water retention. Aldosterone production can also be stimulated by increased potassium levels. Javadi et al. (2005) pointed out that aldosterone leads to glomerular sclerosis, tubular atrophy, arteriosclerosis and interstitial fibrosis, explaining the close relationship between hyperaldosteronism and CKD.[25]

Angiotensin II is also known to act as a very potent vasoconstrictor, directly affecting blood pressure. It increases ADH secretion via stimulation of the pituitary gland, stimulating water absorption in the collecting duct.

All these influences lead to an increase in blood pressure. Angiotensin II further acts on the podocytes of the basal membrane of the glomeruli leading to proteinuria. It is a growth factor and activates other growth factors (e.g. prostaglandin 2∝) resulting in glomerulosclerosis and arterial stiffening, which further increases SVR. Thus angiotensin II and aldosterone both have an effect on endothelial function.

Reliable blood pressure measurement

Since the American College of Veterinary Internal Medicine (ACVIM) Hypertension Consensus Panel published guidelines for the diagnosis and management of hypertension in dogs and cats[8], standards have been set up to evaluate non-invasive blood pressure units.

These guidelines require a unit to be tested against a true gold standard invasive technique. For a direct method to be considered a gold standard, the technique has to be performed properly with the system being calibrated statically but also dynamically and accuracy has to be verified if a water filled catheter with external transducer is used (determination of dynamic range and damping coefficient). Ideally the pressure transducer is placed inside the artery. Direct blood pressure is not a gold standard if not performed correctly and without an understanding of the limitations of this blood pressure measurement technique.[39,21]

ACVIM Guidelines[8]:

- Evaluation in comparison with invasive technology in conscious dogs and cats.
- Evaluation in compliance with adapted standards according to the Association for the Advancement of Medical Instrumentation (AAMI):
  - Mean difference (bias) of paired measurements ± 10 mmHg, standard deviation max. 15 mmHg
  - 50% of measurements within a deviation of max. 10 mmHg, 80% of measurements within a deviation of max. 20 mmHg

Table 2: HDO results compared to ACVIM guideline requirements[36]

Parameter	Bias (mmHg)	% of paired measurement within 10 mmHg	% of paired measurement within 20 mmHg
ACVIM guideline requirements	±10 mmHg	50%	80%
Martel al. (2013) [35]	-2.2 ± 1.1	88 % ± 3	96% ± 2

- Published in a peer reviewed journal

Neither Doppler flow meter nor conventional oscillometric devices (e.g. petMAP®, SurgiVet®, Cardell®) fulfilled these guidelines.[8,35,47,13] Very recent data even suggest that Doppler cannot be considered as a reliable technique in cats to determine blood pressure.[13]

Martel et al. (2013) compared high definition oscillometry (HDO) to a Data Sciences International™ implanted system and challenged blood pressure pharmacologically to reach hypotensive and hypertensive situations in conscious cats.[35] Systolic arterial pressure (SAP) showed a mean correlation coefficient of 0.92 ± 0.02 with individual correlation as high as 0.98 and for DAP 0.81 ± 0.02. The slightly lower correlation for diastolic arterial pressure (DAP) was discussed as being due to the difference of arterial wall structure in more central versus peripheral arteries.[35] In this study, ACVIM requirements have been fulfilled (Table 2). Similar results have been shown in dogs.[37,38]
In summary, the authors conclude that, 'HDO is the first and only validated non-invasive blood pressure device and, as such, it is the only non-invasive reference technique that should be used in future validation studies.'[35]

HDO non-invasive pulse wave analysis (PWA)

HDO is a patented new technology, allowing very sensitive and fast analysis of incoming signals and even real-time assessment of the pulse wave (Fig 1). Due to its speed it scans incoming signals and actually measures all 3 pressures: systolic, diastolic and mean arterial pressure compared to conventional oscillometry which only measures the strongest signal as mean arterial pressure, calculating systolic and diastolic pressure with an algorithm. This also allows for pulse pressure interpretation (pulse pressure = systolic – diastolic pressure), currently considered to be much more closely correlated to pressure induced arterial damage and remodelling than either systolic, diastolic or mean arterial pressure.[6,27]

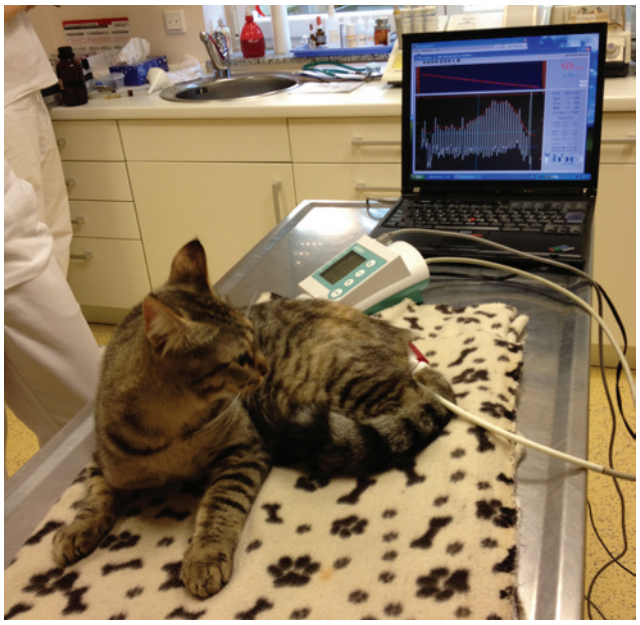

Fig 1. A feline patient linked up to a high definition oscillometry (HDO) device. Blood pressure is also being measured.

HDO visually displays the pulse waves in real time on screen, offering additional features to the practitioner:

1) Visualisation of the reading quality: identify a good reading and immediately realise if artefacts occur.
2) Rhythm information: similar to an ECG. The pulse wave-to-pulse wave interval is the same as R-R intervals on an ECG. Different intervals reflect an arrhythmic situation (Figs. 2a and b).
3) Information on arterial compliance (systemic vascular resistance /SVR): early presystolic amplitudes provide information on arterial compliance.[1,2,16] Main influence on arterial compliance can be expected with an increased activity of angiotensin II and in the case of arterial remodelling (angiotensin II and aldosterone mediated) being present. Impaired arterial compliance/ arterial stiffness can be identified in an increase in size of the pre-systolic amplitudes (Fig. 2c).
4) Information on stroke volume variances (SVV). In a stable cardiac output situation, pulse wave amplitudes increase and later decrease consistently beat by beat, whereas they differ in height if there is any impact on stroke volume, like arrhythmias, mitral regurgitation,

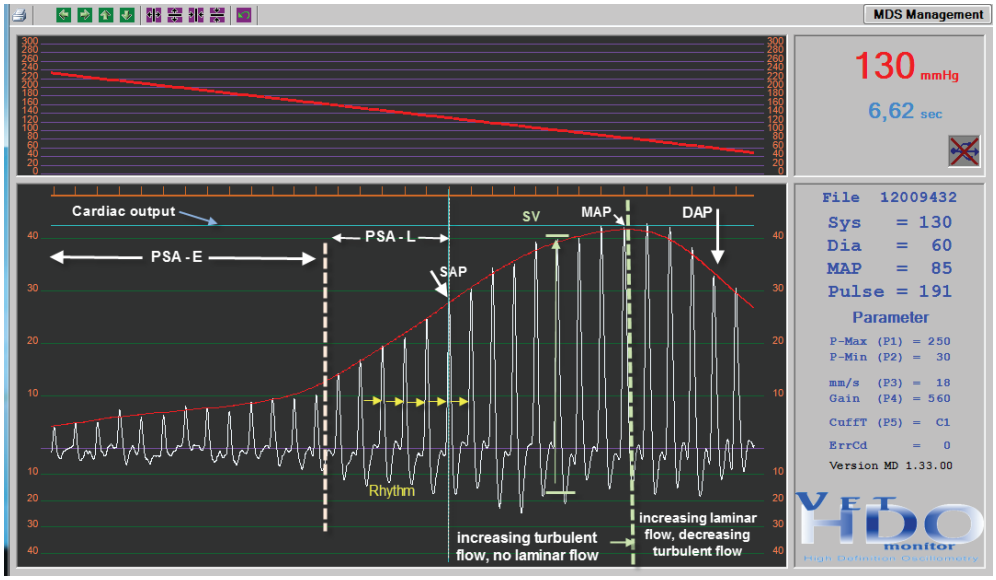

Fig. 2a. Normal HDO curve of a complete reading. From the right: pre-systolic amplitudes (PSA), followed - with continuous deflation of the cuff - by the opening behaviour of the artery (bell shape). Due initially to turbulent flow, amplitudes gradually increase up to a maximum: mean arterial pressure. At this stage, centrally laminar flow can be found resulting in decreasing amplitude height.

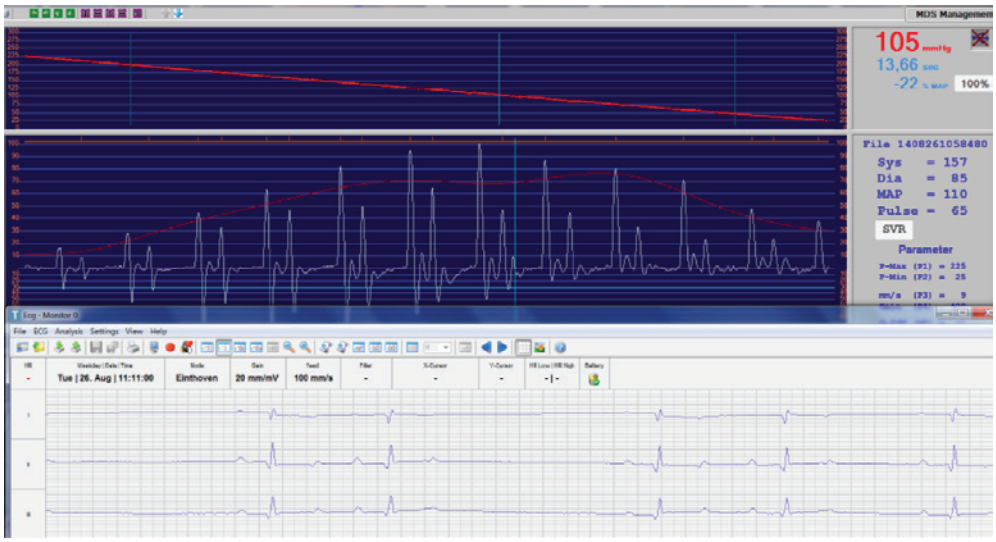

Fig. 2b. HDO curve with intermittent sinus arrest. Note the impact of the arrhythmia on stroke volume (SV) due to prolonged diastolic filling, increased contraction due to the Franck Starling law.

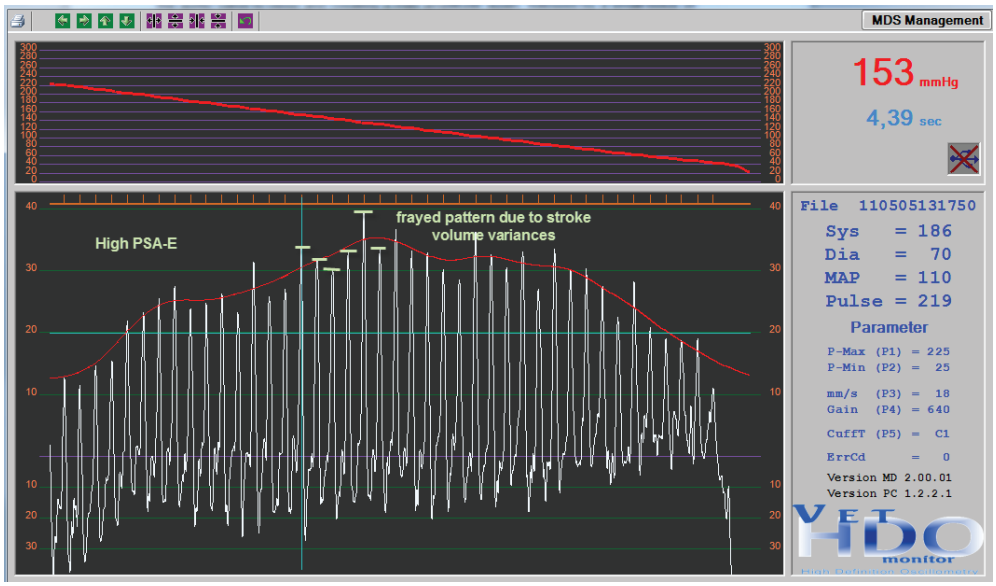

Fig. 2c. HDO curve of a cat with severe systolic hypertension. The first amplitudes - referred to as early Pre-Systolic Amplitudes (PSA - E) - are high, indicating increased systemic vascular resistance (SVR). Stroke volume beat-by-beat varies (height of single amplitudes).

aortic stenosis, myocardial disease etc. (Fig. 2c). SVV can be interpreted qualitatively to add information about the severity of the haemodynamic impact of such a situation and consequently, it may support the decision, how aggressively for e.g. an arrhythmia needs to be treated.

These additional features of the HDO technology might be particularly helpful in diagnosing endocrine hypertension and related cardio-vascular changes.

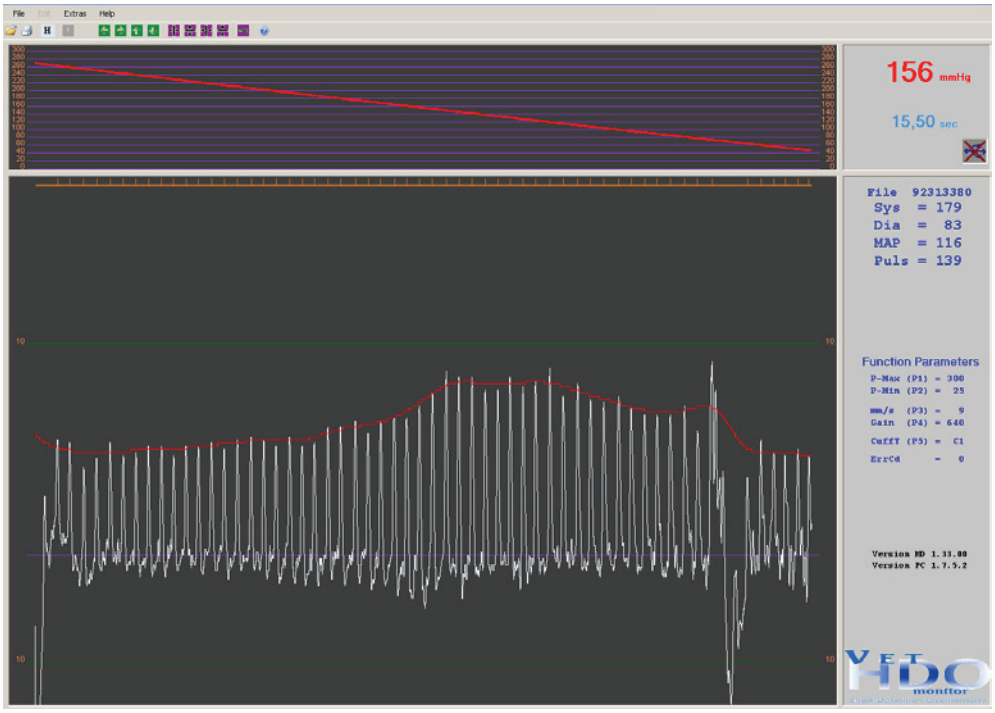

Fig. 2d. A cat with hypertensive left ventricular hypertrophy. High pre-systolic amplitudes (at the beginning of the trace) indicate impaired systemic vascular resistance, overall height of the bell shape curve is below 10% (10 at the left and right side of the window) indicating impaired cardiac output, single amplitude are more or less stable (no significant stroke volume variances). At the last part of the reading, an artefact appears.

Measuring blood pressure in a clinical environment

Blood pressure measurement today can be done easily and rapidly. Blood pressure is continuously influenced by different regulatory mechanisms so that it is possible to see considerable variation in sequential readings. Because of this, a minimum of three or better five consecutive readings should be performed and the average interpreted. With the right protocol, this only takes 2-3 minutes, which can easily be integrated into the normal physical examination of a patient. It is important to follow the ACVIM guidelines[8] for accurate measurement:

1) **Quiet environment.** This simply means: heavy traffic areas and sudden noises need to be avoided. In particular also one should ensure that nobody comes in or leaves the room while running a measurement (Fig 3).
2) **Observe the cat** while you obtain history details from the owner. The observation will give you important information regarding behaviour that can help you decide which position the cat might tolerate. Blood pressure measurement should ideally be at the beginning of a physical exam since taking of rectal temperature and blood sampling, can significantly influence blood pressure.[7] In general; the less an animal needs to be restrained, the better. Cats can be measured in their carrier, on the table (ideally on a blanket or towel) or on the owner's lap.
3) **Special attention should be paid to the animal.** During the measurement, they should be kept calm and reassured to avoid agitation and sudden movements. Watching the pulse waves and the animal during the measurement further aids in detecting artefact and determining its likely source. Readings should be taken one after another. As a single reading only takes 8-15 seconds in cats, the whole measurement cycle can be finished in 2-3 minutes.

Fig 3. A quiet, safe environment is essential for reliable blood pressure measurements in cats.

4) **Position the cuff at the same height as the base of the heart.** This is usually the case when the cuff is positioned on the tail or a limb when the animal is lying down. If an animal is standing this is usually only the case on the base of the tail. Tail measurements are less prone to artefacts even with some movement. Overall, tail measurements are easier, better tolerated and it is usually the fastest way to get 3-5 good readings.
5) **Score the environment and the patient** to better judge the possible influence of stress. Analyse the pulse waves for stress influence, too. This helps to differentiate true hypertension from stress induced or 'white coat' hypertension. Information given by the pulse waves can be: frayed pattern, due to the impact of catecholamines on stroke volume variances, mildly elevated pre-systolic amplitudes as a result of mild vasoconstriction due to catecholamines, and comparing the pulse waves of consecutive readings. With stress related changes, pre-systolic amplitudes should decrease with time (in contrast: hypertensive pulse waves reflect same situation over all readings).

Definition of Hypertension

In 2007, the ACVIM hypertension consensus panel published guidelines, which also included a classification system for hypertension which is widely accepted (Table 3).[8]
It is based on the risk for target organ damage (TOD) in relation to both systolic and diastolic blood pressure. ACVIM consensus guidelines do point out that it is important to evaluate both systolic and diastolic blood pressure.
Prevalence of hypertension in a large feline population was shown to be at least 31%.[11] Based on this, it is vital that blood pressure measurement be carried out in cats with symptoms for which hypertension cannot be excluded. As 84% of the affected cats in that study were older than 10 years, blood pressure should be measured as part of the routine physical examination of geriatric cats.[11] This is also reflected in the AAFP guidelines which recommend blood pressure measurement in all cats over 11 years of age.[54]

The kidney can be involved in hypertension as a target organ for damage but also as the source of hypertension. Kidney disease results in impaired auto-regulation, so that systemic hypertension can easily lead to glomerular hypertension, proteinuria and thus further damage to the kidney. In fact, up to 100% of cats with hypertension and TOD to the eyes show signs of chronic kidney disease.[45,34,32] As azotaemia is not always present in cats with early stages of kidney disease, blood pressure, urine specific gravity, UPC (Urine protein/creatinine ratio) and pulsewave analysis for detection of an increase in systemic vascular resistance (SVR) due to angiotensin II mediated vasoconstriction may increase suspicion of early CRD (Fig. 2d).

Endocrine hypertension in cats

Hyperthyroidism

The published prevalence of hypertension with hyperthyroidism is variable. Values range from 9% to 87%.[31,40,56] Part of this variation can be explained by differing blood pressure technologies, differing definitions of hypertension and variability caused by use of just systolic or systolic and diastolic pressures. In some studies additional criteria were used to define hypertension, especially with regard to the presence of hypertensive retinopathy or choroidopathy.

The pathophysiology of blood pressure related changes in hyperthyroidism has been thoroughly looked at in human medicine. The main trigger has been found to be the direct and indirect impact of tri-iodothyronine (T3). The T3 effect on vascular smooth muscle in combination with an increase of local vasodilators leads to a decrease in systemic vascular resistance (SVR). With an increase of vasodilatory influences, diastolic blood pressure drops, causing a reflex dependent increase in cardiac output due to an increase in stroke volume and heart rate. This

Table 3. ACVIM consensus guidelines for classification of elevated blood pressure[8]

Risk of TOD	Risk category	SBP mmHg	DBP mmHg
Minimal	I	<150	<95
Mild	II	150-159	95-99
Moderate	III	160-179	100-119
Severe	IV	>180	>120

TOD = target organ damage, SBP = systolic blood pressure, DBP = diastolic blood pressure

Table 4: Target organ damage in cats (video for examination for target organ damage to the eyes and to the heart)[17]

Target Organ	Symptoms	Prevalence	Reference
Eye	Hypertensive retinopathy/choroidopathy (tortuous retinal vessels, (punctate) retinal haemorrhage, focal bullous or complete retinal detachment and consequently sudden onset of blindness, hyphaema, mydriasis, anisocoria etc.	60-80% Most often reported with SBP >168 mmHg	Sansom et al. 1994, Syme et al. 2002, Elliott et al. 2001
Cardio-vascular	Left ventricular hypertrophy, Echo: mainly asymmetric concentric hypertrophy resulting in a functional mitral valve insufficiency and systolic murmur, gallop rhythm, arrhythmia, possible findings in EKG: wide QRS complexes, high R wave, wide P wave, deep S wave, X-Ray: wide/tortuous thoracic aorta, epistaxis	Over 70% - 85% If additionally retinal damage can be found, cardiac remodeling is more severe	Elliott et al. 2001, Snyder et al. 2001, Chetboul et al. 2003
CNS	Hypertensive encephalopathy, hyperplastic arteriosclerosis of cerebral vessels, oedema, (micro) haemorrhages and consequently increased intracranial pressure leading to CNS symptoms: ataxia, seizures, vocalization, head pressing, somnolence, sudden onset of aggression or other behavioral changes	29 - 46 % Mainly severe hypertension or sudden severe increase of blood pressure	Littman 1994, Maggio et al 2000 Brown et al. 2005
Kidney	Glomerular hypertrophy, glomerulosclerosis, interstitial fibrosis, development/progression of azotaemia, decrease of GFR, proteinuria, microalbuminuria	53% - 62%	Chetboul et al. 2003 Syme et al. 2006 Jepson et al. 2007

increase is mild and does not lead to a significant increase in systolic blood pressure. Still elevation in systolic blood pressure can be found in some hyperthyroid patients and may be a result of activation of the RAAS in response to a reduced renal perfusion due to vasodilation.[43,42,29,33] Also an up-regulation of RAAS in direct response to hyperthyroidism has been suggested by Williams et al. (2013), as levels became normal with treatment as a result of reaching euthyroidism.[56] Elevated blood pressure might also be attributed to a higher blood viscosity through stimulation of erythropoietin by T3.[33] Additionally, there is a direct effect of T3 on the heart. It upregulates ß-receptors in the myocardium leading to positive inotropy and chronotopy. Additionally, T3 mediated effects on alpha myosin and beta myosin as well as calcium-activated ATPase contribute to increased myocardial contractility.[20] This explains, why hypertension can be seen in some hyperthyroid patients independently of underlying kidney disease. If the unmasking of kidney disease occurs with treatment of hyperthyroidism, blood pressure can rise immediately, while in the absence of underlying kidney disease there was a median time of 5.3 months till blood pressure rose.[40] It is important to realize that initially normotensive cats with hyperthyroidism can develop hypertension with treatment initiation (23% in one study).[56] This supports the importance of implementing regular blood pressure measurements in cats with hyperthyroidism, both at initial diagnosis and during treatment.

What blood pressure-related information can be expected?

- Mild to moderate systolic hypertension
- Normal to decreased diastolic blood pressure
- Increased pulse pressure
- Increased heart rate
- Changes in HDO pulse wave analysis can include: frayed pattern due to stroke volume variances, tachycardia, changes in pre-systolic amplitudes due to effects on SVR

The measurement of cats with hyperthyroidism is not always easy. If a unit with automatic loop function and transfer of saved measurements to a PC for a later evaluation (e.g. HDO) is available, a measurement in a restraint cage could solve the problem. Animals in such a cage cannot turn around. The cuff should be placed around the base of the tail and hooked up outside the cage to the unit, which is set up to loop (automatic measurements, ideally every 1-2 minutes). Then the cat should be placed in a quiet room for 30 – 45 minutes while automatic measurements are taken. Readings can be transferred via Bluetooth to a computer outside the room or downloaded later for analysis. Generally, cats get used to this procedure and the last 10 – 20 readings are rarely affected by excitement. Effect of excitement can be identified in the pulse waves as mentioned above.

Diagnostic test for hyperthyroidism: total thyroxin concentration (TT4) above the reference range (> 55nmol/L; 4.26 µg/dL)

Hyperaldosteronism (HA)

Primary (PHA) and secondary hyperaldosteronism can occur in the cat and seem to be far more prevalent than previously thought. This is of increasing interest as PHA may lead to progression of CKD.[25] More recent studies point out that PHA may not be a rare cause of feline hypertension[25,5,14] and likely up to 20% of hypertensive cats may suffer from PHA.[44]

PHA or Conn's disease can result from hyperplasia or an aldosterone producing adenoma or carcinoma of the adrenal cortex. A familial predisposition may be present.[3,25] Keele et al (2009) reported adrenocortical hyperplasia in 95% of geriatric cats presented with CKD and hypertension.[28]

In comparison to secondary (often renal) hyperaldosteronism, an increased plasma aldosterone concentration (PAC)/plasma renin activation (PRA) ratio is seen with primary PHA.[28] This ratio is decreased in secondary HA.[25]

Normal values are considered to be PAC/PRA ratio 0.3 – 3.8.

Laboratory changes which might occur with PHA are:

- High PAC/PRA ratio
- Hypokalaemia
- Elevated creatinine kinase
- Hypernatraemia
- Increased BUN

Ultrasonographic changes indicating adrenal enlargement/hyperplasia or an adrenal mass may also be helpful.

Adrenal hyperplasia seems to contribute to a more significant increase in blood pressure than adrenal tumours. Hyperplasia also appears to be the more frequent cause of PHA. This may explain why typical symptoms of hypokalaemia, like muscle weakness, paresis and cervical ventroflexion are rather rare in cats with bilateral hyperplasia compared to hypertension. In a study on bilateral hyperplasia systolic blood pressures measured via Doppler were between 185-270 mmHg.[25]

Hypertension is mainly a result of increased blood volume due to aldosterone-mediated sodium retention, potassium diuresis and fluid retention. Extracellular volume increase leads to an increase in cardiac output. More recently, effects on vascular tone and vascular remodelling with resulting endothelial dysfunction have been documented. Arterial hypertension in primary hyperaldosteronism has to be looked at as a multifactorial process, influenced by increased extracellular volume, increased sympathetic activity and increased systemic vascular resistance (SVR).[52,23]

The prevalence of hypertension is high in primary hyperaldosteronism. Over 90% of cats with Conn's disease showed severely elevated systolic pressures.[25,5] It is also very possible that primary hyperaldosteronism has a higher incidence than currently diagnosed. It is one of the most common feline adrenocortical disorders.[14] Feline patients with hypertension may warrant testing for Conn's disease.

Symptoms of PHA: In a study of 11 cats diagnosed with primary hyperaldosteronism: hypokalaemia, paroxysmal flaccid paresis and retinal detachment/severe retinal haemorrhage were the most common presenting complaints (due to hypertension).[25]

Diagnostic tests for PHA include:

- Aldosterone: renin ratio (PAC/PRA)
- Urinary aldosterone-to-creatinine ratio (UACR)
- Oral fludrocortisone suppression test[14]
- Diagnostic imaging

Screening for PHA is recommended whenever a cat is presented with hypokalaemia or hypertension, especially when both are present concurrently. Mild azotaemia could also be an indication.

Treatment of Conn's disease includes potassium supplementation if hypokalaemia is present, amlodipine for blood pressure control and an aldosterone blocker (e.g. spironolactone).

Hyperadrenocorticism

Iatrogenic feline hyperadrenocorticism or Cushing's syndrome is rare. Spontaneous Cushing's disease can occur as a result of adrenal adenoma, carcinoma or pituitary adenoma which leads to an excessive secretion of cortisol. 80% of cats with hyperadrenocorticism are also diabetic.[41]

Symptoms are similar to Cushing's disease in the dog, but some are more specifically found in the cat,[55,24] and some are a result of the concurrent diabetes.

- Polyuria
- Polydipsia
- Polyphagia
- Lethargy
- Potbelly
- Central (mainly abdominal) obesity
- Muscle weakness
- Hepatomegaly
- Panting as a result of obesity, respiratory muscle weakness, decreased elasticity of airways
- Symmetric alopecia

- Secondary diabetes mellitus
- Immunosuppression
- Disturbances of haemostasis

Cutaneous atrophy (with or without open sores) and unregulated diabetes mellitus are specific symptoms in the cat.

The pathophysiology of hypertension in cats has not been investigated. In dogs and humans, RAAS activation may contribute to volume increase and vasoconstriction with increased SVR. Corticosteroids increase vascular sensitivity to catecholamines. Prostaglandin secretion is reduced suppressing vasodilation and thus supporting vasoconstriction and decreased arterial compliance. However effects on blood pressure are only mild to moderate.[30] Often, these cats have concurrent diabetes mellitus and/or glomerulosclerosis so that blood pressure elevation is likely the result of a complex interaction of various mechanisms.[12]

Phaeochromocytoma

Phaeochromocytoma is caused by a tumour of the chromaffin cells (phaeochromocytes) in the adrenal medulla, resulting in excessive but usually paroxysmal secretion of catecholamines. It is a very rare disease in cats but if present, very clinically significant. Phaeochromocytoma often causes episodic severe hypertension followed by normal blood pressure. Up to 325 mmHg systolic pressure has been reported.[44]
Other symptoms described are weight loss, anorexia, panting up to severe dyspnoea, lethargy and tachycardia as well as other cardiovascular symptoms like atrial fibrillation, ventricular fibrillation and pulmonary edema. [30] Hypertensive crisis can further lead to immediate onset of target organ damage, in particular of the eyes and the brain with the described symptoms.
Pathophysiology of hypertension is attributed to alpha and beta- receptor activation by catecholamines. Alpha receptor activation mainly leads to vasoconstrictive effects, leading to an increase of SVR and thus an increase of blood pressure.
Beta receptor activation is responsible for tachycardia but also increased contractility, increasing cardiac output. Both contribute to a substantial rise of blood pressure according to BP = CO x TPR.
Catecholamines further inhibit insulin and lead to a hypersecretion of renin. RAAS is activated as a result, which further contributes to hypertension.[30]
Diagnostic tests include repeated (ideally 24 hour) blood pressure measurements, diagnostic imaging and immunohistochemistry. Catecholamines can be measured in 24-hour urine samples, further laboratory testing should be focused on anaemia, leucocytosis with lymphocytopaenia, elevated alkaline phosphatase and alanine aminotransferase, and decreased levels of albumin.[30]
Treatment of the tumour requires surgical excision or irradiation. If not possible, blood pressure needs to be controlled primarily by using alpha blockers (like phenoxybenzamine or prazosin).[53]

Diabetes mellitus

Both type 1 and type 2 diabetes mellitus occur in the cat, with type 2 being most frequently found.
Diabetes mellitus can – rarely – be a result of Cushing's disease and as a consequence, in cats diagnosed with insulin resistant DM or with fragile, thin skin, testing for Cushing's disease should be considered.
In a large epidemiological study, 6% of hypertensive cats were diagnosed with hyperglycaemia (>200 mg/dL; reference range: 70 – 120 mg/dL[11]). Another study reported 9 out of 21 hypertensive cats to show increased serum glucose concentrations.[32]
Elevation in blood pressure can be partially attributed to an increase of catecholamine secretion as a result of insulin deficiency. Hypovolaemia and loss of sodium can lead to secondary hyperaldosteronism, contributing to hypertension. Diabetic microangiopathy and nephropathy are associated with impairment of arterial elasticity and vasoconstriction, which could predominantly effect diastolic blood pressure and SVR. Diastolic elevation has a clearly higher incidence than systolic hypertension in dogs with DM. Diastolic hypertension had a prevalence of 46% whereas only 12 out of 50 dogs showed systolic hypertension.[49] In humans, hypertension can be diagnosed in up to 60% of diabetic people. In human patients with Type 2 diabetes, blood pressure is often high at the time of diagnosis or even before, whereas in Type 1, hypertension usually develops later and often indicates development of diabetic nephropathy.[4] No study has looked at the importance of diastolic pressure in diabetic cats to date, most likely because most prior studies have been carried out with Doppler.
Given however that renal disease, diabetes and hypertension are intricately related, it is not possible to be certain which disease process is the causative process. When testing for diabetes, look for hyperglycaemia and glycosuria. Additionally, serum fructosamine might

be helpful. Transient diabetes may be present in cats secondary to pancreatitis and in obese cats.[30]
Specific treatment for hypertension is usually not necessary in diabetic cats, as blood pressure is only mildly elevated and treatment of diabetes usually normalizes blood pressure. If blood pressure is high or rises and is not affected by diabetes control, CKD might be the cause requiring antihypertensive medication. In any case, blood pressure should be monitored in diabetic cats.[30,11]

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Commissioned paper*

Early recognition of feline chronic kidney disease

Dominique Paepe[1]

SUMMARY

Feline chronic kidney disease (CKD) is a common, irreversible and progressive disease. Currently, feline CKD is often diagnosed late in the course of the disease limiting the therapeutic options. Detection of mild kidney dysfunction is difficult because the clinical signs, azotaemia and impaired urine concentrating ability may be absent. However, early detection of CKD is important, so early appropriate therapy can be initiated, the aim of which is to slow down declining kidney function and to postpone disease complications. Therefore, veterinarians are encouraged to screen at-risk populations. Research in feline nephrology currently focuses on the search for convenient and cost-effective methods to identify cats with early kidney dysfunction.

Key words: feline chronic kidney disease, recognition, geriatric cats, diagnosis

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Introduction

Chronic kidney disease is a common disease in cats. In veterinary practices and colleges in the United States, the overall prevalence of feline CKD varies between 1 and 3%. The prevalence increases to approximately 7.5% in cats over 10 years and reaches between 15 and 30% in cats over 15 years of age [1-4]. Hence, feline CKD is frequently encountered by veterinarians, especially in older cats. Feline CKD is an irreversible progressive disease and treatment is aimed at slowing down the deterioration of kidney function while managing the complications associated with the disease. Often, the diagnosis is made late in the course of the disease, limiting the therapeutic options. However, it is important to diagnose CKD early to allow for the timely and satisfactory management of these patients [3,5].

Routine diagnosis of feline chronic kidney disease

Currently, feline CKD is commonly diagnosed based upon the presence of renal azotaemia combined with a poorly concentrated urine (urine specific gravity (USG) ≤ 1.035), with compatible historical or physical examination findings [6,7].

Once CKD is diagnosed, the disease needs to be staged according to the guidelines of the International Renal Interest Society (IRIS). Therefore, assessment for proteinuria and hypertension is mandatory [8]. Additional diagnostic tests are recommended in order to find an underlying cause of CKD and to recognise if some of the complications associated with cats with CKD are present [9].

Signalment and clinical signs

Obvious breed and sex predispositions have not been reported for feline CKD, except for specific aetiologies such as polycystic kidney disease (PKD) and amyloidosis. Veterinarians should have an increased awareness for CKD in senior and geriatric cats, as CKD is typically a disease of older cats [1,10-12]. The most common clinical signs are

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non-specific and include inappetence, polyuria, polydipsia, weight loss, lethargy, halitosis and vomiting [1,10,11,13]. Physical examination findings depend on the disease stage and consist of a thin body condition, dehydration, periodontal disease, unkempt hair coat, abnormal kidney palpation (small, irregular or enlarged) and pale mucous membranes [10,11].

Azotaemia and specific gravity

The minimum laboratory database needed to confirm CKD consists of measuring serum creatinine and urea concentrations combined with USG [9]. However, in a recent survey amongst owners of cats with CKD, 23% reported that a urinalysis was never performed in their cat [14]. Thus, veterinarians must make the effort to perform urinalysis in all cats with CKD. Renal azotaemia is defined as increased serum creatinine and urea concentrations due to intrinsic renal pathology [15]. Practitioners should be aware that pre-renal or post-renal factors may also contribute to the degree of azotaemia especially as pre-renal azotaemia frequently occurs in clinically ill (e.g. anorexia, vomiting, diarrhoea) or unstable (e.g. shock, cardiac failure) cats. If overlooked, veterinarians may falsely diagnose CKD or give a poorer prognosis than is likely [8,12].

IRIS staging: serum creatinine, proteinuria and blood pressure

A classification system to stage dogs and cats with CKD has been developed by IRIS. The IRIS CKD stage is based on serum creatinine concentration, assessed on at least two occasions in a stable patient; further sub-staging is based on proteinuria, assessed by measuring the urinary protein: creatinine ratio (UPC) and on systolic blood pressure (SBP) [3,8,16].

Although severe proteinuria is uncommon, low-level proteinuria (UPC < 1) commonly affects feline CKD patients; this is not only an important prognostic factor, but it is also a therapeutic target [13,17-19]. Therefore, quantifying and then monitoring proteinuria is very important in all cats with CKD. Only persistent renal proteinuria indicates CKD and a step-wise diagnostic approach must be followed to eliminate pre-renal, post-renal urinary and post-renal extra-urinary proteinuria [20,21].

Hypertension frequently complicates CKD (20 – 65%) [22-24] and renal dysfunction is the most common underlying cause of feline hypertension (31.9 – 87%) [25-28]. Additionally, regardless of the underlying cause for the hypertension, azotaemia is observed in many hypertensive cats [25,26,28,29]. Therefore, blood pressure should be measured in all cats with kidney disease and renal function should be assessed in all hypertensive cats [26,29,30]. The SBP sub-staging system is used to reflect the risk of end-organ injury arising in the eyes, brain, kidneys or heart. Efforts must be taken to minimise 'white coat hypertension' and SBP must be determined 2 to 3 times over several weeks [3,8,31,32].

Additional laboratory tests

Cats with CKD should be evaluated for anaemia, renal secondary hyperparathyroidism, hypokalaemia, hypercalcaemia, metabolic acidosis, bacterial urinary tract infection and infection with feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) by performing more extensive blood and urine examinations.

Diagnostic imaging

Additionally, especially in cats with unilateral or bilateral renomegaly or obvious asymmetry in kidney size, medical imaging studies should be performed as they may reveal an underlying cause for the CKD. Causes that may be detected are PKD, nephrocalcinosis, urinary obstructive disease and renal neoplasia. Additionally, signs of feline infectious peritonitis or pyelonephritis may be identified [3,7]. Abdominal radiography and ultrasonography may be considered depending on the suspected underlying cause. However, ultrasonography is superior and provides more detailed information when regarding internal renal architecture [33]. Typical renal ultrasonography findings in cats with CKD are small (< 3.2 cm) and irregularly outlined kidneys, a heterogeneous renal parenchyma, a focal or diffusely increased cortical and/or medullar echogenicity, loss of corticomedullary demarcation, areas of mineralisation and poor visualisation of the internal architecture (Fig. 1) [34-37].

A progressive disease

Typically, feline CKD is a progressive disease characterised by a gradual deterioration of the remaining kidney function due to chronic tubulointerstitial fibrosis. This disease progression occurs irrespective of the initiating cause of CKD. One of the main causes of this progression is the continued loss of functioning nephrons as a consequence of prolonged intraglomerular hypertension and glomerular hyperfiltration that arises in cats with CKD in order to maintain total glomerular

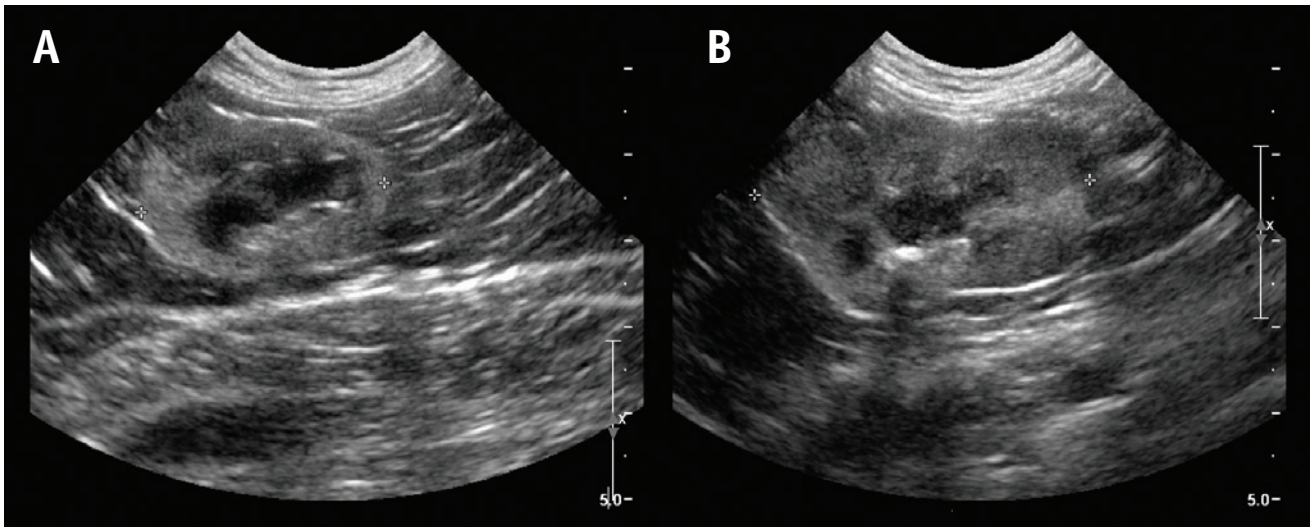

Figure 1. Dorsal longitudinal ultrasound image of the left (A) and right kidney (B) of a 4-year-old British shorthair cat with chronic kidney disease (IRIS stage 2). The left kidney is decreased in size (2.8 cm), has an abnormal shape and hyperechoic cortex. The right kidney has a normal size (3.9 cm) but has an irregular shape and bumpy contour. The cortex is diffusely hyperechoic and shows 2 segmental hyperechoic cortical lesions. Both kidneys have poor corticomedullary demarcation.

filtration rate (GFR). Proteinuria is another important contributor to progressive renal injury as it induces tubular and mesangial damage and toxicity, as well as an inflammatory response [3,38]. The relationship between feline systemic hypertension and progressive kidney disease is less clear, but an association is presumed [3,39]. Hyperphosphataemia may also promote progression of CKD, mainly by causing renal mineralisation leading to an inflammatory response [3,40]. Other factors that can lead to progressive renal injury are hyperlipidaemia, uraemic toxins, metabolic acidosis and chronic hypoxia[3]. The rate of progression of CKD varies widely between cats, but a substantial number of cats have a non-progressive or slowly progressive disease. Proteinuria, anaemia and hyperphosphataemia are associated with CKD progression, indicating that these factors might reflect more progressive types of renal disease or might be markers of disease progression [41]. Management of feline CKD currently aims at slowing down the rate of the deterioration of kidney function mainly by controlling proteinuria, hypertension and hyperphosphataemia, particularly as the initiating cause of CKD can often not be identified or treated [3].

The importance of early detection

More stringent or more timely control of the factors associated with fibrosis and disease progression, might lead to improved survival rates and quality of life [38]. Indeed, cats diagnosed early in the course of the disease live longer than cats diagnosed with more severe azotaemia; survival rates for cats with CKD are significantly associated with azotaemia and proteinuria [12,18]. Consequently, an even better prognosis might be

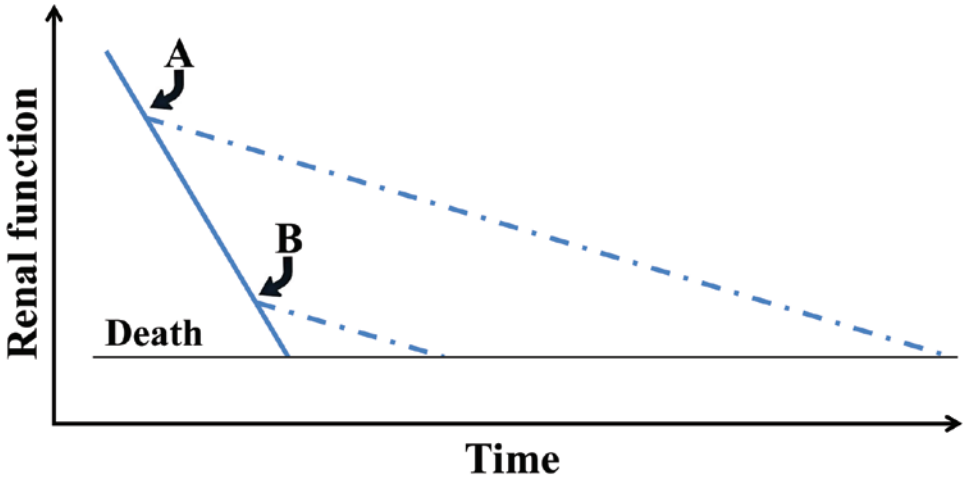

Figure 2. Hypothetic effects of altering the rate of disease progression at early (point A) or later (point B) time in the course of renal disease. Equally effective treatments to slow progression of renal dysfunction result in a longer prolongation of survival with early intervention (at point A) compared to later intervention (point B). (Based on Lees 2004[5]).

expected for cats diagnosed early, namely in the non-azotaemic disease stage (IRIS stage 1), because timely therapeutic intervention might prevent or delay disease progression and complications (Fig. 2) [5,42].

In humans, many adverse events of CKD such as progressive deterioration of kidney function, complications of decreased kidney function and cardiovascular disease can be prevented or delayed by early detection and treatment [43-47]. Hence, screening is regarded as an important public health tool for the early detection of CKD in people and screening is strongly recommended in patient groups at-risk for CKD (e.g. patients diagnosed with hypertension or diabetes) and close relatives of patients with nephropathy [48,49]. Both in cats and in dogs, CKD is often diagnosed late in the disease course (IRIS stages 3-4), limiting the therapeutic options [10-12,50]. As early intervention might result in longer survival times when compared to later interventions with equally effective treatment strategies[5], veterinarians are strongly encouraged to screen at-risk feline populations for CKD.

Which cats to screen for CKD?

Elderly cats

The prevalence of CKD increases with age and CKD affects one third of geriatric cats (> 15 years) [1-4]. A recent study diagnosed CKD in 80% of a small number of randomly selected non-acutely ill geriatric cats [5]. Thus, screening for feline CKD is highly recommended in apparently healthy aged cats. It is important to realise that old cats are also susceptible to many other chronic conditions (e.g. hyperthyroidism, hepatopathy, neoplasia) that may remain unnoticed by the owner. Ideally, screening for CKD must be part of a more extensive health-screening programme. The goal of health screening is to detect subclinical abnormalities, at a time when therapeutic interventions may have the most benefit [52]. This is more thoroughly discussed in the first article of this issue. In addition, kidney function should be evaluated in aging cats whenever they present with acute or chronic illness (e.g. anorexia, lethargy, weakness, gastrointestinal signs, constipation) or prior to anaesthesia (e.g. for a dental procedure) [53].

Endocrine disease

Feline endocrine diseases such as hyperthyroidism and diabetes mellitus (DM) may affect kidney function. Like CKD, these endocrine diseases are common in older cats and they may exist concurrently [54,55].

There is a strong link between thyroid and kidney function which becomes very important in cats if hyperthyroidism develops. Excessive thyroid hormone concentrations result in an increased GFR through increased cardiac output and diminished peripheral vascular resistance. The increased GFR and muscle atrophy in untreated hyperthyroid cats may mask concurrent CKD by diminishing the serum creatinine concentration. Normalisation of total thyroxin concentration due to treatment reverses the glomerular hyperfiltration and may unmask kidney function abnormalities. It is therefore important to closely evaluate kidney function in hyperthyroid cats before, during (e.g. medical treatment) or after treatment (e.g. surgery, radioiodine treatment). This area has been extensively studied in veterinary medicine and has recently been summarised [56-58].

Diabetic kidney disease (DKD) or diabetic nephropathy is a very common and serious complication in human diabetics, particularly in type 2 DM. Diabetic nephropathy in humans is characterised by glomerular alterations, resulting in altered GFR and micro- or macroalbuminuria, tubular damage and hypertension [59-61]. As feline diabetic patients mostly suffer from type 2 DM, cats may be susceptible to develop DKD [55,62]. However, current veterinary literature suggests that DKD is less important in feline than in human diabetic patients. Hypertension, changes in glomerular filtration rate and tubular damage seem to be infrequent in cats with diabetes mellitus [63-67]. Also, histological renal lesions are not more common in diabetic cats when compared to cats who have died from other diseases [68]. Only proteinuria and microalbuminuria were more frequent in diabetic cats when compared to non-diabetic cats [66,67]. So, it might be prudent to assess and monitor UPC in all diabetic cats [67].

Predisposed breeds

Pre-breeding screening for CKD is advised for cat breeds predisposed to PKD, namely Persian and related breeds. PKD is an inherited condition that results in the formation of fluid-filled renal and, occasionally, hepatic cysts [69]. Affected cats are heterozygous for a stop mutation in the PKD-1 gene that is inherited in an autosomal dominant manner [70-72]. Testing for PKD should be established via a combination of genetic testing and ultrasonography [73]. To avoid false negative results, cats should be at least 10 months before they undergo

ultrasonographic examination [74,75].

Pre-breeding screening may also be warranted for other familial renal diseases such as amyloidosis in Abyssinian, Siamese and Oriental shorthair cats [69]. Siamese and Oriental shorthair cats usually present with hepatic disease because amyloid is predominantly deposited in the liver. In Abyssinians, amyloid is deposited primarily in the renal medulla which leads to CKD without marked proteinuria [76]. Therefore, screening by assessing UPC usually is not rewarding. Confirmation of the diagnosis is only possible through histological examination, but biopsy of the renal medulla is associated with too high a degree of risk to be warranted [76]. A genetic test would be very helpful for pre-breeding screening for renal amyloidosis but this is, to the author's knowledge, currently unavailable.

Other cat breeds, such as Ragdoll cats or Maine Coons undergo pre-breeding screening, at least in some European countries. Several European Ragdoll breeder organisations recommend screening Ragdoll cats for chronic interstitial nephritis and PKD, by performing abdominal ultrasonography, measuring serum urea and creatinine concentrations and performing genetic testing for the PKD-1 mutation [77,78]. However, recent studies revealed that PKD is uncommon in the breeding population of healthy juvenile Ragdoll cats. In contrast, CKD was suspected after ultrasound examination in 5 to almost 10% of the same population and Ragdoll cats were predisposed for segmental cortical lesions on renal ultrasonography [77,78]. Therefore, there seems to be a rationale to continue pre-breeding screening of Ragdoll cats for CKD, but further research is needed. Until more data are available, urinalysis should be added to the currently applied screening protocols and a standard protocol should be followed when performing the abdominal ultrasonography. PKD screening, on the contrary, does not appear to be mandatory in Ragdoll cats, except if there is no or dubious information regarding the PKD status of the parents or if cysts are detected on ultrasonography [79]. Recently, renal ultrasonographic findings were retrospectively evaluated in juvenile healthy Maine Coon cats. Ultrasonographic findings compatible with CKD were found in 5.3% of cats, changes of unknown significance in 5.9% of cats, and renal cysts in 3.7% of cats. Renal cysts were mostly singular, small, unilateral and located at the corticomedullary junction [80]. Further studies will need to be performed to reveal the clinical significance of these findings and whether pre-breeding screening of Maine Coon cats for juvenile nephropathy is warranted.

Diseases that may lead to CKD

Next to the cat groups discussed above, evaluation of kidney function is also recommended in cats with diseases that might lead to CKD such as infectious diseases (e.g. bacterial pyelonephritis, FIV, FeLV), metabolic conditions (e.g. hypercalcaemia, hypokalaemia), renal neoplasia (e.g. lymphoma, carcinoma), urolithiasis (e.g. ureterolithiasis, nephrolithiasis), conditions that may be associated with renal ischemia (e.g. dehydration, cardiovascular disease) and diseases that may be associated with glomerulopathy (e.g. feline infectious peritonitis, pancreatitis,

Table 1. Cat populations to consider screening for chronic kidney disease.

HEALTHY CATS	DISEASED CATS
Aged cats (>10 years)	Hyperthyroidism
• Healthy	Diabetes mellitus: proteinuria
• Prior to anaesthesia	Viral diseases: FIV, FeLV, FIP
• Prior to NSAIDs or other potentially nephrotoxic drugs	Hypercalcaemia, hypokalaemia
Cats of all ages, particularly pre-breeding	Bacterial pyelonephritis
• Persian and related breeds: PKD	Renal neoplasia
• Amyloidosis: Abyssinian, Siamese, Oriental shorthair	Urolithiasis
• Ragdoll, Maine Coon?	Cardiovascular disease, hypertension
	Dehydration
	Unexplained weight loss, polyuria or polydipsia
	Potentially nephrotoxic drugs
	After episode of acute kidney injury
	Other: pancreatitis, cholangiohepatitis, neoplasia

(NSAIDs = Non-steroidal anti-inflammatory drugs; FIV = Feline immunodeficiency virus; FeLV = Feline leukemia virus; FIP = Feline infectious peritonitis)

cholangiohepatitis, neoplasia). In cats with unexplained weight loss, polyuria/polydipsia (PU/PD) or hypertension, CKD is also an important differential diagnosis. Further, screening for CKD should be considered in cats that need treatment with potentially nephrotoxic agents (e.g. non-steroidal anti-inflammatory drugs, doxorubicin). Finally, cats that have been treated for acute kidney injury must be monitored carefully for persistent CKD [3,76]. An overview of the cat populations to consider screening for CKD is given in Table 1.

Screening for chronic kidney disease

Unfortunately, the routine diagnostic tests for CKD have limitations for the early detection of kidney dysfunction and early feline CKD (IRIS stage 1 CKD) is challenging to diagnose.

Clinical signs and owner awareness

Clinical signs and physical examination abnormalities may be absent in cats with early CKD (IRIS stages 1-2) [10,11]. Also, the early or subtle signs of CKD such as polyuria/polydipsia, weight loss and poor body condition are not always recognised by cat owners [81-84]. According to a recent study, clinical signs that are risk factors for CKD include weight loss, a thin body condition, dehydration, diagnosis of periodontal disease or cystitis, or undergoing general anaesthesia in the preceding year [85]. Particularly in aging pets, owners may view these clinical signs as part of the normal aging process [86]. Therefore, veterinarians should improve the owner awareness for these early CKD signs; they should perform a thorough nutritional assessment at each examination and compare the physical findings with previous health examinations. A nutritional assessment includes the recording of diet history, body weight, body condition score (preferably on a 9-point scale) and muscle condition score (mild, moderate or severe muscle atrophy) [87].

Interpreting laboratory findings

False-normal creatinine and urea values

The minimum laboratory database for CKD screening consists of measuring serum creatinine, USG and proteinuria (Fig. 3) [86,88]. In comparison, a spot urine sample for protein and an estimate of GFR based on serum creatinine concentration are the recommended tests to screen human patients for CKD [44]. In healthy non-azotaemic geriatric cats, plasma creatinine concentration combined with UPC were predictive of azotaemia developing, indicating that high-normal creatinine concentrations and/or UPC values consistent with borderline or overt proteinuria might indicate early kidney dysfunction [89]. Unfortunately, it is assumed that over two-thirds of functional renal mass must be lost before kidneys lose their urinary concentrating ability and over three-quarters must be lost before azotaemia

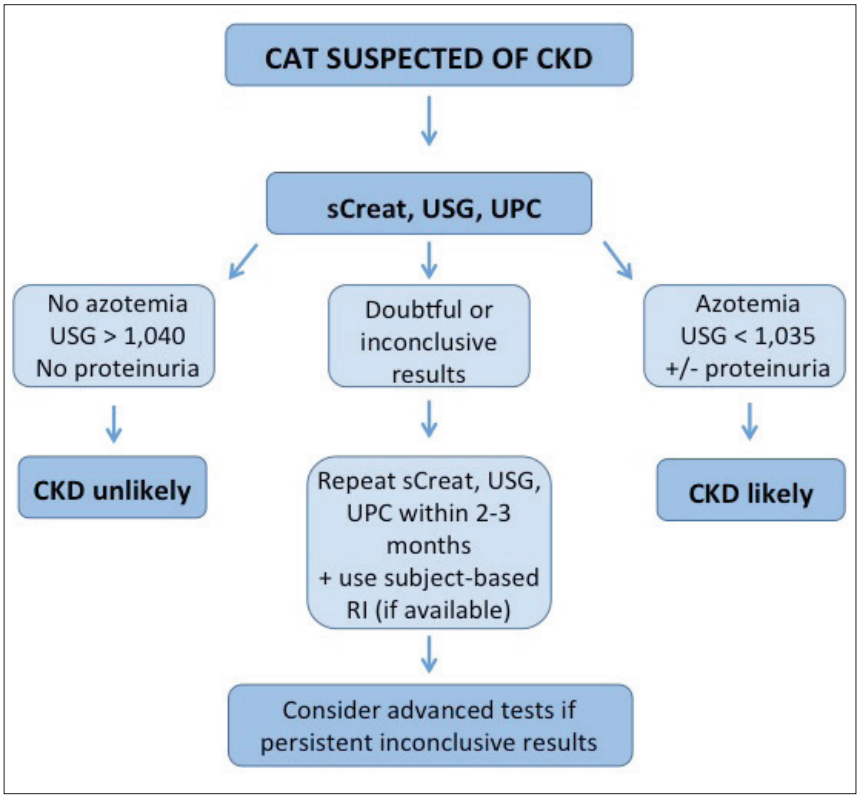

Figure 3. Diagnostic flow-chart to screen cats with one or more risk factor(s) for chronic kidney disease, using routine laboratory tests.
(CKD = Chronic kidney disease; sCreat = Serum creatinine concentration; UPC = Urinary protein: creatinine ratio ; RI = reference interval; USG = Urine specific gravity)

develops. Thus, serum creatinine and urea concentrations and USG are often within reference intervals (RIs) in cats with early CKD, particularly because some cats may maintain their urinary concentrating ability [15,33,90].

Muscle atrophy

An additional problem with the interpretation of serum creatinine is the potential influence of muscle atrophy on serum creatinine. The daily production rate of creatinine depends on the muscle mass, so muscle wasting due to aging (Fig. 4) or concurrent conditions might affect serum creatinine concentrations [3,5,33]. This may obscure mild increases in serum creatinine concentration.

Creatinine reference values

Furthermore, studies indicate that RIs for serum creatinine can differ widely between laboratories and may be inappropriate which may lead to misclassification of samples as normal or abnormal [84,91,92]. The reference population to establish the RI should reflect the animal population for which the RI is used [93-95] and for specific laboratory variables such as serum creatinine or serum phosphorus concentrations age-specific RIs may be indicated [84,96]. To overcome calibration bias and measurement imprecision between and within laboratories, guidelines for the standardisation of creatinine measurements have been described in human medicine [97]. It is important to use a laboratory with good quality control that consistently reviews RIs and perform patient follow-up using the same laboratory [5,95,98].

Figure 4. A 20-year-old cat that presented because of constipation. The cat was otherwise healthy and had normal blood (including serum total thyroxine) and urine examinations. Some age-related changes such as muscle atrophy and unkempt hair coat are visible in the pictures.

In addition, veterinarians should compare laboratory variables with values of previous health screenings to detect clinically relevant changes. Increasing serum creatinine concentrations, even within a RI, may indicate early kidney dysfunction, particularly in cats with weight loss or muscle wasting or USG consistently below 1.035 [5,42,82]. To evaluate the clinical relevance of changes in serial laboratory measurements, subject-based RIs may be considered. These are referred to as reference change values or critical differences (i.e. a meaningful change between 2 successive measurements) [99,100]. Recent findings indicate that for some feline biochemistry variables, such as creatinine, the use of subject-based RIs would be more appropriate for detecting pathologic changes in an individual rather than population-based RIs [100]. The calculation of the reference change value is simple for laboratories to perform and will allow the detection of clinically meaningful changes on regular laboratory assessments of mature and elderly patients more readily [101]. For example, the reference change value or critical difference for plasma creatinine measured with an enzymatic assay in healthy cats was determined to be 17.4%. In serial measurements in a feline patient using that assay, increases or decreases in plasma creatinine larger than 17.4% are clinically relevant, even if plasma creatinine remains within the RI [100]. Using subject-based reference values and standardisation of laboratory tests in veterinary medicine will be important future steps to ameliorate the accuracy of laboratory measurements.

False-normal SG values

Cats with CKD typically lose their urine concentrating ability whereas healthy cats are able to concentrate their urine [3]. Most cats with CKD have isosthenuric urine (USG 1.007 – 1.015) [10,11], but this is less consistent in cats when compared with dogs [102]. Some cats, with either spontaneous or experimentally induced CKD, can retain their urine concentrating ability despite being azotaemic. This is

particularly true in the early stages of CKD and most cats with early CKD have marginally concentrated urine (USG 1.015-1.035) [1,10,11,103,104]. In contrast, approximately 90% of healthy cats have a USG > 1.035 [78,84,105] and approximately three quarters of healthy aged cats have a USG > 1.040 [84]. This makes CKD less likely in cats with USG > 1.040. It is important to realise that many factors influence USG and daily USG fluctuations can be seen in healthy animals. Thus, low USG without other indications for CKD does not necessarily suggest kidney dysfunction [5,15]. A USG consistently below 1.035 or a USG below 1.035 found together with either azotaemia or a physiologic state for which concentrated urine is expected (e.g. dehydration) may indicate impaired urine-concentrating ability and warrants further investigation [1,5,42].

Borderline proteinuria

In healthy non-azotaemic geriatric cats, UPC was predictive of azotaemia developing, indicating that UPC values consistent with borderline or overt proteinuria might indicate early kidney dysfunction [89]. However, recent studies revealed borderline proteinuria in approximately a quarter of healthy cats, also juvenile cats. In most of these cats, borderline proteinuria was not explained by pre-renal or post-renal factors, suggesting a renal origin of the borderline proteinuria. Although persistence was not evaluated, the borderline proteinuria was unlikely to be caused by early CKD in all these cats, particularly in the juvenile healthy population [78,84]. It is possible that at least some of these cats did not actually have borderline proteinuria, but were incorrectly classified as such due to technical or methodological factors. Misclassification might be a consequence of the assay used [106] or due to inappropriate storage or dilution of urine samples [107]. In dogs, sample dilution or storage errors mainly affect UPC ratios close to the threshold limits 0.2 or 0.5 [107]. Further research is needed to reveal the clinical relevance of borderline proteinuria in healthy cats of different ages. In addition, standardisation of UPC measurements in veterinary laboratories might improve the accuracy of proteinuria assessment [79].

False-positive ultrasound findings

According to IRIS guidelines, a non-azotaemic cat with US abnormalities at the level of the kidney is a cat with CKD IRIS stage 1 [8,16]. However, veterinarians must be aware that ultrasonographic renal abnormalities often

Table 2. Frequency of renal ultrasonographic abnormalities in a population of 62 juvenile healthy cats using a standard protocol to perform renal ultrasonography (based on Paepe et al 2013 [78]).

Frequency	Finding
17.7%	Presence of medullary rim sign
12.9%	Abnormal cortical echogenicity
9.7%	Abnormal renal shape One or two small kidneys (< 3.2 cm)
8.1%	Abnormal renal capsule Abnormal corticomedullary demarcation
3.2%	Abnormal medullary echogenicity
1.6%	Presence of cavitary lesion in cortex Presence of nodules in the cortex Large (>0.7 cm) difference in kidney size
0%	Presence of segmental cortical lesion Presence of dystrophic mineralisation Abnormal renal pelvis or proximal ureter

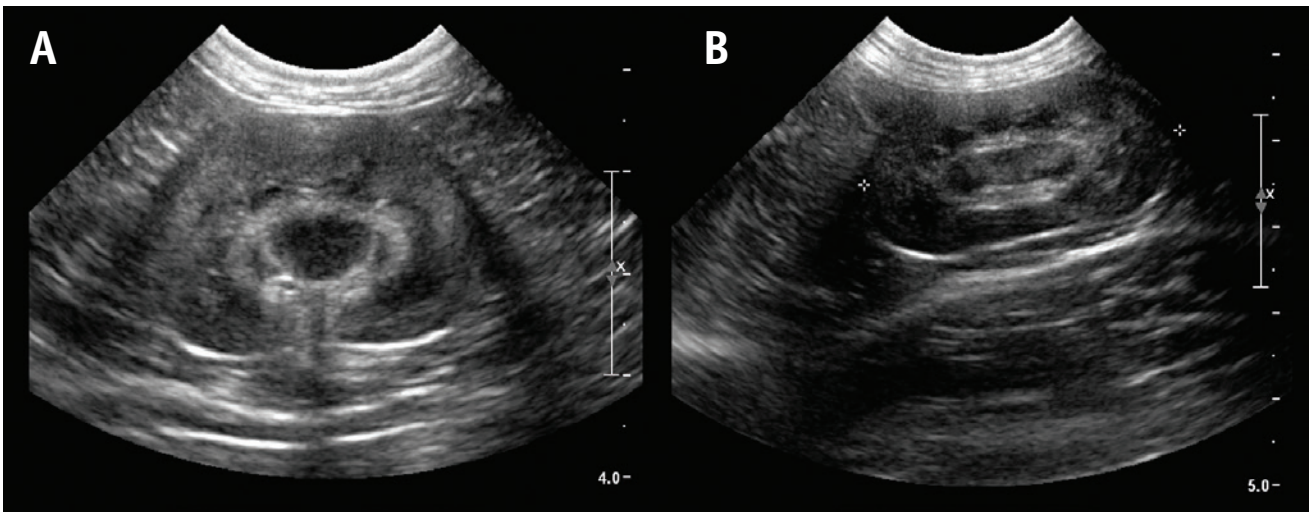

Figure 5. Sagittal longitudinal ultrasound image of the left kidney (3.4 cm; A) and dorsal longitudinal ultrasound image of the right kidney (3.7 cm; B) of a 2-year-old healthy domestic shorthair cat. Both kidneys show a marked medullary rim sign as single abnormality.

occur in healthy cats and are not always clinically relevant. In a recent study, at least one ultrasonographic renal abnormality was observed in 40% of juvenile healthy cats (Table 2). The most common abnormalities were the presence of a medullary rim sign (Fig. 5) and changes in cortical echogenicity, especially hyperechoic renal cortices [78]. In the absence of other abnormal findings, these are probably not clinically relevant [78,108]. Furthermore, if ultrasonographic abnormalities are present, veterinarians must realise that ultrasonographic abnormalities do not correlate with renal function and cannot predict which cats will progress to azotaemic CKD [34]. Thus, until proven otherwise, ultrasonography is not sufficient as a sole test to diagnose CKD and current scientific data do not support feeding a renal diet solely based on ultrasonographic findings. In humans, contrast-enhanced ultrasonography (CEUS) is a valuable additional test for the evaluation of renal diseases [109,110]. Whether CEUS is of diagnostic value for feline CKD is currently unknown.

Advanced diagnostic tests for early diagnosis

More advanced tests to evaluate kidney function might be considered in cats with one or more risk factor(s) for CKD, in cats with unexplained clinical signs (e.g. unexplained weight loss, PU/PD or hypertension), in patients with questionable routine blood and urine tests (e.g. azotaemia, poorly concentrated urine or pathologic renal proteinuria as single abnormality) or in patients with CKD IRIS stage 1 (e.g. ultrasonographic findings compatible with CKD in non-azotaemic cats). A schematic overview of the possible advanced tests available is given in Fig. 6.

Glomerular filtration rate

Filtration markers

Determination of GFR – i.e. the volume of ultrafiltrate produced per unit of time – is considered to be the gold standard to evaluate kidney function [90]. Glomerular filtration rate is mostly determined by plasma clearance of a filtration marker. Appropriate filtration markers are freely filtered through the glomerulus, not protein-bound, not toxic, do not undergo tubular secretion or absorption and do not alter GFR [33,111-113]. For research purposes, plasma clearance of iohexol or creatinine administered by single intravenous injection is frequently used in cats to estimate GFR [114-129]. Unfortunately, iohexol assays are not widely available and injectable creatinine is not commercially available. Also inulin and radioisotopes have been used as clearance markers, but inulin assays are technically challenging and not widely available, while radioisotopes require specialised equipment and carry the risk of radiation exposure [33,112]. Measurement of GFR is also limited because GFR reference intervals are poorly reported for healthy cats [112,130]. Using 43 healthy cats, the reference interval for plasma exogenous creatinine clearance was recently defined as 1.2-4.9 mL/min/kg [130]. Finally, multi-sample techniques for GFR estimation are labour-intensive, time-consuming and may be stressful or painful for the patient, which limits their practical use in cats [129].

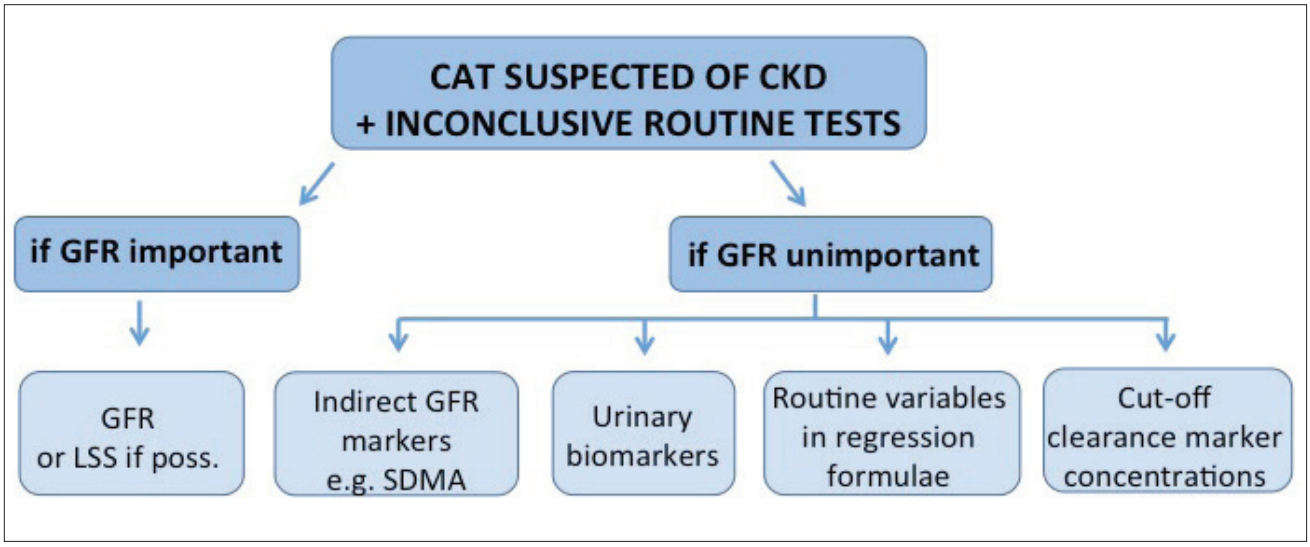

Figure 6. Schematic overview of the possible strategies to diagnose early feline chronic kidney disease in cats with one or more risk factor(s) for chronic kidney disease and doubtful routine laboratory tests. Unfortunately, not all these methods are widely available at this time point (see text).
(CKD = Chronic kidney disease; GFR = Glomerular filtration rate; LSS = Limited sampling strategy; SDMA = Symmetric dimethyl arginine)

Limited sampling strategies

Because of the practical limitations of multi-sample clearance techniques, efforts have been taken to simplify GFR determination in humans by using the least number of possible blood samples, particularly in children [131,132]. Limited sampling strategies (LSSs) – i.e. clearance techniques based on a reduced number of blood samples – are a suitable compromise between practical convenience and clinical accuracy for GFR determination [133]. In comparison, several LSSs have been described to estimate feline GFR. Unfortunately, in many veterinary studies reported to date, no or only a few renal-impaired cats were evaluated. Additionally the reference GFR, which is used to design LSS, was often calculated using a clearance technique with less than 5 blood samples taken during a sampling period of 5 hours or less [119,123,126,128,134-139]. One group recently developed a single sample method for estimating feline GFR in both non-azotaemic and azotaemic cats [129], using a modification of the Jacobsson method that was originally developed for human patients [140]. As yet, it is unknown whether the assumptions that are inherent to this Jacobsson method are applicable to cats as well. Our research group recently published LSSs for 3 different clearance markers (creatinine, exo-iohexol, endo-iohexol) in a cat population with wide range of GFR. The reference GFR used was based on multiple blood samples taken over a 10 hour period, both in the distribution and elimination phases of the clearance marker and computed using an assumption free non-compartmental approach. Based on this non-compartmental approach, at least 3 or 4 blood samples after the injection of the clearance marker are needed to estimate GFR with an acceptable margin of error (errors below 20%) [104].

Estimations using equations

In human medicine, GFR is usually estimated using equations based on serum creatinine concentration and demographic variables such as age, gender, ethnicity and body size. These equations are more reliable than estimates of GFR from the measurement of serum creatinine alone, mainly because they compensate for substantial variation in creatinine production across sex, age and ethnicity [44]. Similarly, the endogenous creatinine production rate has a high inter-individual variability in cats [120], but which factors (e.g. age, breed, sex) are responsible for this variation is currently unknown. At this time point, equations to reliably estimate GFR are not available for cats.

In daily practice, knowledge of the actual GFR value is often not mandatory. More importantly, clinicians need to be able to predict which patients have a decreased GFR based on routine blood and urine variables or based on other methods, requiring only a minimal number of blood samples. Therefore, our group developed two simple and cost-effective methods to identify cats with borderline or low GFR. The first method uses a regression formula based on routine variables including serum creatinine, serum urea, USG and UPC. This method could predict, with very good sensitivity and moderate to good specificity, if a cat had a GFR value below the proposed GFR cut-offs. The second method uses the clearance marker concentration at 60, 120 or 180 minutes after marker injection and must be compared with cut-off marker concentrations. For each time point and for each clearance marker (creatinine, exo-iohexol, endo-iohexol), three cut-off marker concentrations were given, which allows the veterinarian to choose a cut-off marker concentration depending if they want to predict borderline or low GFR with high sensitivity, high specificity or both. The reader is referred to Paepe et al [104] for a more detailed description of these methods.

Indirect GFR markers

Another approach to estimate GFR is by measuring indirect GFR markers. Serum Cystatin C (sCysC), is a low-molecular-weight protein produced at constant rate by all nucleated cells that meets all the criteria required for endogenous GFR markers [141]. Serum CysC is superior to serum creatinine to detect renal dysfunction in humans [141] and also has some advantages over serum creatinine in dogs [142]. Cats with CKD have higher sCysC concentrations when compared with healthy cats [143,144]. Also, in healthy cats, feline sCysC appears to be less influenced by biological variables such as breed, age and sex compared to serum creatinine [145]. Whether sCysC has advantages over serum creatinine to detect early feline CKD is still under investigation.
A very promising indirect marker to detect early kidney dysfunction in cats is serum symmetric dimethylarginine (SDMA), a by-product of protein methylation. SDMA is excreted primarily (≥ 90%) by renal clearance and plasma or serum SDMA concentrations show an inversely linear relationship with GFR [146,147]. In cats with CKD, SDMA is increased and correlates with serum creatinine concentration [146,148]. More importantly, in cats developing CKD, SDMA increased on average 17 months prior to serum creatinine, indicating that SDMA might be useful as biomarker for early detection of feline CKD [147].

Biomarkers

Another pathway to identify kidney disease is by using urinary biomarkers for tubular or glomerular damage [149-151]. Retinol-binding protein (RBP), N-acetyl-β-glucosaminidase activity (NAG), urinary Cystatin C (uCysC), transforming growth factor-β1, interleukin-8 and (micro)albuminuria are promising candidates for urinary biomarkers for cats [144,151,152-159].

Microalbuminuria is defined as the presence of a small amount (1–30 mg/dL) of albumin in the urine, beneath the limit of detection of urinary dipstick tests [152,160]. It may also remain undetected by UPC determination [161]. Persistent renal (micro)albuminuria may be indicative of renal disease [20,152], however, (micro)albuminuria has been observed in healthy cats and in cats with a wide variety of non-renal diseases (e.g. infectious, inflammatory, endocrine, neoplastic, urinary tract disease) [66,152,155,162,163]. (Micro)albuminuria can be measured with the urinary albumin: creatinine ratio (UAC) or a commercial in-house semi-quantitative enzyme-linked immunosorbent assay (ELISA)-based dipstick test (E.R.D-Health Screen, Heska Corporation, Fort Collins, Colorado, United States) [152,155,164]. Routine evaluation for presence of (micro)albuminuria in cats is not warranted because (micro)albuminuria occurs with various diseases, UAC measurement is not widely commercially available, it lacks a benefit over UPC, semi-quantitative test interpretation might be difficult and negative microalbuminuria tests do not rule out proteinuria [5,165]. However, there are some indications where assessing for (micro)albuminuria is warranted, particularly in cats at risk for renal disease without overt proteinuria [5,160].

Low-molecular-weight proteins (NAG, uCysC, RBP) and tubular enzymes (NAG) are not present in the urine of healthy animals, but patients with CKD might have detectable urinary concentrations secondary to tubulointerstitial damage or inflammation. Also, tubulointerstitial inflammation or fibrosis might result in overexpression and increased urinary concentrations of inflammatory cytokines (transforming growth factor-β1, interleukin-8) [149,151]. In humans, careful selection of biomarkers will allow detection of site specific changes (glomerular versus tubular) [149]. Whether the latter is true in cats and whether these urinary biomarkers have benefit over routine variables to detect early feline CKD is currently unknown.

Biopsies

Finally, kidney biopsies may be considered where knowledge of morphologic alterations in renal structure will substantially influence patient management, for example in cats suspected of glomerulonephritis, amyloidosis or renal lymphoma that could not be identified with fine-needle aspiration. However, this is not true for the majority of CKD cats that suffer from chronic generalised tubulointerstitial nephritis, glomerulosclerosis, tubular necrosis or PKD, nor for cats with significant azotaemia or end-stage CKD regardless of the underlying cause [1,3,166]. In cats with CKD, pathological lesions of a specific renal disease are detected in 18 to 50% of cases [10,166,167]. In patients with severe persistent renal proteinuria (UPC ≥ 2), maximal information will be obtained by evaluating kidney biopsies with light, electron and immunofluorescent microscopy. Potential underlying diseases leading to proteinuria should be ruled out before taking kidney biopsies [21,76]. The diagnostic value of kidney biopsies in the management of cats with CKD is currently poorly studied.

Conclusion

First opinion veterinarians play a major role in the detection of early feline CKD. Through educating cat owners, regular thorough physical examinations and performing routine laboratory tests in cats with increased risk for CKD, kidney dysfunction may be diagnosed at earlier stages.

In cats with equivocal routine tests, close follow-up or advanced diagnostic tests might be considered. Unfortunately, currently only few advanced diagnostic tests are widely available that are both convenient and cost-effective.

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Commissioned paper*

Feline chronic enteropathies

Sina Marsilio[1] and Jörg Steiner

SUMMARY

Signs consistent with chronic gastrointestinal disease (e.g. diarrhoea, weight loss, anorexia, vomiting) are very common in cats. While there are many underlying causes of these clinical signs, chronic enteropathy is one of the most common. The goal of this review is to give a detailed summary of chronic enteropathies in cats.

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Introduction

The term chronic enteropathy describes a group of diseases that cause chronic gastrointestinal signs including the following entities:
1. Idiopathic inflammatory bowel disease (IBD)
2. Food-responsive enteropathy (FRE)
3. Fibre-responsive diarrhoea
4. Antibiotic-responsive enteropathy (ARE)

The term IBD is reserved for patients in which all (currently) known causes for gastrointestinal signs have been excluded and histopathologic examination of gastrointestinal biopsies proves mucosal inflammation; thus the disease can be assumed to be idiopathic. In reality, this is often very difficult to achieve in small animal medicine and sometimes impossible in cats. For example, many cats that are already inappetent will refuse to eat a new diet, owners struggle to pill their cat and test results have equivocal results. Moreover, the terminology is not consistent among publications and oftentimes, the term IBD and other forms of enteropathies are used arbitrarily and interchangeably.
For these reasons, the authors prefer to use the term feline chronic enteropathy (FCE).

Aetiopathogenesis

There is good evidence across species that three factors play a central role in gastrointestinal health and, if disrupted, lead to uncontrolled gastrointestinal inflammation in a genetically susceptible host:
1. the immune system
2. the microbiome
3. the environment

The intestinal immune system is a complex system. Every day, the mucosa is confronted with a myriad of antigens from pathogens (e.g. parasites, bacteria, viruses, fungi), dietary antigens, the resident microbiota and even some randomly swallowed material (e.g. pollen and dust in swallowed sputum). A fine balance between intestinal tolerance and mucosal immune defence is crucial in order to be able to accept vital nutrients, ignore the resident microbiota and harmless substances and combat pathogens. This balance is achieved by a number of mechanisms including regulatory T-cells (T_{reg} cells), which control immune responses to self-antigens thereby preventing autoimmunity and maintaining self-tolerance. Whereas, pro-inflammatory effector CD4+ T-cells mediate immune responses to potentially harmful pathogens.

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In humans with Crohn's disease, this balance is shifted towards an inflammatory Th1 dominated cellular immune response. This shift has been linked to certain mutations of receptors involved in the innate immune response, such as NOD2 and CARD15 in humans. Similar mutations have been described in the German Shepherd dog[1]. In cats, Siamese and other Asian breeds have been anecdotally found to be predisposed to chronic enteropathies, but a genetic cause has not yet been identified.

Besides the immune system, the microbiome and its metabolites play an important role in the aethiopathogenesis of IBD. Bacterial metabolites, such as short chain fatty acids, are nutrients for colonocytes and have anti-inflammatory activity. In addition, the microbiome has been shown to directly influence cytokine profile. Cytokines determine the character of an immune response towards pro- or anti-inflammatory activity by controlling T-cell differentiation. In cats, it has been shown that the numbers of *Enterobacteriaceae*, (e.g. *E.coli*) and *Clostridium* spp., correlate with the severity of clinical signs, mucosal inflammation and an up-regulation of pro-inflammatory cytokine mRNA (mainly IL-1, -8 and -12)[2].

While in humans, various environmental factors (e.g. NSAIDs, oral contraceptives, appendectomy and others) have been identified as a trigger for IBD, the role of such factors has not yet been studied in cats and in any case they are likely to be very different for this species given their different nutritional needs and lifestyle[3].

Signalment, history and clinical signs

FCE affects mainly middle-aged to older cats [4, 5]. Some studies have reported a breed predisposition for Siamese and other Asian breeds, while this has not been supported by others [2, 5, 6].

Weight loss is by far the most common clinical sign in cats with FCE, ranging in reported frequency from 63 to 90% of cases, followed by vomiting (61 – 75%) and anorexia (20 – 41%). Diarrhoea seems to be less common, but numbers vary extensively between studies (12 -75%) [2, 5-8]. A recent study in cats reported that of 100 cats ultimately diagnosed with chronic small bowel disease, 26 cats were initially presented for a wellness examination [5]. The histories of these cats indicated that clinical signs of small intestinal disease were present but that the owners were simply unaware of their relevance. This illustrates the importance of collecting a thorough clinical history and physical examination. Cats that predominantly or exclusively have large bowel disease were more consistently observed to have diarrhoea together with haematochezia by their owners [4, 5, 9].
Generally, weight loss is associated with small bowel diarrhoea, while haematochezia, mucus and tenesmus are associated with large bowel disease (see table 1). Vomiting and diarrhoea may occur with both disease locations and most cats with FCE will have mixed bowel involvement.
Frequently, cats with FCE suffer from concurrent inflammation of the pancreas or liver [2, 5, 6, 10, 11]. In the past, this concurrent inflammatory condition of the intestines, the pancreas and the hepatobiliary system has been referred to as *triaditis* and a common underlying disease mechanism such as dysbiosis and secondary ascending infection has been assumed to be the underlying cause, but this remains to be proven. Moreover, exocrine pancreatic insufficiency (EPI) is a disease that is becoming more frequently recognised in feline patients and it has clinical signs which overlap with those of FCE. In 2006, only 177 cats were diagnose with EPI by measurement of feline fTLI

Table 1. Differentiation of small vs. large bowel diarrhoea

	Clinical sign	Small intestinal disease	Large intestinal disease
Faeces	**mucus**	rare	common
	blood	melena	haematochezia
	volume	large	small
	fat	occasionally	absent
Defecation	**frequency**	normal to slightly increased (2-3/d)	increased (>3/d)
	tenesmus	rare	common
	urgency	rare	common
Other signs	**weight loss**	common	rare
	vomiting	common	rare
	faecal incontinence	absent	possible

at the Gastrointestinal Laboratory at Texas A&M University. Whereas 476 were diagnosed with EPI in 2010 and 942 in 2013 (unpublished data). Signs of EPI largely overlap with those of FCE. Weight loss appears to be the predominant clinical sign in feline EPI (91%), followed by loose stools (62%). Interestingly, about 42% of patients are reportedly polyphagic and 45% are anorectic, while only 28% of cats with EPI have been reported to have diarrhoea [12-14]. As pancreatic disease might occur concurrently in FCE, patients with EPI should be evaluated for concurrent gastrointestinal disease and vice versa.

Diagnosis

Exclusion of extra-gastrointestinal diseases

There are numerous diseases that can cause the same clinical signs as FCE. Therefore, other diseases need to be excluded first and gastrointestinal biopsy collection is the last step in the diagnostic process. Usually, extra-gastrointestinal and gastrointestinal infectious causes are excluded first unless the physical examination directs the clinician in a different direction (e.g. cardiac arrhythmia and murmur, abdominal mass, or other; see table 2 and 3).

Table 2. Differential diagnoses for extra-gastrointestinal diseases

Categories		Diagnostic tests	Diagnostic clue
Pancreas	exocrine pancreatic insufficiency	fTLI cobalamin folate	↓ ↓ ↓ ↑
	pancreatitis	fPLI	↑
Endocrine	hyperthyroidism	tT4 fT4	↑ ↑
	diabetes mellitus	blood glucose glucosuria serum fructosamine	↑ ↑ ↑
Metabolic	renal disease	urinalysis creatinine BUN phosphorus	USG < 1035, UPC >0.4, pyuria > 140µmol/l / 1.6mg/dl ↑ ↑
	hepatic disease	enzyme activity (AP, ALT, AST, GGT) function parameter albumin BUN cholesterol bilirubin glucose PT/PTT ammonia bile acid stimulation test	↑ ↓ ↓ ↓ insufficiency / ↑ obstruction ↑ ↓ ↑ ↑ ↑
	cardiac disease	NTproBNP troponin I	↑ ↑
Intra-abdominal disease	neoplasia peritonitis (including FIP)	n/a abdominal ultrasound fluid/ organ aspiration	n/a hyperechogenicity, abdominal fluid etc.
Miscellaneous	drug induced (e.g. NSAIDS, steroids)	n/a	indication of GI bleeding: thrombocytosis, BUN, anaemia
	hypereosinophilic syndrome	CBC bone marrow aspiration/ biopsy organ aspiration/ biopsy	eosinophilia eosinophilic infiltration eosinophilic infiltration
	FIV	serum antibody ELISA	
Summary of baseline tests to exclude extra-gastrointestinal disease; additional tests as needed based on baseline tests		1. CBC, biochemistry, UA	2. tT4 or fT4 3. fPLI, fTLI

Table 3. Differential diagnoses for chronic gastrointestinal disease (continued on next page)

Categories			Diagnostic test	Comment
Dietary	food intolerance	e.g. lactose intolerance	Diet change	
	food hypersensitivity		response to exclusion diet (see also ARE)	often accompanied by dermatologic signs
Inflammatory – infectious (chronic)	parasites	Roundworms (*Toxocara, Toxascaris*) Hookworms (*Ancylostoma, Uncinaria*) Whipworms (*Trichuris*) Tapeworms (*Taenia, Dipylidium, Diphylobothrium*)	faecal flotation	false negatives possible, deworming recommended regardless
		Giardia spp.	direct faecal smear, zinc sulphate concentration technique, faecal antigen ELISA, faecal PCR	
		Tritrichomonas foetus	faecal culture, faecal PCR, (direct faecal smear)	
		Toxoplasma gondii	faecal flotation for oocysts	
	bacteria	*Campylobacter jejuni, Salmonella* spp., pathogenic *E.coli*	bacterial isolation, faecal PCR (*Campylobacter* spp., pathogenic *E.coli*)	usually acute GI signs with diarrhoea and/or vomiting
	fungi	*Histoplasma capsulatum*	cytology (FNA, rectal scrape) / histology of affected tissue, serum/ urine antigen ELISA	other clinical signs such as fever, respiratory, ocular, etc.) are more common, GI signs are rare
Inflammatory – non-infectious	inflammatory bowel disease (IBD)	• lymphoplasmacytic • eosinophilic • granulomatous • suppurative (neutrophilic)	histology, immunohistochemistry	additional testing such as PARR might be needed for differentiation of LPE from LGAL
	food responsive enteropathy (FRE)	see above	dietary trial	novel protein or hydrolysed diet ± dietary challenge
	antibiotic responsive enteropathy (ARE)	dysbiosis, yet to be defined	antibiotic trial	commonly used: tylosin, metronidazole
	fibre-responsive diarrhoea		high fibre diet	prescription diet, supplementation with psyllium, pumpkin etc.

Summary of diagnostic tests (having ruled out extra-GI diseases)

1. faecal examination for parasites
2. exclusion diet (maybe high fibre diet trial if large intestinal symptoms predominate)
3. imaging
4. biopsies and/or fine-needle aspirates (FNA)

(This table continues on the next page)

Table 3. Differential diagnoses for chronic gastrointestinal disease (continued)

Categories			Diagnostic test	Comment
Neoplastic	round cell tumours	low-grade alimentary lymphoma	histology, immunohistochemistry, PARR	most often T-cell origin, diffuse
		high-grade (alimentary) lymphoma	FNA, histology, PARR	B- or T-cell origin, often solitary or multiple intestinal mass(es)
		mast cell tumour	FNA, histology	usually small intestinal, solitary or multiple intestinal masses
	carcinomas	adenocarcinoma	histology, (FNA)	usually small intestinal, solitary mass
	sarcomas	leiomyoma/-myosarcoma	histology, (FNA) C-kit/CD117 - SMA + Desmin +/- S-100 -	rare; usually small intestinal, solitary mass; many tumours previously diagnosed as leiomyosacomas were reclassified based on immunohistochemistry
		GIST	histology, (FNA) C-kit/ CD117 +/- SMA +/- Desmin - DS-100 -	rare; usually small intestinal, solitary mass; previously often mistaken for leiomyosarcoma
	other round cell, epithelial, mesenchymal and neuroendocrine tumours have been reported, but are rare			
Miscellaneous	Drug-induced	NSAIDs, corticosteroids		Indication of GI bleeding: thrombocytosis, BUN ↑, anaemia
	foreign bodies	hairballs, toys etc.	imaging (radiographs, ultrasound)	hairballs often in long hair breeds or psychogenic alopecia, other foreign bodies are usually associated with acute signs
	lymphangiectasia		panhypoproteinaemia	Rare in cats
	short bowel syndrome			Medical history of intestinal resection

Summary of diagnostic tests (having ruled out extra-GI diseases)

1. faecal examination for parasites
2. exclusion diet (maybe high fibre diet trial if large intestinal symptoms predominate)
3. imaging
4. biopsies and/or fine-needle aspirates (FNA)

Baseline tests should include a complete blood count (CBC), biochemistry profile (BC) and urinalysis (UA), FIV and FeLV tests, testing for pancreatic disease (fPLI and fTLI) and serum total T4 (tT4) concentration. In sick cats, serum tT4 might be falsely decreased and in clinically ill patients with a tT4 in the upper reference range and a strong suspicion of hyperthyroidism (e.g. large palpable thyroid gland(s)), further testing to exclude hyperthyroidism by measurement of a free T4 (fT4) should be considered.

Laboratory abnormalities that are frequently seen in cats with FCE include hyperproteinaemia (consistent with hyperglobulinaemia), increased ALT and ALP activity and increased serum fPLI concentration; these serve as evidence of chronic inflammation of the gastrointestinal tract, the liver and the pancreas, respectively. Other common abnormalities are hypophosphatemia, hypocobalaminaemia and hyper- or hypofolataemia. The cause of hypophosphatemia in cats with FCE remains to be elucidated but may be due to malabsorption,

maldistribution (intracellular shift), or increased loss. Concentrations will usually normalise if the disease is under good therapeutic control [15]. Dietary cobalamin is bound to intrinsic factor, which in cats stems exclusively from the pancreas. It is absorbed in the ileum via receptor-mediated endocytosis [16]. Therefore, decreased serum cobalamin concentrations most commonly occur in exocrine pancreatic insufficiency or diffuse ileal disease. A decreased serum cobalamin concentration has been associated with more severe disease, but the prognostic significance has not yet been established [10]. Serum folate concentration may be increased due to bacterial folate synthesis in patients with dysbiosis or may be decreased due to malabsorption in patients with diffuse upper small intestinal disease.

Imaging, such as abdominal ultrasound, might be useful as part of the initial work-up if there is evidence of intra-abdominal disease based on the physical examination, or if obstructive or other diseases that require immediate and/or surgical resolution are of concern. Nevertheless, one should be aware of the limitations since the utility of abdominal ultrasound in cases of chronic GI are limited. A recent study showed that although a muscularis propria to submucosa ratio > 1 reliably identified cats with diffuse infiltrative disease, neither the thickness of the muscularis (or mucosal) layer nor the presence of lymphadenopathy could distinguish cats with low-grade alimentary lymphoma (LGAL) from those with FCE [17, 18].

Differential diagnoses for chronic intestinal disease

After extra-intestinal and infectious diseases have been excluded, two major disease groups remain – feline chronic enteropathy and alimentary lymphoma. If the cat is relatively stable, dietary trials should be performed first to exclude food-responsive and fibre-responsive enteropathy.

Before a dietary trial is started, the cat's disease activity should be classified using the feline chronic enteropathy activity index (FCEAI) [15]. Due to its good inter-observer agreement it is an excellent tool to objectively assess a patients response to therapy, especially when initial assessment and re-evaluation are performed by different people or even at different hospitals.

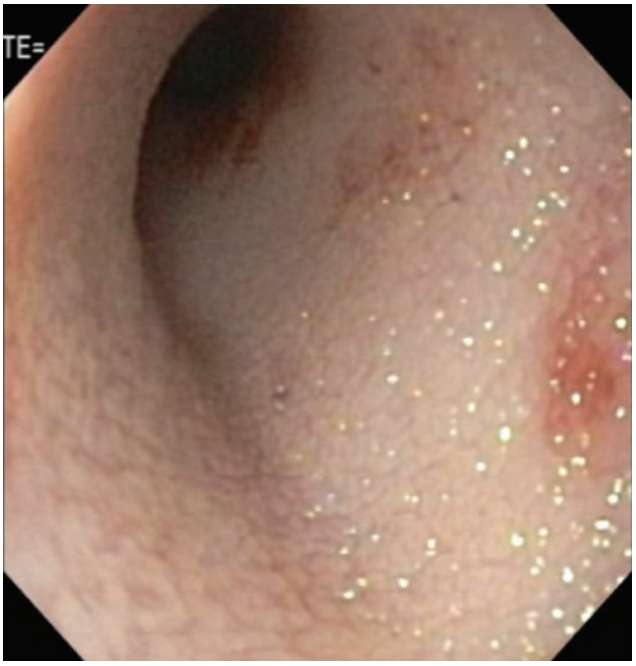
A cat that fails to respond to a dietary trial should be evaluated for the correct administration of the diet by the owners first. Ideally, multiple diets should be tested. If there is a true lack of response to diet, an antibiotic trial should be performed next (see "therapy" section for details of the diet and antibiotic trial).

If both dietary and antibiotic trials have failed, biopsies of intestinal tissue and, if possible, other organs (e.g. lymph nodes, pancreas and liver) are indicated. The cat's clinical, laboratory and imaging findings will guide our decision on how and where to take samples. Tenesmus, mucus and/or haematochezia point to large intestinal disease, while weight loss, vomiting, hypocobalaminaemia and/or hyper- or hypofolataemia are consistent with small bowel disease. Cats often show signs of mixed upper and lower gastrointestinal disease and thus samples should be obtained from the small and large bowel accordingly. Of special note is the presence of hypocobalaminaemia.

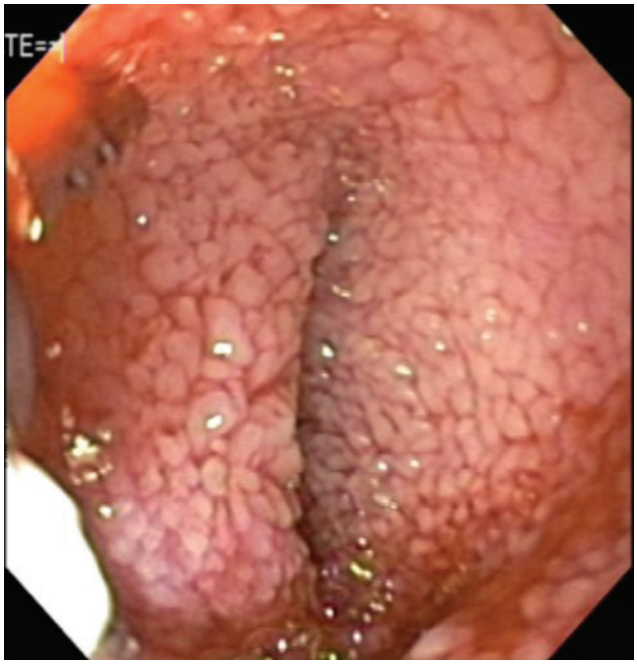
In the absence of EPI, hypocobalaminaemia is indicative of ileal involvement and collection of ileal biopsies is strongly recommended in those patients. This is even more important in the light of results from a recent study of cats with IBD or LGAL. The study compared histopathological diagnoses from the duodenum and ileum in cats with clinical signs of chronic small intestinal disease and found that in 44% of cases small cell lymphoma was only diagnosed in samples from the ileum and thus would have been missed on samples from the duodenum [19].

In patients with a single or multiple intestinal or abdominal masses, or those in which abdominal ultrasound showed the presence of jejunal or other lesions that cannot be reached via endoscopy, laparotomy or laparoscopy and full-thickness intestinal biopsies may be required. However, endoscopic biopsies have some advantages over surgical ones, especially now that advanced diagnostic techniques are available to help differentiate lymphoplasmacytic inflammation from small cell lymphoma, such as immunohistochemistry and PCR for antigen receptor rearrangement (PARR) [20-24]. In FCE, abnormalities noted during endoscopy correlate well with clinical disease activity and histopathologic findings [2, 15]. Flexible endoscopy allows for direct assessment of mucosal abnormalities and targeted biopsy collection (see figure 1). Multiple biopsies from each location are taken to increase the diagnostic yield in case of a patchy infiltrative disease. Recovery from endoscopy is usually substantially quicker than from laparoscopy or laparotomy and treatment can be started immediately after the histopathological report has been received.

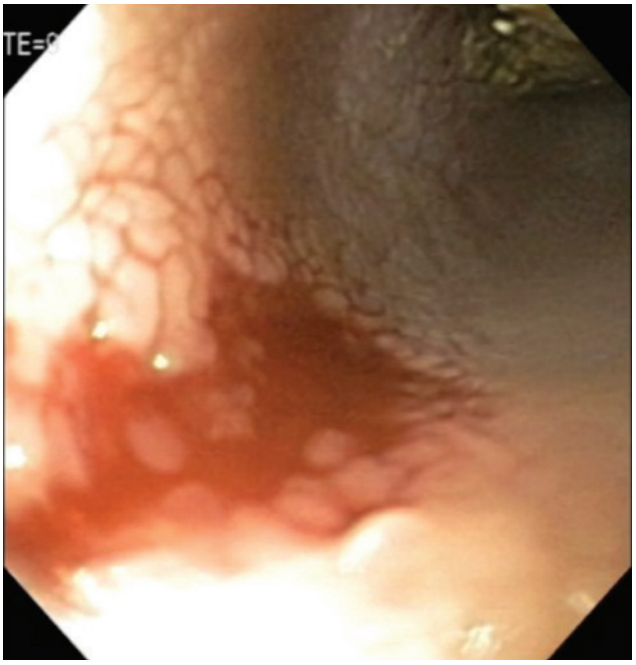
Figure 1. Endoscopic changes in cats with feline chronic enteropathy



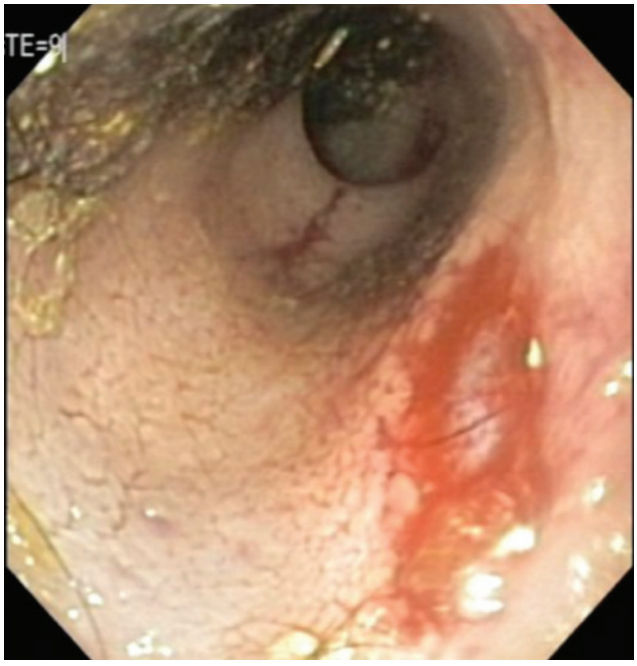
Increased granularity



Increased friability



Villus blunting and increased friability



Erosions

Extra-intestinal biopsies might be collected via cutting-type needle biopsy (e.g. tru-cut needle) or fine needle aspiration.

Interpretation of histopathology reports

A basic knowledge of histopathology, including its limitations is essential for the clinicians to get the most information from histopathological reports (see table 4). The best pathologist can only give a report based on the available information, which consists of a detailed report on history, physical and laboratory findings. An association between sample quality as well as number and the sensitivity of the detection of certain lesions in endoscopic biopsy specimens has been shown [2, 5, 20]. Histopathological evaluation assesses the inflammatory cellular infiltrate and the architectural changes of the tissue.

The most common form of FCE is lymphoplasmacytic enteropathy (LPE). Inflammation is found in the mucosa and sometimes the epithelium and the submucosa and is characterised by increased numbers of well-differentiated lymphocytes and plasma cells accompanied by destruction of the normal architecture.

Table 4. Summary of histologic changes associated with Feline Chronic Enteropathy

inflammation	
cellular infiltrate dominated by:	**+ architectural changes**
lymphocytes/ plasma cells	villus stunting (shortening, fusion)
eosinophils	epithelial injury (flattening, erosion, ulceration)
neutrophils (suppurative)	crypt dilatation/ distortion/ (colon) hyperplasia
macrophages (histiocytic)	mucosal atrophy/ fibrosis

For a more comprehensive review on standardization of gastrointestinal samples, please refer to Day et al., 2008 [22] and Washabau et al., 2010 [21]

LGAL is characterised by infiltration of the epithelium, the mucose and sometimes the entire intestinal wall (transmural) with well-differentiated lymphocytes mostly accompanied by lymphoplasmacytic inflammation in the same and/or other parts of the intestinal tract [4-6, 23, 24]. Not surprisingly, severe cases of LPE can be difficult to distinguish from LGAL (see figure 2-4) and transformation of LPE into LGLA has been suspected. For these reasons, the degree of architectural changes rather than the degree of the cellular infiltrate should be assessed and advanced diagnostics such as PARR may be needed to identify LGAL in equivocal cases [24, 25]. For example, architectural changes in the intestinal mucosa can be observed even if the cellular infiltrate is only mild or even absent. These features are thought to be associated with a "post-

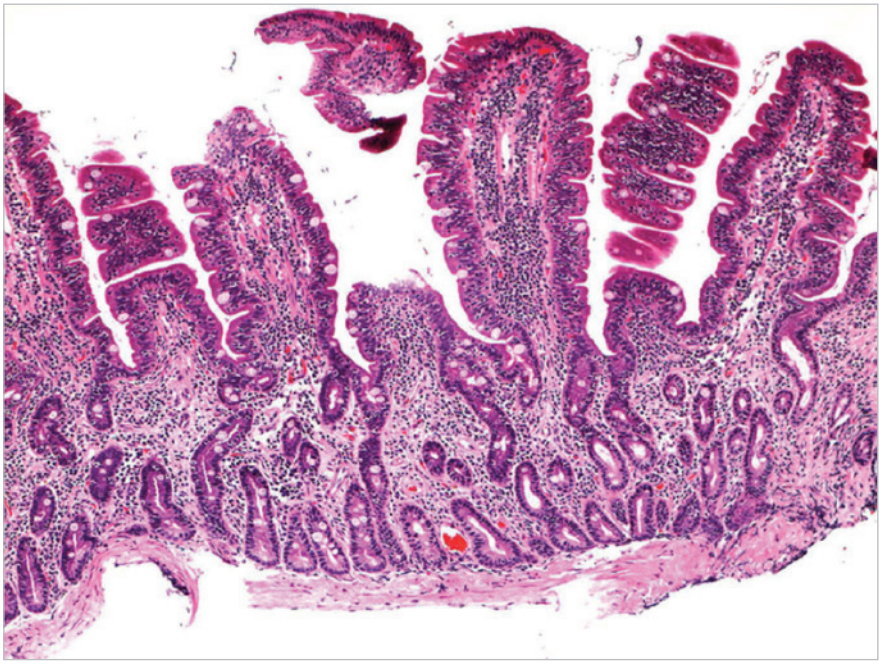


Figure 2. Mild to moderate lymphoplasmacytic enteritis

Histopathology (H&E staining) of an endoscopic biopsy from the small intestine of a cat with FCE. The lamina propria is diffusely infiltrated by lymphocytes and plasma cells, while the architecture is mostly unchanged.
(Image courtesy of Joanne Mansell and Kathrin Burke)

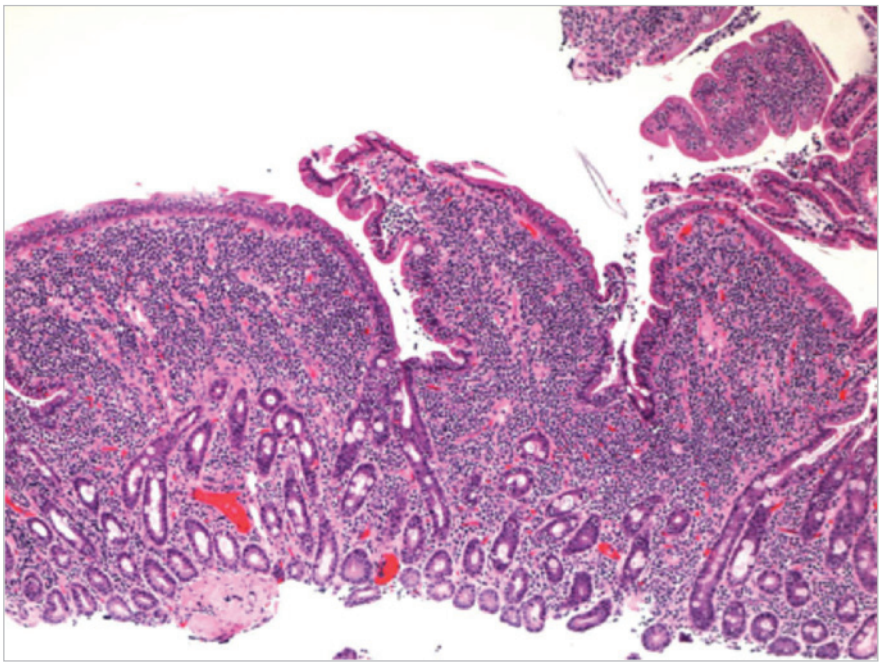


Figure 3. Moderate to severe lymphoplasmacytic enteritis

Histopathology (H&E staining) of an endoscopic biopsy from the small intestine of a cat with FCE. Severe lymphocytic enteritis. There is villus blunting and some fusion. The lamina propria and epithelium are moderately to severely infiltrated with small (mature) lymphocytes. The histologic appearance closely resembles a small cell lymphoma. Additional tests such as immunohistochemistry and PARR are indicated.
(Image courtesy of Joanne Mansell and Kathrin Burke)

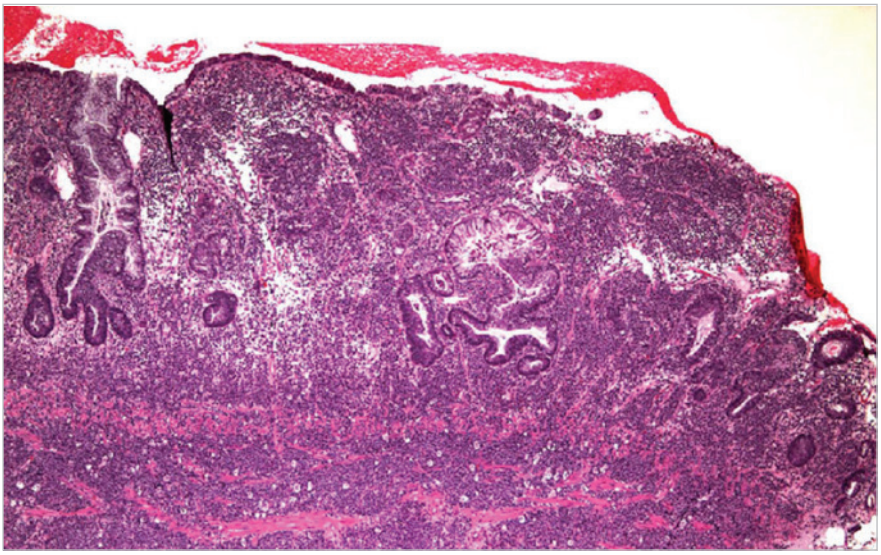


Figure 4. Feline low-grade alimentary lymphoma

Histopathology (H&E staining) of an endoscopic biopsy from the small intestine of a cat with LGAL. Major architectural changes with epithelial erosions. Villi are stunted and fused to the extent that no visible villi are left. Dilation and distortion of the remaining crypts are present. The lamina propria shows marked and diffuse infiltration by a monomorphic population of small (mature) lymphoid cells with extension into the submucosa.
(Image courtesy of Joanne Mansell and Kathrin Burke)

inflammatory" state and suggestive of previous severe and chronic inflammation and possibly on-going inflammation in other parts of the GI tract (patchy disease). Finally, a diagnosis of LPE is not equivalent to a diagnosis of IBD. LPE may be associated with intestinal parasites, food hypersensitivity, or even hyperthyroidism. This illustrates why other differential diagnoses need to be excluded before tissue sampling [26].

While architectural changes are a good indicator of the degree of inflammation itself, cellular infiltrates are still valuable as they may give us clues concerning the underling aetiology. A distinct eosinophilic infiltrate is often associated with food hypersensitivity or parasitic infection. Thus parasitic infection must be properly excluded by a negative faecal sample (3 day pooled sample) and deworming prior to collection of biopsies. Eosinophilic enteropathy may also occur as a part of the hyper-eosinophilic syndrome (HES). This systemic eosinophilic disorder is characterised by an increased production of eosinophilic precursors in the bone marrow. Patients display peripheral (mature) eosinophilia and eosinophilic infiltration in multiple tissues (e.g. gastrointestinal tract, spleen, liver, lymph nodes, heart and lungs) with subsequent organ damage [27-29].

Neutrophilic (suppurative) and/or histiocytic infiltration may suggest an infectious cause and additional testing including faecal culture, special staining and possibly fluorescence in situ hybridization (FISH) are indicated.

Concurrent diseases

Although diseases of the liver and exocrine pancreas are important differential diagnoses for FCE, unfortunately they may also be present as concurrent conditions to FCE, further complicating the clinical picture and treatment regime. Concurrent inflammatory diseases of FCE include cholangitis and pancreatitis, a pattern that has been referred to as *triaditis* in the past [11,15]. It has been hypothesised that cats are particularly prone to develop inflammatory conditions of the liver and pancreas because of their unique anatomy. The pancreatic and biliary tracts merge and open together in the duodenum. It is thought that dysbiosis and disrupted immune function in cats with FCE promotes ascending bacterial infections and/or ductal obstruction, causing cholangitis and pancreatitis. However, the most common form of concurrent inflammatory liver disease is lymphocytic cholangitis. Neutrophils are only found as additional infiltrates in about half of the patients [11]. Moreover, a study on bacterial cultures in cats and dogs with inflammatory liver disease showed that, although the prevalence of bacterial growth in hepatic cultures was significantly higher in cats than in dogs, only 14% of hepatic cultures and 32% of biliary cultures were positive [30]. In addition, 83% of cultures only grew a single bacterial isolate. These patterns do not support the hypothesis of an ascending infection from the duodenum. Therefore, the true aetiology of concurrent cholangitis in cats with IBD remains to be determined.

Pancreatitis is recognised in a substantial portion of cats with FCE and increased serum fPLI concentrations in cats with IBD have been repeatedly reported [9,11,29]. A recent study in 23 cats with confirmed FCE and concurrent fPLI measurements found increased serum fPLI concentrations in 70% of cats with FCE, of which 39% were in the questionable range and 31% were above the cut-off value for a diagnosis of pancreatitis [31]. The latter group also showed significantly lower serum albumin and cobalamin concentrations.

As indicated above, EPI is not only an important differential diagnosis in cats with chronic gastrointestinal signs, but may also occur concurrently with FCE. This illustrates why serum fPLI, fTLI, cobalamin and folate should be included as a part of the routine workup of cats with chronic signs of gastrointestinal disease. Although fTLI is a very stable analyte at room temperature, it is influenced by feeding and thus food should be withheld for 12 hours prior to blood sampling. Especially if TLI is in the questionable range, the test should be repeated after one month, paying particular attention to the withholding of food prior to blood collection.

Also, LGAL should always be considered as a possible differential diagnosis in cats with FCE. The vast majority of cats with LGAL show lymphoplasmacytic inflammation in other parts of their gastrointestinal tract and, as mentioned earlier, progression of chronic enteropathy to alimentary lymphoma has been proposed. Thus, re-evaluation of the whole case including history, physical examination, histopathology and additional tests such as immunohistochemistry and possibly PARR, is indicated in refractory cases (see table 5).

Table 5. Keys to achieve a correct diagnosis

A. Know your patient	Perform a thorough history and physical examination
B. Know your rule-outs	Exclude all possible extra-intestinal diseases
C. Know your rule-ins	Carefully interpret laboratory, imaging and histopathologic results
D. Know the limitations of your work-up	All diagnostic tests have limitations. Contacting the laboratory/ radiologist/ pathologist can be very helpful. Request of additional tests or repetitive testing might be indicated.
E. Know your follow-up/ outcome	Start from A, if a patient is refractory to treatment

Therapy

Nutritional therapy

As stated above, dietary trials have been found to be extremely useful with most studies indicating a response rate of about 50% or more in cats with FCE [6, 9, 15, 32, 33]. Depending on the primary clinical sign, responses can be seen very quickly. One study reported that vomiting resolved in all affected cats immediately and diarrhoea after 2 to 3 days [32]. In another study of 23 cats with chronic signs of GI disease, all cats responded to a dietary trial with complete resolution of clinical signs within 10 days [15]. However, when weight loss is the primary clinical sign, it may take up to 2 months to see a significant effect [33]. However, even though it sounds like the ideal therapy as it is inexpensive, simple and without side effects, there are some pitfalls. Two things are extremely important to consider for a successful dietary therapy, firstly to choose the optimal diet and secondly to introduce the diet the correct way.

One dietary option is an antigen-restricted diet that consists either of an intact but novel protein source or a hydrolysed protein source. Both types of diets have been shown to be effective in some cats with food responsive enteropathy [15, 32, 33]. In some cases, a home-cooked diet or individual diet may be beneficial. As true carnivores, cats have very special dietary requirements such as an usually high maintenance requirement for protein and arachidonic acid. Therefore, it is strongly advised to consult a nutritional specialist if owners want to prepare the diet at home or if the cat has special requirements (e.g. because it has multiple diseases). The amount of dietary fat has not been proven to significantly affect stool consistency in cats with chronic diarrhoea [34]. However, in cats with concurrent pancreatitis a diet with a lower fat content is advisable.

The best diet is worthless if refused by the patient. Many cats have fixed-food preferences. Those patients need to be transitioned to the new food over a prolonged period of 14 days. Initially 10 to 20% of the usual food is replaced by the new diet and the percentage is gradually increased over time. If food intake drops below 70% or the cat is selectively eating the former diet, the transition time needs to be prolonged. In rare cases, in which patients refuse to eat one diet entirely, trying another diet might be successful. Educating owners about the importance of feeding the new diet consequently and exclusively is crucial. However, understanding the dynamics of the owner-cat interaction is equally important. If food plays a major role in this interaction, suggestions of alternatives and "indulgences" are necessary. Many companies offer cat treats of dried meat from a protein source of choice (e.g. rabbit, venison, ostrich). Alternatively, owners can buy the meat of choice (often available online), cook it at home and use this as

treats. These suggestions often help owners to stick to the suggested diet.

Pre- and probiotics

Prebiotics are defined as substances that promote the proliferation of beneficial species of the intestinal microbiota. Prebiotics are non-digestible carbohydrates (oligosaccharides) that are selectively fermented by the intestinal microbiota. Examples of prebiotics that are commonly used are fructo-oligosaccharides (FOS), pectin, cellulose, psyllium, beet pulp or pumpkin. Although cats, as strict carnivores, do not require dietary fibre, it has been shown that the feline intestinal microbiota is able to ferment those substances and that they do have measureable beneficial effects on the microbiota [35-38]. Among these positive effects were increased faecal numbers of *Bifidobacterium* spp., increased faecal short-chain fatty acid content, more solid stools and lower concentration of faecal *E.coli*. In the authors' clinical experience, supplementation of dietary fibre can have beneficial effects on gastrointestinal function and motility and stool quality. Fermentation of prebiotics by the intestinal microbiota results in the production of short-chain fatty acids (mostly acetate, propionate and butyrate). Short chain fatty acids serve as a primary energy source for intestinal mucosal cells, especially colonocytes and are thought to have significant anti-inflammatory action [39, 40]. Fermentable fibre sources that are commonly added to the diet in the current clinical settings include beet pulp, pumpkin, psyllium (1 to 4 g/kg per meal, titrated to provide the ideal stool consistency). Care should be taken if these supplements are combined with an antigen elimination dietary trial, since some of them contain common proteins. In addition to specific supplements, commercial diets from many different brands are available for cats that are high in prebiotics.

Probiotics are microorganisms that are meant to colonise the intestinal tract after their consumption in order to exert beneficial effects to the host. The typical mammalian intestine hosts between 10^4 to 10^{10} microorganisms which are comprised of hundreds to thousands of phylotypes with different density and distribution in each segment of the gut. Therefore, a simple definition of "normal" and "beneficial" becomes difficult. Most studies to date have been performed in cats with acute diarrhoea; *Bifidobacteria* spp., *Enterococcus faecium, Lactobacillus* spp., or a combination of pre- and probiotics (synbiotics) were mostly studied [41-46]. A double-blinded placebo controlled study on the use of the probiotic *Enterococcus faecium* SF68 (FortiFlora®, Purina Veterinary Diets®) in 217 cats from an animal shelter revealed a significant reduction in episodes of diarrhoea [44]. An open-label clinical trial on 63 cats with chronic diarrhoea revealed a significantly improved faecal score after 21 days of treatment with a multistrain synbiotic (Proviable–DC®; Nutramax Laboratories), with 72% of owners reporting an improvement in their cat´s diarrhoea [46].

In summary, although the level of evidence to support the use of pre- and probiotics in cats with FCE is currently low, the use of pre- and probiotics in cats with chronic enteropathies is certainly an option as an additional treatment together with a dietary trial and/or medical therapy.

Antibiotics

Antibiotics are typically given to patients with diarrhoea rather than other signs of gastrointestinal disease. Tylosin and metronidazole are the most frequently used antimicrobials. Besides their antimicrobial action both drugs are believed to have anti-inflammatory or immunomodulatory actions [47, 48]. Given the current lack of knowledge about feline microbiota in patients with FCE, it is currently not fully understood how or why they work. Administration of tylosin is often difficult because it is mostly available in powder form for use in food animals. Anecdotally, doses of 25 mg/kg are recommended orally twice daily. If cats do not readily consume tylosin it can be reformulated into capsules. Metronidazole is given at a dose of 10 to 15mg/kg twice daily. Usually, antibiotic trials are performed for 2 to 3 weeks. Palatability of both antibiotics can make compliance challenging. Alternatives to the conventional metronidazole formulation might be metronidazole benzoate. This appears to be better tolerated by most cats; however, the dose needs to be adjusted because metronidazole benzoate contains only about 60% of metronidazole (20 mg/kg metronidazole benzoate equals 12.4 mg/kg metronidazole) [49]. Treatment can be discontinued in some cats, which can eventually be managed with diet alone, while others need repeated treatments or even the addition of immunosuppressive drugs. Care should be taken with long-term treatment. The mutagenic and carcinogenic potential of metronidazole is well documented in rodents [50, 51]. In vitro data on feline cell lines (including a feline T-cell lymphoma line) also showed genotoxicity (DNA disruptions) [49]. Progression from LPE to LGAL (which is

mostly of T-cell origin) in cats has been suspected and this appears (among many other reasons) a reason not to treat FCE patients with metronidazole long-term.

Immunosuppressive therapy

Options for medical management of chronic enteropathies are still limited in veterinary medicine today.
Besides the use of antibiotics for cases of antibiotic-responsive diarrhoea, treatment mainly consists of immunosuppressive drugs such as prednisolone, chlorambucil or cyclosporine. These therapeutic modalities are very powerful, but equally untargeted, inhibiting the undesirable as much as desirable effects of the immune system and are associated with a variety of side effects. Although targeted therapy of ulcerative colitis and Crohn´s disease in humans is also still at its infancy, there are more options available for human patients with IBD. One target is the pro-inflammatory cytokine TNF-α, which has been shown to play a critical role in the pathogenesis of IBD in humans. It is produced by T-lymphocytes and macrophages during inflammation and thus is primarily a consequence of inflammation. However, it also acts on perpetuating the inflammatory cycle by stimulating the production of other pro-inflammatory cytokines, such as Interleukin-1 (IL-1) and IL-6 and recruiting leukocytes by induction of adhesion molecule expression on endothelial cells. Therefore targeting cytokine signalling in general and TNF-α in particular has been a popular treatment strategy for humans with IBD. Today, anti-TNF-α antibodies such as infliximab are widely used in human patients with IBD [52, 53]. For various reasons, those therapeutic options are not yet available in veterinary medicine. However, with the progression in our understanding of the disease pathogenesis more targeted therapies for use in cats will hopefully become available.

Glucocorticoids
Several older studies document the efficacy of prednisone or prednisolone alone or in combination with other drugs (e.g. tylosin, metronidazole, sulfasalazine) in cats with FCE [6,8,9]. A more recent study using clinical scores (feline chronic enteropathy activity index or FCEAI) reported full clinical remission in all cats (17/17) with chronic enteropathy after treatment with an elimination diet and oral prednisolone [15]. Typically, prednisolone is started at 2 to 4 mg/kg/d; usually the dose is split and 1 to 2 mg/kg can be given q12 h, which might result in better efficacy. However, there are no studies to support this and the frequency should be determined based on the cat´s compliance and owners abilities to regularly pill the cat. The dose should be reduced every 4 to 6 weeks until the lowest possible dose. Some patients can eventually be managed with dietary therapy alone [9]. Cats should be monitored for clinical signs of insulin resistance and might benefit from regular blood glucose measurements upon re-evaluation. If, for any reason, a quicker taper might be required, prednisolone also might be combined with chlorambucil or cyclosporine. These drugs can have a "steroid-sparing effect" in that steroids might be tapered quicker without loss of immunosuppression.

Although this or similar dosing regimens have been used for decades, there are no data on the optimal dose and tapering regimen of immunosuppressive doses of prednisolone in cats with FCE.

Chlorambucil
Chlorambucil is an alkylating immunosuppressive/antineoplastic agent often used in addition to prednisolone and can be used in severe and/or refractory cases of FCE. It is typically introduced at a starting dose of 2 mg/cat q48h for the first 2 to 4 weeks and tapered thereafter to 2 mg/cat every 72-96h, although a variety of other dosing regimens have been described. The main side effect seen with chlorambucil administration is myelosuppression. The nadir usually occurs between day 7 and day 14 of the start of therapy with recovery taking equally long. Therefore, the nadir should initially be checked around this time and the dose should be adjusted if necessary (e.g. changing from every 48h to every 72 or 96h). There may also be an accumulative effect. Thus, cats that are on long-term therapy should also undergo regular complete blood counts every 2 to 4 months or if the cat is unwell. Owners should be instructed to never crush or split the tablets. If a cat needs a dose <2 mg or another specific dose, special compounding is necessary [54-56]. It should be noted that refractory cases of FCE are always suspicious for having undiagnosed LGAL. Combination therapy of prednisolone and chlorambucil is the treatment of choice for LGAL in cats and a lot of cases classified as "refractory FCE" probably have LGAL. The possibility of misclassification should always be discussed with the owner of a cat with FCE, but even more so if the patient is not responding to standard therapy.

Cyclosporine

Cyclosporine is a calcineurin-inhibitor, especially in T-lymphocytes and thus interferes with the development and activation of T-cells. Although cyclosporine has been widely studied in feline dermatology and stomatology, there are no published studies on the treatment of cats with FCE.

Typically, a dose of 5 mg/kg is given initially orally once or twice a day. However, due to the great variation in individual bioavailability, the dose can differ significantly between patients. Food reduces the bioavailability and thus cyclosporine should be given on an empty stomach [55]. However, side effects often affect the gastrointestinal tract (i.e. anorexia, vomiting, diarrhoea) and may be confused with worsening of clinical signs especially at initial drug introduction. In the authors' experience, the drug is often better tolerated if initially given with some food. The amount of food can gradually be tapered over 1 to 2 weeks until it can be given on an empty stomach; it is usually well tolerated thereafter.

Ancillary therapy

Cobalamin

Hypocobalaminaemia needs to be corrected in cats with FCE and early supplementation has been associated with weight gain and improved clinical signs [57]. The authors' current recommendation is to give 250 µg/cat subcutaneously every 7 days for 6 weeks, then one dose after 30 days and retesting 30 days after the last dose. If the underlying disease process has resolved and cobalamin body stores have been replenished, serum cobalamin concentration should be supranormal at the time of re-evaluation. If serum cobalamin concentrations remain within the reference interval, treatment should be continued at least monthly and the owner should be forewarned that clinical signs may recur sometime in the future. Finally, if the serum cobalamin concentration at the time of re-evaluation is subnormal, further work-up is required to definitively diagnose the underlying disease process and cobalamin supplementation should be continued weekly or bi-weekly.

Cobalamin may also have a pharmacologic effect as an appetite stimulant. Anorectic feline patients with cobalamin deficiency often start to eat again once they are being supplemented and appetite wanes once again when cobalamin is no longer administered weekly, despite a normal serum cobalamin concentration. In these patients, cobalamin supplementation should be continued on a weekly or biweekly dosing schedule.

Folate

The question of whether hypofolatemia should be corrected and if so what dosing schedule should be used is a matter of on-going debate. The authors supplement folate in patients with low serum folate concentrations using a dose of 200 to 400 µg per cat PO q24 [58].

Prognosis

Given the different forms of FCE and changes and inconsistencies in the classification of a case, data on the actual prognosis or prognostic indicators for FCE are very limited. As indicated above, a significant percentage of cats can be managed with diet alone and thus quality of life and life expectancy should not be significantly affected. However, there are refractory cases. A better co-operation and communication between referral centres and primary veterinarians as well as the use of standardised disease activity measures such as the FCEAI are necessary in order to gather more information about the long term outcome of cats with FCE. In contrast to cats with FCE, the median survival time for cats with LGAL has been well characterised and is reportedly >700 days with treatment with prednisolone and chlorambucil with a significant proportion of cats showing long-term survival of well above 2 years [56, 59]. Intuitively, at the very least this should be true for patients with FCE as well. However, this remains to be proven.

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Commissioned paper*

Environmental enrichment for cats with OA

Vicky Halls[1]

SUMMARY

The clinical presentation of osteoarthritis in cats is variable and studies suggest that changes in patterns of behaviour or lifestyle are much more commonly reported than overt lameness. Part of the treatment protocol for osteoarthritis is environmental modification, based on the cat's needs, to make adaptations to compensate for the changes associated with the disease.

Managing the arthritic cat at home requires a flexible approach, based on the individual's level of immobility, any concurrent disease and the general ageing process.

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Introduction

The clinical presentation of osteoarthritis (OA) in cats is variable and studies suggest that changes in patterns of behaviour or lifestyle are much more commonly reported than overt lameness[2]. Common signs include:

- Reduced ability (increased reluctance) to jump – cats will appear to prepare for a prolonged period before jumping, drag themselves up with the forelimbs or negotiate much shorter distances, e.g. from floor to chair to windowsill rather than directly in one jump
- Reduced overall activity – going outdoors less, possibly due to difficulties in using a cat flap or increased insecurity associated with mobility deficits
- Increased sleep – spending more time asleep or resting with eyes closed, possibly to avoid painful movement
- Reduced (difficult) grooming – less thorough grooming resulting in clumped fur at the base of the spine and hindquarters where spine flexibility are necessary in order to perform the grooming function
- Stiffness, unusual gait (particularly after rest) – resulting from pain and/or reduced range of movement, often making going up or down stairs difficult
- Change in social interaction – withdrawal from people or defensive aggression associated with the discomfort of handling. Changes may also be seen in relationships with conspecifics
- House soiling – associated with difficulties in using litter trays

Environmental enrichment

Environmental modification is part of the OA treatment protocol [1]. The American Association of Feline Practitioners and the International Society of Feline Medicine have published joint guidelines defining the environmental needs of the companion cat, stating that a cat's physical and emotional wellbeing were directly linked to the level of comfort and suitability of the environment for the individual. The guidelines identified five key elements[3] for the species:

Safety, multiple environmental resources located appropriately, opportunity to play and indulge in predatory behaviour, consistent and predictable owner-cat social interaction and recognition of the significance of the cat's sense of smell and potential olfactory stressors. These needs should be reflected in any modifications made.

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The term environmental enrichment is defined as additions to a relatively impoverished environment that enhance the psychological or physical wellbeing of the individual and can be sub-divided into the following categories[4]:

1. Social enrichment (either intra- or inter-species)
2. Occupational enrichment (psychological challenges or encouraging exercise)
3. Physical enrichment (altering size or complexity by adding objects or structures for example)
4. Sensory enrichment, visual, auditory, olfactory, tactile, taste
5. Nutritional enrichment, varied or novel food types

Social enrichment

Social interaction

Social interaction between people and cats takes many forms and includes petting and stroking, talking, greeting after a period of absence, playing using interactive games such as fishing rod toys and feeding high value treats. Spending time with the arthritic cat can involve sedentary or active contact, depending on the level of debilitation and chronic discomfort. Cats with OA tend to rest for prolonged periods and many relish the opportunity to do so on their owner's lap as this represents a warm place with a strong olfactory association with security and safety. If the cat is particularly thin then it may be helpful to provide a thick thermal blanket for further comfort.

Routine

Cats thrive on routine and predictability, particularly as they age, so any social contact should be consistent and positive. Interaction should not be forced with a cat; ideally the cat should be allowed to dictate the quality, quantity and frequency of interaction. As insecurity increases with age, some elderly cats will develop increased attachment to their familiar carers and may even start to seek attention at night or at a level during the day that interrupts the normal household routines. Providing the boundaries are established, e.g. no attention-seeking will be rewarded at night, and the cat has access to a warm bed, food, water, toys and litter tray, the behaviour can be safely ignored if it is considered excessive or at these inappropriate times.

Exercising

Gentle exercise, in combination with social contact, should be encouraged, particularly in those cats that previously spent a great deal of time outside. Many cats curtail their activity outdoors partly through insecurity and pressure from other younger, fitter cats in the territory. Owners can accompany their cats and take a walk round the garden, for example, where the cats will have the opportunity to explore in the knowledge that the human presence means they are safe to do so. Restricting the activity to times when the weather is warm and dry will further enhance the experience.

Resting

The arthritic cat, like any other, needs to be able to have uninterrupted rest and occasionally this will be in a place well away from children, family and other pets in the household. These areas should be kept accessible and new ones created if lack of mobility prevents the cat from using those previously favoured. Private places should be warm with a padded and thermal bed and the cat should not be approached when they are there unless the owner has any concerns about their wellbeing.

Grooming

If exercise is to be encouraged, it is important that the cat feels sufficiently comfortable to do so. Cats with OA are less able to groom efficiently so may need owners to wipe away any discharge around the eyes, nose or anus, using separate pieces of cotton wool moistened in warm water for each area. Brushing, using a soft bristle or rubber brush, for example, may be tolerated but care should be taken as arthritic cats may be thin with very little padding over their bones and vigorous combing or brushing can be painful. Grooming shorthaired cats only needs to be done thoroughly if there is any matting, although some cats consider this to be a pleasing social bonding exercise. Matting often occurs on the lower spine and hind quarters as an arthritic cat may be less flexible and therefore unable to reach these areas to self-groom. General tips for grooming the arthritic cat include:

- Groom at least once a week
- Use a flea comb first to check for any flea excreta but concentrate on areas around the neck and tail, avoiding those areas where the bones are prominent.
- Use fingers to gently loosen the dead hairs in the coat by massaging against the hair growth in the direction of the cat's head, always checking that the cat is comfortable and not resistant.
- Any knotted lumps should be teased out gently with the fingers, ensuring at all times that the hairs are not pulled directly from the skin. If the owner has

any doubt that this can be done without causing discomfort then they should consult their veterinarian for assistance. Matted fur should not be removed using scissors as it is often adhered to the skin and cutting can cause injury.

- The cat's coat should be groomed with a soft bristle brush or rubber-toothed device, taking care to avoid any known arthritic joints or bony prominences, stroking in the direction that the hair grows.
- A soft rubber grooming glove (with small rubber bumps on the surface to attract the hairs) or slightly damp rubber gloves can then be used, stroking from head to tail, to remove the loose dead hair and stimulate the blood supply to the skin.

If the cat is longhaired and is having difficulties keeping clean it may be advisable to have the coat around the anus, underside of the tail and back legs trimmed to avoid severe soiling or matting in that area.

Occupational enrichment

Time spent hunting and patrolling territory will have decreased in the arthritic cat, often resulting in more sleep to fill the void, which in consequence leads to stiffness and a decrease in mobility. Regular activity helps to retain muscle mass and aids circulation; it is also useful to assist bladder and bowel function.

Playing

Stimulating the arthritic cat should encourage both physical and mental activity. Exercise can be interactive or solitary and take the form of predatory play, exploration of new objects, patrolling or foraging for food. The nature of the activity undertaken should be appropriate for the cat's mobility deficits; gentle and regular playtime for short periods is the most suitable regime. The result may be as little as gentle waving of legs in the air to catch a feather; whatever the cat feels able to achieve is beneficial as it still constitutes positive exercise.

A variety of wand toys (also called fishing rod toys) is available, or can easily be made, that enable the owner to agitate a small object in front of the cat for them to chase, bat and catch. Objects should be soft without sharp points or containing anything that can cause harm. Popular choices include feathers, lengths of string, ribbons or fabric. Movements should be random rather than rhythmic to mimic the pattern of prey animals. The object should be kept at a distance of more than 20cm (8 inches) from the cat as this will help them focus on it better. If they show little interest then it can sometimes be useful to allow the object to touch them to encourage a swat with their paw, this is often sufficient to start the game in earnest. If they prefer to lie down while playing, this still enables them to move their legs and encourage a wider range of motion in each limb (Fig 1). The owner will need to be vigilant and watch out for signs that the cat is tiring e.g. becoming breathless and if necessary allow them to rest. It will also be apparent when they just 'aren't in the mood'; ensuring the cat is receptive to play maximises the benefit.

Fig 1 – Lying down to play encourages a wider range of motion in each limb for the cat with OA

Walking

In order to make activity and movement in general easier for the cat with OA, it is important that they feel comfortable walking. Laminate, tiled or wooden flooring can be slippery and arthritic cats can become unstable on these surfaces making them less inclined to be active. Equally, carpet can catch on the cat's claws that overgrow easily without regular stropping (sharpening) and remain protracted as the muscles weaken. Cut pile carpets are more comfortable for the arthritic cat than loop pile so if flooring consists of the latter a compromise can be achieved by providing cut pile runners throughout the home to enable the cat to walk unhindered. This is also the ideal surface on which to play, particularly if the cat likes to lie down in the process.

Toys

If the cat has always had a favourite toy there is no reason why this cannot still be of interest as mobility declines. Toys are best removed from view regularly and rotated with others to maintain their novelty value if

the cat needs encouragement to play on a daily basis. If the cat doesn't favour a particular object then it is worth experimenting with toys that are considered to have a majority appeal. These tend to be the size of a small rodent (mimicking the size of the cat's natural prey) and be made from a material that is close to the texture of fur. Toys are commercially available that are made from fur that is a by-product of a food source (rabbit) and these are particularly attractive. Synthetic fur fabric or leather 'mice' are also available and these can stimulate cats in a similar way. Any toys made with feathers are also popular.

Larger toys may also be useful to encourage the arthritic cat to lie on their side, grab the toy with their front paws and kick with their back legs. This gives important 'range of movement' exercise for stiff hind limbs and is a form of play enjoyed by many. The ideal 'kick toy' is rectangular or cylindrical, between 15-20 cm long (approx. 6-8 inches) and made of a durable fabric such as drill cotton or towelling. Some of the best commercially produced toys also have high quality catnip added.

All sorts of rubbish can be recycled as a toy for a cat, including screwed up paper, corks, walnuts, ping pong balls, cellophane and newspaper.

The cardboard box is a real favourite for many cats but the principle may need adapting for the arthritic individual. Cats love to explore boxes, often rubbing their faces on the edges and hiding inside. Older cats may like the idea of investigating but find the flexibility lacking to jump in and move around. This can be combatted by cutting a section out of one side to enable the less agile to step into the box. Placing it on its side with the opening facing the cat will enable them to walk in to carry out their investigation. Tucking some catnip, biscuits, treats or a toy in a corner will give the cat a reward for their perseverance. (All extra biscuits or treats should be approved as suitable). Larger boxes will be easier for the cat to explore as they aid comfortable movement inside.

Smaller boxes can be useful too if they are sealed and paw-sized holes are cut into the upper surface. Toys or kibble can be dropped inside, see below, and the cat can spend time manipulating the object through the holes with their paw.

Paper bags can also provide opportunities for exploration, particularly if they crinkle, but handles should be removed to avoid any accidents as cats can easily get them caught round their necks.

Claw trimming

Although not always considered enriching, there are necessary tasks to perform that are particularly pertinent to the arthritic cat, including claw trimming. This can be perceived by the cat as positive if associated with food treats, for example, and every effort is made to keep the process as comfortable and non-painful as possible. Some cats will tolerate this better than others so careful thought is necessary regarding how the task should be completed, and by whom, rather than failing to do so. Older cats shed their claws less easily so the claws can become very thickened and gnarled. Regular trimming, for example monthly, will be necessary, either at home or at the veterinary clinic. However the positioning of the cat's legs and paws during this process should take into account any range of movement deficits in arthritic joints. It is usually necessary to trim both front and back claws in the elderly.

Avoid conflict

Arthritic cats may be less tolerant of other cats in the same household, particularly if they do not have a high motivation to play or there is any conflict between members. Under these circumstances it is helpful to position all the arthritic cat's essential resources (food, water, litter tray, bed, hiding place) in one accessible area to enable them to have the choice to avoid contact with other cats if necessary.

Physical enrichment

Perches

Adding to, adapting or changing the physical environment will further aid the arthritic cat to perform basic functions with ease and enjoy things such as resting in high places or looking out of a window that may no longer be possible without help. There is rarely the need to make drastic changes to the home to accommodate a cat with OA but small adaptations to the existing cat resources can make a significant difference to quality of life. If the cat, for example, is finding stairs difficult to negotiate then they may be spending prolonged periods on one level, either up or down stairs. Ensuring that all their needs are met on that one level will avoid any risk of being unable to access important resources.

Feed & water bowls

Food bowls should be located well away from litter trays, thoroughfares, full length glass windows and cat flaps. Ideally they should be placed so that the cat can approach

the bowl from any direction, thereby avoiding the need to have their back to any other cats that may be in the household. If the bowl is positioned on a raised platform the cat will not need to lower their head in order to drink or eat and this will make it easier to do so for those with stiffness or discomfort in their neck, shoulders, forelimbs or thoracic spine (Fig 2). The availability of attractive sources of water is also essential, provided in a similar raised fashion. Water bowls should be placed away from the feeding areas to encourage older cats to drink as much as possible.

Litter trays

Many behaviourists recommend that litter trays be provided in the formula of one per cat in the household plus one extra, positioned in different locations. They should be

Fig 2 – Raised food and water bowls can be more comfortable for those cats with osteoarthritic in the forelimb, shoulder or neck (photo courtesy Sarah Caney)

located in different areas so that it is not possible for one cat to prevent another from having access to a litter tray. In the case of a single cat household two trays can be positioned in close proximity to each other. In the very elderly or those cats suffering from cognitive dysfunction it is appropriate for all of the cat's resources to be located in easy reach of the cat to avoid confusion.

Covered trays (those with hoods and flap entrances) can be difficult to negotiate for cats with OA. Open trays with low sides are ideal[5] and they should be firmly fixed to prevent them from being tipped up if the cat is weak and becomes clumsy when using a tray. Polythene litter tray liners should be avoided as they can catch in the cat's claws. Indoor trays should be cleaned regularly, a general recommendation for cleaning, using a clumping* substrate, would be:

Clumps of urine and solids should be removed once or twice a day and the litter topped up with fresh if necessary to an optimum depth of approximately 3-4 cm (approx. 1½ inches). If the cat has concurrent disease associated with polydipsia/polyuria this depth should be increased to 5-6 cm (approx. 2½ inches) to accommodate. Once a week the entire contents of the tray should be emptied, washed with hot water and mild detergent then filled to the original depth with fresh litter.

**If a non-clumping litter is used it is difficult to remove urine, so solids should be removed once or twice a day and the whole litter changed 2-3 times a week.*

Resting places

Many favoured resting locations for cats are on raised surfaces, such as the owner's bed or a window sill, so it may become difficult with time for a cat with OA to access these important places. The positioning of ramps, steps and platforms will enable the cat to reach the area in gentle stages rather than aborting attempts due to their inability to jump. If the cat rests on the owner's bed, chair or sofa, it is useful to provide a thermal blanket that is warm and washable. If the cat with OA likes to sleep on window sills or other narrow platforms, it is advisable to place a soft padded object on the ground underneath to prevent injury as many older cats have impaired balance and could easily fall. Ideally elderly cats, especially those with OA, should be encouraged to use secure or wider surfaces for sleep.

Electric or microwave heated pads are available to provide extra heat for cats that find warmth therapeutic. These should also be raised off the floor at an accessible level as most cats prefer to sleep off the ground, particularly when living in a multi-cat household (Fig 3).

Views

Cats often enjoy a view of outdoors and most favour sitting on high windowsills. Jumping up can prove difficult if not impossible for some so provision should be made for easy access up to and down from these favourite lookouts. A series of shallow steps offer the best solution, ramps can be used but only if they are angled to represent a slight incline rather than a steep slope.

Ramps

Ramps can be constructed that are based on the deckchair design using notches in the base to allow a prop to adjust the angle of the ramp. A non-slip surface,

Fig 3 – A soft, padded bed with integral heat pad positioned in a sunny window for maximum benefit

such as carpet, should be adhered to the ramp or wooden battens fixed at intervals to provide ladder-like rungs. The angle of this ramp is best at no more than 30 degrees from the horizontal so their use is limited to gradual inclines only; any steeper gradient would be better serviced using steps.

If steps are built to reach a particular area the distance should be measured and the height of each step calculated based on a three step unit (usually the device becomes bulky if there are any more than three steps). The steps should be constructed in such a way that they will support the cat's weight and be comfortable to use (Fig 4).

Cat flaps

Some cats with OA will reduce the frequency of excursions outside as a result of difficulty negotiating the cat flap. It may be helpful to build a step, inside and outside, to make it easier to use the flap but eventually it is almost inevitable that the cat flap will be replaced by escorted trips into the garden, as described previously. When this occurs, if no other cats in the household are using the flap, it would be advisable to block off or remove the flap to prevent invasion from other cats outside. This can be distressing for the elderly particularly as they are less able to defend their territory.

Territory

A significant reason why arthritic cat spent less time outdoors is likely to be other cats in their territory and a sense that they are no longer able to actively defend their patch. If the owner is able to secure the garden, it will exclude other cats and contain the resident cat within the safety of their own property. Various systems are available, including inverted brackets and netting, and even outdoor enclosures may be considered (Fig 5). Other suggestions, regarding the garden include the following:

- Stock flower borders with a variety of plants and dense shrubbery to provide the cat with private areas, shade in hot weather and protection from rain.
- Protect any fishponds with cat-proof netting and, ideally, a small fence around its perimeter.
- The cat may want to scratch in the garden so horizontal surfaces should be available, soft woods are a popular material.
- All wood preservatives, weed killers and any other products used in the garden should be safe for use around cats and stored appropriately.
- Ramps or steps for access can also be used in the garden to favoured high perches.

Fig 4 – Steps can give the arthritic cat easy access to favoured high resting areas

Fig 5 – An outdoor enclosure may be a safe place for the arthritic cat to enjoy some sun

Sensory enrichment

Synthetic feline facial pheromones can be used in diffuser and spray form to reinforce security in the areas where the cat rests for prolonged periods, reinforcing the location as a safe core area.

Catnip

Approximately two-thirds of all domestic cats exhibit a response to the scent of the herb *Nepeta cataria*, referred to as catnip. This can have either an excitatory or calming effect and is used to encourage activity (it is often placed inside toys) and even promote appetite if the dry herb is sprinkled on food. This is best offered for short periods several times a week to maintain a strong appeal. All catnip should be kept out of reach in sealed containers when not in use to preserve its potency. The best quality and most appealing varieties are those made from the leaves and flowers of the plant.

House smells

If the cat is kept exclusively indoors, objects can be brought into the home that may arouse their interest. Logs or thick branches, large stones or feathers collected from the garden for example can all be brought inside from time to time.

Elderly cats become more dependent on routine and a predictable environment and this includes the maintenance of a familiar scent profile to the home. Potential olfactory stressors include room air fresheners (plug-in or aerosol), strong-smelling cleaning products or perfumes, paint and large, new objects such as sofas and carpets.

Nutritional enrichment

If part or all of the cat's diet consists of dry kibble then they may enjoy a challenge to acquire some of their daily ration. Placing kibble or biscuits inside cardboard egg boxes, tubes or paper bags requires some paw dexterity to remove them, for example:

- Drop one or two biscuits in each section of a cardboard egg box.
- Place a few biscuits at the bottom of a paper bag with the top folded over.
- Attach decreasing numbers of toilet roll tubes to each other, five at the base, then decreasing numbers in each layer to form a triangle shape. Secure this to a raised base, to prevent the cat from having to crouch. The kibble can then be placed half way down each tube for the cat to see and retrieve with its paw.
- Wrap kibble in tissue paper and place in a cardboard box.
- Make paw-sized holes in a sealed cardboard box and put biscuits inside.

Fig 6 – Arthritic cats may enjoy pushing a ball containing kibble rather than more complex feeding devices

Care should always be taken to ensure that any interactive feeding of this kind takes the cat's mobility into consideration, for example if the cat has elbow or shoulder arthritis it would not be appropriate to provide a feeder that requires a full range of movement of the forelimbs. This cat may prefer a feeding ball that releases food when pushed along the ground (Fig 6).

In conclusion

Some adaptations represent one-off changes to the environment and others require the owner to perform daily chores based on the cat's needs. Monitoring of any changes in the cat's general health or level of discomfort is also essential. There is however scope for a rich and mutually beneficial relationship for owner and cat, based on these recommendations.

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