European College of Veterinary Pharmacology and Therapeutics

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European Society of Veterinary Nephrology and Urology

Symposium: Pharmacology and the kidney

19th July 2019
Royal Veterinary College, London, Camden

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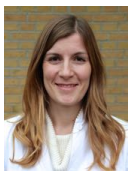

Programme

9.00-9.05	Welcome address
9.05-9.50	Pharmacology of emesis and nausea in renal disease *(Ludovic Pelligand)*
9.50-10.35	Nausea, appetite and lean body composition in the renal patient *(Yann Queau)*
10.35-11.20	---Coffee break---
11.20-11.50	Antimicrobial testing and break points: what do they mean? *(Luca Guardabassi & Ludovic Pelligand)*
11.50-12.30	What's new in managing sporadic cystitis *(Tina Sorensen)*
12.30-13.30	---Lunch break---
13.30-13.45	---Abstract presentation---
13.45-14.30	Angiotensin receptor blockers *(Herve Lefebvre)*
14.30-15.15	Clinical management of hypertension and proteinuria in the dog *(Thierry Francey)*
15.15-15.45	---Coffee break---
15.45-16.30	Understanding hypoxia and HIF with clinical application *(Caroline Wheeler-Jones)*
16.30-17.15	Drugs targeting bone and mineral disturbances *(Rebecca Geddes)*
17.15-17.30	Closing remarks

Welcome from ECVPT and ESVNU

On behalf of the ECVPT and ESVNU we are delighted to welcome you to this symposium with a focus on nephrology and pharmacology. If you have any concerns during the event please do not hesitate to contact one of the event organisers. We hope that you enjoy your day at the symposium.

Prof Jonathan Elliott President of ECVPT
Dr Rosanne Jepson President of ESVNU

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MERCURY CHALLENGE

NEWSLETTER #3

5596 CATS MEASURED BY 641 VETS IN 15 COUNTRIES

NUMBER OF CATS PER COUNTRY

UK	1744
Spain	1085
Italy	1039
Denmark	447
Sweden	432
Germany	343
France	255
Austria	127
Czech Republic	86
Belgium	7
Argentina	4
Mexico	4
Chili	1
Turkey	1
USA	1

→ **BP MEASUREMENT**
< 10 min

→ **DEMEANOUR**
Calm or cooperative but anxious

IN 91% OF CATS

1914 HYPERTENSIVE (HT) CATS*

AGE
13,6 ± 3,7 years

BODY WEIGHT
4,2 ± 1,3 kg

FEMALE 48 % | **MALE** 52 %

MEAN BLOOD PRESSURE

HT CATS*
186 ± 25 mmHg

NON HT CATS**
132 ± 18 mmHg

Category according to ACVIM classification[1]	N=5596	% of total pop	% of cats receiving anti-HT treatment
Normotensive (minimal TOD risk) SBP < 140 mmHg	2089	37,3%	7%
Prehypertensive (low TOD risk) SBP 140-159 mmHg	1513	28,8%	14%
Hypertensive (moderate TOD risk) SBP 160-179 mmHg	954	17%	40%
Severely hypertensive (high TOD risk) SBP ≥ 180 mmHg	960	17,2%	67%

CONCURRENT DISEASES

26% cats with **Chronic Kidney Disease (CKD)**

4% cats with **CKD + Hyperthyroidism**

14% cats with **Hyperthyroidism**

*BP ≥ 160 mmHg / **BP < 160 mmHg

[1]Acierno et al. 2018 ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats

Pharmacology of nausea and emesis in renal disease

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Associate Professor in Clinical Pharmacology and Anaesthesia, Royal Veterinary College, London

Biography: Ludovic graduated from the École Nationale Vétérinaire d'Alfort (Paris, France). Ludovic gained the European Diploma in Veterinary Anaesthesia and Analgesia in 2006 and his European Diploma in Veterinary Pharmacology and Toxicology in 2014. He is currently Associate Professor in Veterinary Clinical Pharmacology and Anaesthesia at the Royal Veterinary College.

Abstract:

1) Mechanisms of nausea and emesis in general and in patients with chronic kidney disease (CKD)

Nausea is a subjective phenomenon in human medicine, which is reported by patients (i.e. it is a symptom). We usually associate the feeling of nausea with the urge to vomit. It is often described as 'feeling sick to the stomach' and it is usually considered that when nausea reaches intolerable levels (i.e. a threshold is reached), vomiting occurs. In veterinary practice, we observe the physiological and behavioural responses in canine patients, which we associate with the feeling of nausea (Kenward et al. 2015).
Common clinical signs observed in patients believed to be nauseous are drooling or ptyalism, inappetence, restlessness and anxiety, lip licking or smacking and gagging/retching. Other signs observed may include lethargy, polypnoea, excessive chewing, pica, exaggerated swallowing and walking away from the food bowl. We suspect than in practice, nausea in veterinary patients is under-recognised and under-treated.
In the context of renal disease in the cat, nausea and vomiting might result from central effects (uraemic toxins stimulating the chemoreceptor trigger zone, for example) and peripheral mechanisms (uraemic gastritis due to a combination of gastric hyperacidity and the irritant effects of urea at high concentrations on gut mucous membranes) (Batchelor et al, 2013).

2) Pharmacology of drugs that prevent nausea and vomiting:

Dopamine D_2 receptor antagonists

Metoclopramide, a dopamine2 (D_2) antagonist is a commonly used antiemetic in veterinary medicine and is effective against apomorphine and cisplatin-induced emesis in dogs. It is licensed as an antiemetic and a prokinetic stimulant licensed at the dose of 0.5 mg/kg intravenous, intramuscular, subcutaneous or oral every 12h. It can be used for infusion at rates of 1 to 2 mg/kg/24h. A search of the published literature provides no evidence for specific anti-nausea effects of metoclopramide in the dog or cat or for placebo-controlled efficacy trial in animals in the presence of CKD. However, in human medicine, metoclopramide is reported to have efficacy against post-operative nausea following abdominal surgery and reduces the duration of cisplatin-induced nausea.

Neurokinin 1 (NK_1) receptor antagonists

The NK_1 antagonist maropitant is an anti-emetic specifically designed for veterinary use and is licensed dogs and cats. Maropitant is effective at preventing emesis induced by apomorphine, ipecac, chemotherapeutic agents and motion. It is licensed at a dose of 1 mg/kg IV or SC and due to the high degree of target binding, the effect extends for up to 24h. The oral dose (dog license only) is 2 mg/kg per emesis and 8 mg/kg for motion sickness.

Quimby et al. (2015) reported a randomised double masked placebo controlled clinical trial of maropitant in cats with CKD. Maropitant significantly reduced the frequency of vomiting seen when

compared to placebo but had no effect on appetite score, activity score or body weight. Maropitant tablets are not licensed for cats, but basic information on bioavailability (50%) and short-term effect of oral maropitant in cats is available (Hickman 2008)

Maropitant demonstrated anti-nausiogenic efficacy in dogs treated with cisplatin, significantly reducing measurements for nausea (Visual Analog Scale, VAS) when given up to 19 h prior to or following IV high dose cisplatin infusion (de la Puente-Redondo et al. 2007). However, maropitant did not significantly change nausea scores compared with placebo in dogs receiving doxorubicin treatment for cancer (Rau et al. 2010).

Serotonin (5-HT_3) receptor antagonists

The 5-HT_3 receptors are present on abdominal vagal afferents and are involved in the detection of emetogens in the gastrointestinal tract. The 5-HT receptors also have a central role in emesis. Many types of 5-HT_3 antagonists are commercially available as antiemetics, and all use the suffix 'setron'. Of these, ondansetron is the most widely used in humans and in dogs (no veterinary license); it is efficacious against acute emesis but not delayed emesis occurring from 1-3 days following the administration of chemotherapy. Ondansetron is indicated in veterinary patients when clinical signs cannot be controlled by other drugs (metoclopramide and maropitant). The initial dose is 0.5 mg/kg IV and can be followed up with infusion (0.5 mg/kg/h for 6h) or orally 0.5-1 mg/kg every 12 to 24h.

The anti-nausea effect of ondansetron is well documented in human patients but less so in veterinary species. Ondansetron has been shown to significantly reduce nausea induced by anaesthesia, cyclophosphamide and cisplatin in humans. Ondansetron delayed emesis and significantly decreased the nausea scores compared with placebo in beagle dogs administered the daffodil alkaloid lycorine by IV injection (Kretzing et al. 2011). One research group reported the pharmacokinetics of ondansetron administered by IV, SC, oral (Quimby et al. 2014) and transdermal (Zajib et al. 2017) in normal cats and cats with CKD (Fitzpatrick et al. 2016). However, ondansetron was only tested in the context of premedication-induced vomiting in the cat, not in CKD.

Mirtazapine, a tetracyclic antidepressant with activity as a 5-HT3 antagonist, has been shown to improve appetite, reduce vomiting and increase weight gain in cats with naturally occurring CKD (Quimby and Lunn 2013). This study, a well-designed randomised controlled masked clinical trial with clear inclusion and exclusion criteria, provided Level 1 evidence of efficacy. This possibly suggests an anti-nausea action; however, nausea was not specifically measured in this study
This dose rate was selected following earlier single dose pharmacokinetic studies in healthy older cats and cats suffering from CKD and in young healthy cats (Quimby et al., 2011a,b). Two doses were tested: low (1.88 mg) and high (3.75 mg) doses. Mirtazapine shows non-linear clearance and increased exposure in patients with kidney disease.

3) Models for the development of new nausea and emesis drugs

There is a need to identify models of nausea relevant to the one experienced by animals with renal disease, especially in the cat, as xylazine-induced vomiting is not relevant anymore. In some cases, nausea and vomiting are dissociated: there are only very few studies comparing of the anti-emetic and anti-nausea effects of the three classes of drugs. One blinded placebo-controlled study compared the anti-emetic and anti-nausea properties of metoclopramide, maropitant and ondansetron in a low dose cisplatin model (Kenward et al. 2017). None of the dogs in either the ondansetron or maropitant treated groups vomited but ondansetron was far more effective at suppressing nausea behaviour or its biomarker (vasopressin). Metoclopramide had no more effect than placebo on either vomiting or nausea.

In conclusion, the two main concepts are that i) drugs can be very effective anti-emetics but not effective anti-nausea agents and ii) poorly managed nausea has patient welfare implications just as poorly managed pain does.

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Nausea, appetite and lean body composition in the renal patient

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Biography: After graduation from the National Veterinary School of Toulouse (France) in 2007, Yann Quéau completed an internship in Renal Medicine & Hemodialysis and a residency in Small Animal Clinical Nutrition at the University of California, Davis. He became a Diplomate of the American College of Veterinary Nutrition (ACVN) in 2011 and joined the Royal Canin Research & Development center in France as Clinical & Research Nutritionist, leading the urinary and nephrology research programs. Since 2017, he is in charge of the research team dedicated to clinical nutrition and veterinary diets.

Abstract:
As kidneys regulate fluid, electrolyte and acid-base balances, and excrete numerous waste products, renal failure has multiple systemic consequences. This presentation reviews in particular the effect of renal disease and uraemia on dysorexia and lean body mass (LBM) alterations.

1. Consequences of renal disease on nausea and appetite

1.1. Nausea

Assessing nausea objectively in animals is challenging. Clinical manifestations can be non-specific and result from other processes happening as a consequence of renal disease. While salivating is often attributed to nausea, altered appetite or vomiting are multifactorial (*see 1.2.*). Nausea can find its etiology in uremic toxin retention, but non-renal causes should not be overlooked. Some commonly used drugs can cause nausea (opioids, antibiotics, anti-inflammatory drugs etc.).

Nausea and vomiting are treated with dopamine antagonists (metoclopramide), serotonin 5-HT3 receptor antagonist (ondansetron, dolasetron) or neurokinin receptor antagonist (maropitant).

1.2. Dysorexia

Inappetence is reported in 21-92% cats (1) and in 58% dogs (2) with chronic kidney disease (CKD). In an unpublished retrospective study, the author found that hyporexia (defined as reduced food intake compared to usual) reported by the owners afflicted up to 90% dogs and 80% cats with CKD, and anorexia (defined as complete absence of intake) was reported in up to 40% dogs and 50% cats with CKD. Prevalence of both conditions significantly increased with the stage of CKD.

Dysorexia in renal disease is likely multifactorial.

- Accumulation of toxic metabolic waste products (among which unidentified anorexigenic compounds) and decreased clearance of hormones (leptin, ghrelin) involved in the appetite regulation center in the brain are thought to play a key role (3). Hyperserotoninergic state from increased tryptophan transport to the brain has also been postulated (4).
- Some gastrointestinal consequences of uraemia can also play a role. Buccal and lingual ulcerations can occur, possibly as a result of excessive conversion of urea to ammonia by urease producing bacteria present in the oral cavity. Gastric edema and mineralization were significantly more frequent in dogs with CKD (5), and the prevalence of lesions increased with the severity of azotaemia. All these dogs presented with gastrointestinal signs including inappetence and vomiting. Likewise, gastric fibrosis and mineralization was significantly more present in CKD cats (38% and 43% respectively) than in control cats (0%) (6). Gastric ulcerations however do not appear to be frequent in either species with CKD (5,6). Despite

the absence of data in dogs and cats, pancreatitis may also be seen concurrently especially in dogs with acute kidney injury or end-stage CKD, as reported in humans (7).
- Other metabolic consequences of renal failure, such as dehydration, anemia, metabolic acidosis or hypokalemia also contribute to anorexia.
- Finally some commonly used drugs also affect appetite by causing nausea or altering smell or taste (opioids, antibiotics, anti-inflammatory drugs, ...).

Although difficult to evaluate objectively, food aversion may contribute to the phenomenon of anorexia in renal disease. It can result from the association of adverse or stressful events (hospitalization, sickness) with a certain food/flavour.

To address hyporexia, all underlying metabolic disturbances should first be addressed medically. Orexigenic drugs evaluated in animals with CKD include mirtazapine in cats (1.88 mg PO q2d) (8), and recently, capromorelin in dogs (tested short term in a cohort of sick dogs, including 14 dogs with unknown stage of CKD) (9). Assisted enteral feeding (via feeding tubes) allows the delivery of the daily calories, an appropriate diet, as well as medications and water needs of dogs and cats with CKD provided the diameter is large enough, but this option must be carefully discussed with owners for acceptance and compliance. Oesophageal tube feedings have for example been used successfully in cats with CKD to normalize their body condition score (10).

2. Lean body mass alterations in renal disease

Unfortunately there is little published on LBM metabolism in animals with acute or chronic kidney disease, but some physiologic bases from other species are likely to apply. When extrapolating from human studies however, some caution must be used as treatment modalities can differ (especially dialysis) and impact muscle metabolism.

2.1. Muscle mass metabolism

To the author's knowledge, there is no study evaluating LBM metabolism in dogs and cats with kidney disease. One difficulty is the lack of precision of some methods to assess protein metabolism. Nitrogen balance studies have been used for decades for the determination of the minimum protein intake that is necessary to compensate for faecal, urinary and other miscellaneous nitrogen losses. However some consistent errors in this technique can lead to overestimation of nitrogen retention, and therefore underestimation of protein requirements when compared to techniques such as LBM determination (11). More precise methods of LBM determination such as deuterium oxide, bioelectrical impedance or Dual X-Ray Absorptiometry (DEXA), or of muscle catabolism, such as 3-methylhistidine excretion, are not always practical in a clinical setting with patients with naturally occurring kidney disease. A muscle condition score (WSAVA) has recently developed to be an integral part of a clinical examination but is too crude for research purposes.

One study reported higher urea generation rates in dogs with very low GFR (12), but further research is warranted to determine whether the course of the disease (acute vs. chronic, early stage vs. late stage), but also the type of disease (glomerular vs. tubulointerstitial) affect protein needs substantially.

Finally, when considering LBM, the modality of treatment should also be considered: human patients undergoing hemodialysis experience enhanced protein catabolism and muscle breakdown (13), in part mediated by inflammatory cytokines. Similar data are again not available in animals, but it is known that amino acids are lost during hemodialysis treatments (14).

2.2. Effects of diet composition and intake on muscle mass metabolism

As previously mentioned, it is not known whether protein requirements in renal disease differ from healthy animals. Providing sufficient protein is nonetheless capital as protein malnutrition is associated with higher morbidity and mortality, at least in human patients (15). Commercially available renal diets for dogs and cats provide various levels of dietary protein, usually below levels of maintenance diets but above recommended allowances established by the National Research Council (NRC, 2006) for healthy adult dogs and cats.

Over the past years, some have questioned the adequacy of those levels to maintain LBM in animals with CKD, principally cats (16-18). However to date there is no published evidence that cats fed protein levels close to the published recommended allowance develop protein malnutrition. In cats with naturally occurring CKD, there was no apparent negative effect of feeding a protein restricted diet (23% ME) on body weight and BCS over two years, although lean body mass could not be evaluated in this clinical setting (19).

The complexity of this debate is that dietary protein level is not the only factor to consider for maintenance of lean body mass. Overall caloric intake (which ultimately conditions the amount of protein ingested), protein quality (i.e. digestibility and essential amino acid profile), the role of other nutrients (such as carbohydrate) in protein turnover, or acid-base status can all contribute to changes in lean body mass, may in fact dictate the optimal protein level to be fed to an individual animal with kidney disease to maintain LBM.

Increasing dietary protein content may therefore not be the first and foremost consideration when facing a renal patient with loss of muscle mass, especially since protein also contains phosphorus, a nutrient to restrict in renal disease. Instead, assessing and addressing caloric intake should come first (*see 1.2.*).

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Antimicrobial testing and break points: what do they mean?

Ludovic Pelligand and Luca Guardabassi
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Biography (Luca Guardabassi): Luca Guardabassi (LG) is professor at the Faculty of Health and Medical Sciences, University of Copenhagen and at the Royal Veterinary College. He is an internationally recognized One Health microbiologist specialized in antimicrobial resistance. As part of his honorary office, he chairs the ESCMID Study Group for Veterinary Microbiology (ESGVM) and the Therapeutic Guidelines Group in WSAVA, and is member of the WSAVA One Health Committee, the European veterinary subcommittee on antimicrobial susceptibility testing (VetCAST) and various national and international working groups for antimicrobial guidelines in veterinary medicine.

Abstract:

Antimicrobial susceptibility testing is an essential diagnostic tool to optimize antimicrobial therapy in clinical practice. The results are interpreted using breakpoints, which are host- and drug-specific interpretive criteria allowing definition of susceptibility and resistance to antimicrobials. Despite of the progress being made in recent years, the procedure used for setting breakpoints is still not an exact science. This lecture will draw the attention to the significant consequences that inaccuracy of a breakpoint may have on patient care and antimicrobial use for management of urinary tract infections (UTI). The two speakers will present the microbiologist's and pharmacologist's perspectives on this topic with particular regard to management of uncomplicated cystitis, a frequent infection in dogs.

The breakpoint of an antimicrobial is set by international organizations taking into account *in vitro* susceptibility of the target pathogen (MIC data), plasma concentration-time profiles following standard dosage (pharmacokinetics data, PK) and antimicrobial effects on the pathogen over time (pharmacodynamics data, PD) [1]. As most antimicrobials are excreted and concentrated in urine, UTI-specific breakpoints are determined considering the higher concentrations achieved in urine compared to serum. Traditionally breakpoints are calculated using the lowest label dosage. This strategy has the advantage of generating susceptibility results that are valid for any label dosage regimen used. However, it implies a risk that some strains that could potentially be cured (e.g. using the highest label dose or the most frequent administration frequency) may be falsely reported as resistant, limiting therapeutic options and favouring the use of second line drugs with broader spectrum of antimicrobial activity.

It should be noted that in the lack of pharmacological and clinical data, some veterinary breakpoints are currently determined on the basis of *in vitro* microbiological data only. This is the case for the current UTI breakpoint for amoxicillin, a first line agent for treatment of uncomplicated cystitis. Resistance to this clinically important antimicrobial is solely reported on the basis of the *in vitro* susceptibility data without knowing the actual efficacy of the drug under *in vivo* conditions. According to the current CLSI breakpoint, a canine UTI caused by an *Escherichia coli* strain with MIC > 8 µg/ml should not be treated with amoxicillin although this antibiotic may reach urine concentrations of 201 +/- 93 µg/mL following administration of 11 mg/kg q 8h [2]. Notably, a human UTI caused by the same strain would be deemed as susceptible according to the current EUCAST UTI breakpoint (32 µg/ml). The latter discrepancy between humans and dogs is hard to explain since *E. coli* strains causing canine and human UTI are indistinguishable and the PK profiles of amoxicillin in the two species are similar. Consequently, the present veterinary breakpoint may erroneously induce to prescribe fluoroquinolones or human drugs that are not authorised for veterinary use (e.g.

carbapenems) instead of amoxicillin. The latter has important clinical and public health implications in view of the increasing frequency of UTI caused by multidrug-resistant *E. coli* and the limited 'on-label' treatment options available in small animal practice.

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What's new in managing sporadic cystitis?

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Biography: Tina graduated from the Royal Veterinary and Agricultural University in Copenhagen, Denmark, in 2006 and started her career in private first- and second-opinion practice. In 2018 she finished her PhD studies in canine urinary tract infections with a strong focus on the diagnostic process, clinical decision-making and prudent use of antimicrobials in first-opinion practice.

Abstract:
Sporadic bacterial cystitis is a sporadic bacterial infection of the urinary bladder *with compatible lower urinary tract signs* in dogs and cats, regardless of the presence of other concurrent conditions. Thus the term sporadic cystitis substitutes the former category of uncomplicated cystitis (Weese et al., 2019).

In dogs presented to primary practice with lower urinary tract signs, a bacterial pathogen could be identified in only 51% of the cases (Sørensen et al., 2018). Although the prevalence is higher in females and with the presence of multiple clinical signs (Sorensen et al., 2019), performing aerobic bacterial culture is preferred for all cases to avoid unnecessary prescription of antimicrobials. However, it is important to realize that the performing bacterial cultures in itself did not automatically facilitate prudent use of antimicrobials (Sørensen et al., 2018), but an active strategy to withhold antimicrobials until culture results where available caused a significant higher proportion of correctly treated dogs (Sørensen et al., 2019). An initial course of analgesics (e.g. NSAIDs) to alleviate clinical discomfort while culture results are pending should be considered, as human evidence suggest that analgesics alone may be as effective as antimicrobials in uncomplicated cases (Bleidorn et al., 2016; Gagyor et al., 2015).

The primary goal of treatment is "clinical cure with minimal risk of adverse effects (including antimicrobial resistance)" as opposed to the microbiological cure we have hunted for years. Although microbiological cure (elimination of the pathogen from the urine) is desirable, it is not necessarily required for short- or long-term clinical resolution (Weese et al., 2019).
There is still no good veterinary evidence to guide the duration of treatment for urinary tract infections, but few studies suggest that a short duration of treatment is non-inferior to the currently applied treatment length (Clare et al., 2014; Jessen et al., 2015; Westropp et al., 2012). Therefore the currently recommended treatment duration is 3-5 days for sporadic bacterial cystitis (Jessen et al., 2018; Weese et al., 2019).

Optimal antimicrobial choices vary depending on the pathogen and local resistance patterns, but agents like amoxicillin or trimethoprim-sulfonamides is still recommended as reasonable first-line treatment in most areas. Follow-up should focus on clinical resolution with re-examination of animals with partial or complete clinical failure to treatment, and re-evaluation of initial prescription with regard to dose, dosing regimen, susceptibility pattern and client compliance to determine if appropriate initial treatment was provided (Jessen et al., 2018; Weese et al., 2019).
A new term is subclinical bacteriuria defined as "the presence of bacteria in urine as determined by positive bacterial culture from a properly collected urine specimen, in the absence of clinical evidence of infectious urinary tract disease" (Weese et al., 2019). Treatment of subclinical bacteriuria with antimicrobial is generally not recommended – regardless if pyuria can be identified or not. The revised ISCAID guidelines also recommends a shorter duration of treatment for other urinary tract infections including pyelonephritis (10-14 days duration) and recurrent bacterial cystitis (3-5 days duration).

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Angiotensin receptor blockers: effects beyond efferent arteriolar dilation

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Biography: Herve is currently Professor in Physiology at the National Veterinary School of Toulouse, France. He is an IRIS Board Member. He is the author of more than 100 peer-reviewed articles and book chapters. His current research interests are renal pharmacology, kidney functional testing, the disposition of creatinine in dogs and early diagnosis of chronic kidney disease in at-risk populations.

Abstract:
Development and approval of angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) has provided a new effective and selective pharmacological approach to interfere with RAAS in renal disease.

1- Mode of action of ARBs

In the renin-angiotensin-aldosterone system (RAAS), the inactive peptide angiotensin I is converted into angiotensin II by the enzyme angiotensin-converting enzyme (ACE). Angiotensin II is also produced by ACE-independent pathways, such as chymase. Angiotensin II acts at 2 receptors, the angiotensin type-1 and type-2 receptors (AT1R and AT2R). Angiotensin II also stimulates the production and release of aldosterone from the adrenal glands.[1-2] Inappropriate activation of intrarenal RAAS induces kidney damage.[3] The AT1R mediates the adverse effects of angiotensin II, whereas AT2 activation counterbalances these effects.[4]
ARBs displace Angiotensin II from its binding site at the AT1R. Because ARBs do not block AT2Rs, increased levels of angiotensin II and other active RAAS peptides remain free to activate these receptors. Pharmacological effects of ARBs are attributable, at least in part, to concurrent AT2R activation.[5]

2- Clinical benefits of ARBs in small animals

ARBs are anti-proteinuric and anti-hypertensive drugs. ARBs induce vasodilatation by inhibiting the vasoconstrictive effect of endogenous angiotensin II. Telmisartan attenuates an angiotensin 1-induced blood pressure response and reduces systolic blood pressure in healthy cats.[6] In clinical trials in cats with spontaneous systemic hypertension, telmisartan was also effective in reducing systolic arterial blood pressure.[7-8]
ARBs are also anti-proteinuric drugs in naturally occurring renal disease. Underlying mechanisms are the antihypertensive effect, reduction of mesangial cell proliferation, and renal vasodilatory effects.[1] In a clinical trial, telmisartan was shown to be non-inferior to benazepril in preventing an increase in proteinuria in cats with CKD.[9] In dogs, there is limited evidence on the effectiveness of ARBs as anti-proteinuric and anti-hypertensive agents.[10-12]

3- ARBs vs ACE inhibitors, and mono- vs dual therapy

Additional potential benefits of AT1R blockers compared with ACE inhibitors may be due to stimulation of AT2Rs.[5] Other theoretical benefits of ARBs may be: i) Angiotensin II may be produced through a non ACE-dependent pathway (eg, chymase), ii) ACE inhibitors also inhibit kinin degradation, iii) ACE inhibition also is associated with a fall in GFR in volume- and sodium-depleted patients.[13-14] In human patients, ARBs have an improved safety

profile.[15] Whether ARBs are superior to ACE inhibitors in dogs and cats with renal disease is not known.

Angiotensin II and aldosterone levels increase after chronic ACE inhibitors or ARBs treatment. ACE inhibitor or ARB monotherapy cannot provide full blockade of the RAAS cascade, suggesting dual therapy may be more efficient. In human patients, combining renin-angiotensin system therapies however did not result in significant clinical benefit but increased risk of adverse events.[16] Controlled clinical trials in dogs and cats evaluating combination of ACEI and ARB treatment have not been performed.

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Clinical management of hypertension and proteinuria in the dog

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Biography: Thierry graduated from the University of Bern and undertook a residency at University of Bern and Louisiana State University followed by a fellowship in nephrology and haemodialysis at University of California Davis. He is currently Lecturer and Head of small animal nephrology/urology (Vetsuisse Faculty University of Bern) and part of the teaching faculty for the Hemodialysis Academy (UC Davis, USA).

Abstract:

Despite the advances made in the diagnosis and in the treatment of kidney diseases in dogs and the general recognition of the key roles of proteinuria and systemic hypertension in these diseases, we still lack solid data on these two central aspects of nephrology in this species. Most of our clinical recommendations are extrapolated from other species and only rarely are they based on evidence from clinical research.

The importance of proteinuria and systemic hypertension in dogs with chronic kidney disease (CKD) was emphasized in a key study in which both were strongly associated with outcome, suggesting their intricately linked involvement in the disease progression.[1-2] However, only few studies have addressed specifically the management of proteinuria and systemic hypertension and its effect on outcome in dogs. A randomized open-label clinical trial with 22 dogs with proteinuric CKD suggested that dietary modification with a therapeutic renal diet could help controlling proteinuria and blood pressure, but the conclusions were limited by the low power of the study.[3] Treatment with the ACE inhibitor benazepril in a multicentric randomized clinical trial with 49 dogs with CKD showed lower proteinuria in dogs treated with benazepril compared to placebo, but no difference in renal survival, a conclusion limited again by the low power of the study.[4]

The central role of proteinuria in the pathophysiology of glomerular diseases (GD) is well accepted.[5-6] Despite a lack of direct evidence in canine GD, the antiproteinuric therapy remains one of the central goals of the management. In a blinded multicenter prospective clinical trial with 29 dogs, the ACE inhibitor enalapril led to a stronger reduction of UPC and systemic blood pressure, compared to placebo.[7] Although GD are often associated with severe hypertension, the effect of its treatment has received limited specific attention and current recommendations are based on the management of dogs with proteinuric CKD.[6]
The management of acute kidney injury (AKI) is centered around the acute symptomatic care and the resolution of life-threatening metabolic disturbances. The proteinuria in AKI is mainly tubulointerstitial in origin and it is rarely considered a target of therapy. The newer concept of acute kidney disease (AKD) for the phase following the early AKI may however emerge with an important role for antiproteinuric therapies, minimizing the transition to CKD and improving renal outcome.[8]
Systemic hypertension has been shown to be common in dogs with AKI and the calcium channel blocker amlodipine rapidly and efficiently corrected it in these dogs.[9] However, the effect of therapy on outcome could not be assessed in this retrospective study.
Altogether, despite limited evidence, the coordinated management of proteinuria and systemic hypertension remains central in our approach of all types of kidney diseases in the dog. An individualized medical and dietary treatment should be designed based on the type of disease, its expected progression, the level of renal function loss, and the magnitude of the observed derangements. Overall, research in canine kidney diseases urgently needs to address these central aspects with appropriate studies to guide our clinical practice.

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Understanding hypoxia and HIF with clinical application

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Biography: Caroline began her studies with a BSc (Hons) in Physiology followed by a PhD in Placental Physiology at the University of London. Caroline's initial post-doctoral studies in human platelets (Thrombosis Research Unit; King's College London) fuelled her interest in vascular cellular signalling and her subsequent post-doctoral position at King's College London (KCL) allowed her to pursue this interest in human endothelial cells. She currently holds a Chair in Vascular Cell Biology. Her research focus is primarily on vascular cell function with emphasis on understanding molecular control mechanisms. *Current projects cover:* Lipoprotein- and GPCR-mediated regulation of endothelial, vascular smooth muscle, progenitor and immune cell function; Regulation of cyclo-oxygenase expression and roles of lipid mediators in angiogenesis, fibrosis and calcification; Pathophysiological roles of GPCRs in the cardiovascular system with a focus on protease-activated receptors; lipid- and inflammation-mediated insulin resistance in skeletal muscle and vasculature.

Abstract:
Oxygen tension within a tissue is dependent upon the balance between oxygen supply and oxygen consumption, and tissues are characterised by oxygen tensions that reflect their individual metabolic status. Hypoxia, defined as an inadequate oxygen supply at the tissue level, drives specific transcriptional programmes in cells that permits their adaptation to lower oxygen levels. HIFs are particularly important for metabolic adaptation to hypoxia as their cellular concentration is finely tuned by oxygen tension. These transcription factors are the primary mediators of altered gene expression in hypoxic cells and their stabilisation regulates numerous genes involved in protective processes including angiogenesis, erythropoiesis, glucose metabolism, and cell proliferation and survival. Chronic HIF activation, however, is strongly implicated in tissue dysfunction, particularly fibrosis, and in the kidney this involves hypoxia-sensing pathways in several cell types. Experimental investigation of the molecular mechanisms of hypoxia-driven renal fibrosis offers particular challenges. Unique structural, functional and metabolic demands mean that the kidney normally operates under conditions of relative hypoxia and is particularly susceptible to hypoxic injury. Meaningful translational studies involving *in vitro* and *ex vivo* investigation of the consequences of hypoxia (≤ 1% O_2) on renal cells and tissues therefore require direct comparison to oxygen tensions that reflect kidney tissue 'physioxia' (~5% O_2), together with an appreciation that most tissue culture is conducted at ~18% O_2 (i.e. hyperoxia). The choice of *in vitro* cell model is also crucial, with most published studies using cell lines that do not resemble the relevant primary cell types. Focusing on the kidney this presentation will give a brief overview of the cellular mechanisms regulating the tissue response to hypoxia, the links between hypoxia and fibrosis, and the potential for targeting components of hypoxia-driven pathways to ameliorate disease and to provide information about disease progression. It will also highlight some recent findings using newly developed *in vitro* cell models that add to our knowledge of how feline renal cell types respond to hypoxia.

Drugs targeting bone and mineral disturbances

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Biography: Rebecca graduated in 2007 from Cambridge University and worked for three years in small animal practice in Cheshire. Rebecca moved to the Royal Veterinary College (RVC) where she spent four years completing a PhD examining calcium-phosphate homeostasis in cats with chronic kidney disease. She subsequently completed an internship and a residency in small animal internal medicine at the RVC, gaining her specialist diploma from ACVIM in 2018. Rebecca now works at the RVC as a Lecturer in small animal medicine and is performing research into the development of upper urinary tract stones

Abstract:

Coined in 2006, the term chronic kidney disease-mineral and bone disorder (CKD-MBD) was introduced to reflect the growing understanding of the complex and diverse sequelae resulting from chronic phosphate retention that occurs with a sustained and progressive reduction in functioning nephron number. CKD-MBD is a collective term that includes the changes in variables involved in calcium-phosphate homeostasis, soft tissue and vascular calcification, parathyroid gland hyperplasia and renal osteodystrophy. In human patients, CKD-MBD becomes most clinically apparent once they become dialysis dependent, but it is recognised that the syndrome starts well before this stage is reached. We have evidence for all aspects of CKD-MBD in dogs and cats, and although clinical signs are usually not appreciated, the contribution of these changes to disease progression and morbidity has been clearly documented.

Drugs used for treatment of CKD-MBD fall into three categories:

- Drugs used to alleviate hyperphosphataemia, but maintain serum calcium
- Drugs used to target renal secondary hyperparathyroidism
- Drugs used to target bone

Reducing oral phosphate intake is the only way to lower total body phosphate once CKD is established. Phosphate binders have long been used to address this, although it has more recently been recognised that there should also be a focus on lowering phosphate intake by addressing the bioavailability of phosphate in food sources (organic versus inorganic) and by considering the phosphate contained in medications and supplements. Interestingly, current meta-analyses of phosphate binder use in human patients are struggling to find clear evidence that they improve outcomes and recommendations for their use have been altered in recent years.

Traditionally, calcitriol and vitamin D analogues have been used to reduce hyperparathyroidism in CKD patients, as they directly and indirectly inhibit PTH secretion via increasing calcium (and phosphate) absorption from the intestines. More recently, the calcimimetics have been used instead of, or in combination with vitamin D analogues. Calcimimetics, including the oral agent cinacalcet and the novel intravenous agent etelcalcetide act directly on the calcium sensing receptor, changing the calcium set-point and thereby inhibiting PTH synthesis and secretion at lower serum calcium concentrations.

Calcimimetics also have effects on bone, but additional agents used to target renal osteodystrophy have a number of different actions, reflecting the spectrum of skeletal changes seen with this disorder. Renal osteodystrophy with high bone turnover can be addressed with anti-resorptive agents including bisphosphonates, which are taken up by osteoclasts and inhibit essential biochemical pathways resulting in apoptosis, and denosumab, a human monoclonal antibody that targets receptor activator of NF-κB ligand (RANKL) inhibiting the development, activation and survival of osteoclasts. However,

renal osteodystrophy with low bone turnover requires treatment with osteoanabolic agents, such as recombinant PTH or PTH-rP.

This presentation will review the indications for using these agents, their mechanisms of action and the body of evidence for their use in human patients, and where available in our companion animal species.

Abstract presentations/posters:

Case report: Emphysematous cystitis in geriatric and polymorbid Staffordshire bull terrier - evaluation of duration of antibiotic treatment

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Introduction. Emphysematous cystitis (EC) is a rare complication of infection of the urinary bladder. It is characterized by presence of gas filled vesicles in the bladder wall that results from gas-producing microorganism infection. Diagnosis is based on ultrasonographic and radiographic findings. EC can be life-threatening, early detection and aggressive treatment is recommended. The optimal duration of antimicrobial treatment for EC is unclear [1], [2]. **Case description:** *History and signalment:* A sixteen-year-old Staffordshire bull terrier, intact male, was presented for one-day *haematuria*, weakness, apathy, anorexia and vomiting. Patient comes with a 9-month long medication of prednisone (0,5 mg/kg q24h) from a private practice (presumably because of the hind limbs immobility). *Clinical findings:* patient was cachectic (BCS 2/9, MCS 3/4 - 1 being normal), moderately dehydrated (5%) with depressed mentation. Other findings were all within normal ranges. CBC uncovered acute leucocytosis and non-regenerative anaemia. Biochemical profile identified increased BUN, SDMA, c-reactive protein and normal levels of creatinine. AUS detected multiple acoustic shadows in the wall of a urine bladder of the opacity of gas. Prostatomegaly with hyperechogenic parenchyma was found with two echogenic cavities and many smaller anechogenic cavities. Multiple hypoechogenic bearing changes were present in the left testicle (susp. tumour). Typical CRD changes were present on both kidneys. Urine obtained by catheterization was turbid and dark red with specific gravity 1026 and dipstick analysis revealed *proteinuria* (3+), *haematuria* (3+), pH 6. Urine sediment revealed massive *pyuria*, *haematuria* and *bacteriuria*. *Treatment:* the dog was hospitalized and received intravenous fluid therapy (Plasmalyte 1/1) and empirical antibiotic therapy was started (Enrofloxacin 10 mg/kg q24h x 42 days). Metamizole was administered once (40 mg/kg q24h). Prednisone administration continued in a daily dose of 0,5 mg/kg. Urine cultivation revealed *Escherichia Coli* susceptible to enrofloxacin. **Aims.** To document the clinical response and the bladder wall gas development during and post antibiotic treatment. **Results.** Clinical signs subside after 48 hours after first enrofloxacin administration. Third day the patient was released for a home care. Gas was detected on the first, 2nd, 4th and 10th day. Twenty-first day the gas disappeared. Forty-second and 56th day no more gas was present in the bladder wall. **Conclusions.** Four-week of antibiotic therapy was described to be effective. Our results show that a shorter duration of antibiotic therapy (3 weeks) could be enough as it was in our geriatric and immunosuppressed patient.

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Title: A pilot study investigating the effect of non-absorbent hydrophobic sand litter on the measurement of urine protein-to-creatinine ratio (UPCR) in cats.

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Background: The UPCR is frequently measured for the diagnosis and prognosis of several diseases including glomerulopathies, chronic kidney disease and hypertension. Strong correlation exists between UPCRs of urine obtained by cystocentesis and free catch methods in both cats and dogs. Obtaining a free catch urine sample without the use of a non-absorbent litter substrate in cats is often not practical. To date the effect of non-absorbent hydrophobic sand litter on the measurement of UPCRs in cats has not been evaluated.
Aim: To investigate whether non-absorbent hydrophobic sand litter[a] affects the measurement of UPCR in cats.
Method: Baseline UPCRs ($UPCR_0$) were measured in duplicate for 15 urine samples obtained by cystocentesis. Up to three millilitres (range 1.5-3.0ml) of urine were placed in a petri-dish containing 4g of non-absorbent hydrophobic sand litter for 24 hours and covered. Urine was recovered using a pipette and repeat UPCRs ($UPCR_{24}$) measured in duplicate. Statistical analyses were performed using SPSS[b] software package. Data were assessed for normality using the Shapiro-Wilk test and transformed to normality using a logarithmic base 10 scale. Differences in UPCRs and the individual components of the ratio, urinary creatinine (UC) and urinary protein (UP) concentrations, were compared using a paired t-test. Correlation between $UPCR_0$ and $UPCR_{24}$ was assessed using the Pearson correlation coefficient. Agreement for IRIS classification between $UPCR_0$ and $UPCR_{24}$ was assessed using Cohen's kappa method.
Results: A paired t-test showed significant difference between UC_0 and UC_{24} concentrations and between $UPCR_0$ and $UPCR_{24}$, p=0.001 and p=0.005 respectively. UC_{24} concentrations were significantly higher than UC_0 and $UPCR_{24}$ were significantly lower than $UPCR_0$. Strong correlation exists between $UPCR_0$ and $UPCR_{24}$, r=0.998. The kappa coefficient was 0.955 corresponding to almost perfect agreement for IRIS classification between $UPCR_0$ and $UPCR_{24}$.
Conclusions: There was a statistically significant difference between $UPCR_0$ and $UPCR_{24}$. This was predominately due to an increase in the creatinine concentrations measured. However, the differences in UP and UC concentrations measured were within the allowable total error for analytical variability of serum analytes of <10% and <20% respectively, as defined by the ASVCP QALS Committee. The change in UPC after 24 hours contact with non-absorbent hydrophobic sand litter did not result in a change in IRIS classification for proteinuria. Our preliminary data suggests urine samples exposed to this litter for 24 hours are acceptable for UPCR measurement.

Abbreviations:
UPCR – Urine protein-to-creatinine ratio.
$UPCR_0$ – Urine protein-to-creatinine ratio at time = 0 hours.
$UPCR_{24}$ – Urine protein-to-creatinine ratio at time = 24 hours.
UC – Urinary creatinine.
UC_0 – Urinary creatinine at time = 0 hours.
UC_{24} – Urinary creatinine at time = 0 hours.
UP – Urinary protein.
UP_0 – Urinary protein at time = 0 hours.
UP_{24} – Urinary protein at time = 0 hours.
ASVCP QALS – American Society for Veterinary Clinical Pathology Quality and Laboratory Standards.
IRIS – International Renal Interest Society.

MEASUREMENT OF ALDOSTERONURIA IN HEALTHY AND CARDIOPATHIC DOGS: EARLY EVALUATION OF TWO ELISA METHODS

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Activation of the renin-angiotensin-aldosterone system (RAAS) leads to increased levels of angiotensin II and plasma aldosterone, and promote arterial vasoconstriction and remodeling, sodium retention, oxidative process, and cardiac fibrosis. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers may modulate this over-activity and improve survival in dogs with congestive heart failure. This pathology is characterized by a long pre-clinical period [1]. Preliminary data showed that plasma aldosterone levels are significantly higher in asymptomatic affected patients than in healthy ones [2]. This observation suggest that aldosterone can be involved in the early phases [3]. ELISA kits to determinate aldosteronuria in dogs are available, but they are very expensive, and consequently not currently used in veterinary practice.

The aim of the present study was to compare two commercial ELISA kits, one specific for canine species, and the other specific for human beings. The human ELISA kit is cheaper than the canine kit and the execution time is shorter (4 hours *vs* 21 hours, respectively).

5 healthy dogs and 5 cardiopathic dogs were recruited in the Veterinary Teaching Hospital of the Department of Veterinary Sciences in Turin. Urine samples were collected by cystocentesis and they were analyzed using the two kits, twice and in duplicate. Urine samples of healthy dogs were stripped using dextran charcoal (0.5 g/ml) and fortified with different concentrations (0, 20, 200, 500, 1000 pg/ml) of aldosterone (Sigma Aldrich, Milan, Italy) to evaluate the sensibility and the accuracy of the two kits. A single concentration (500 pg/ml) of cortisone was added to all stripped samples and they were analyzed with both kits to verify cross-reactions. Data were analyzed with GraphPad Prism 5.0 software using One-way Anova and Bonferroni's post test ($p<0.05$).

No statically significant differences were highlighted among all the samples analyzed with both kits. The results of this study seemed to highlight that human ELISA kit to measure aldosteronuria might be use also for dogs.

Further studies should be encouraged to improve specificity and sensibility of this test, comparing this trial with a gold standard method (i.e. LS-MS) and using a greater number of dogs to prove if this method might be a useful diagnostic and prognostic tool.

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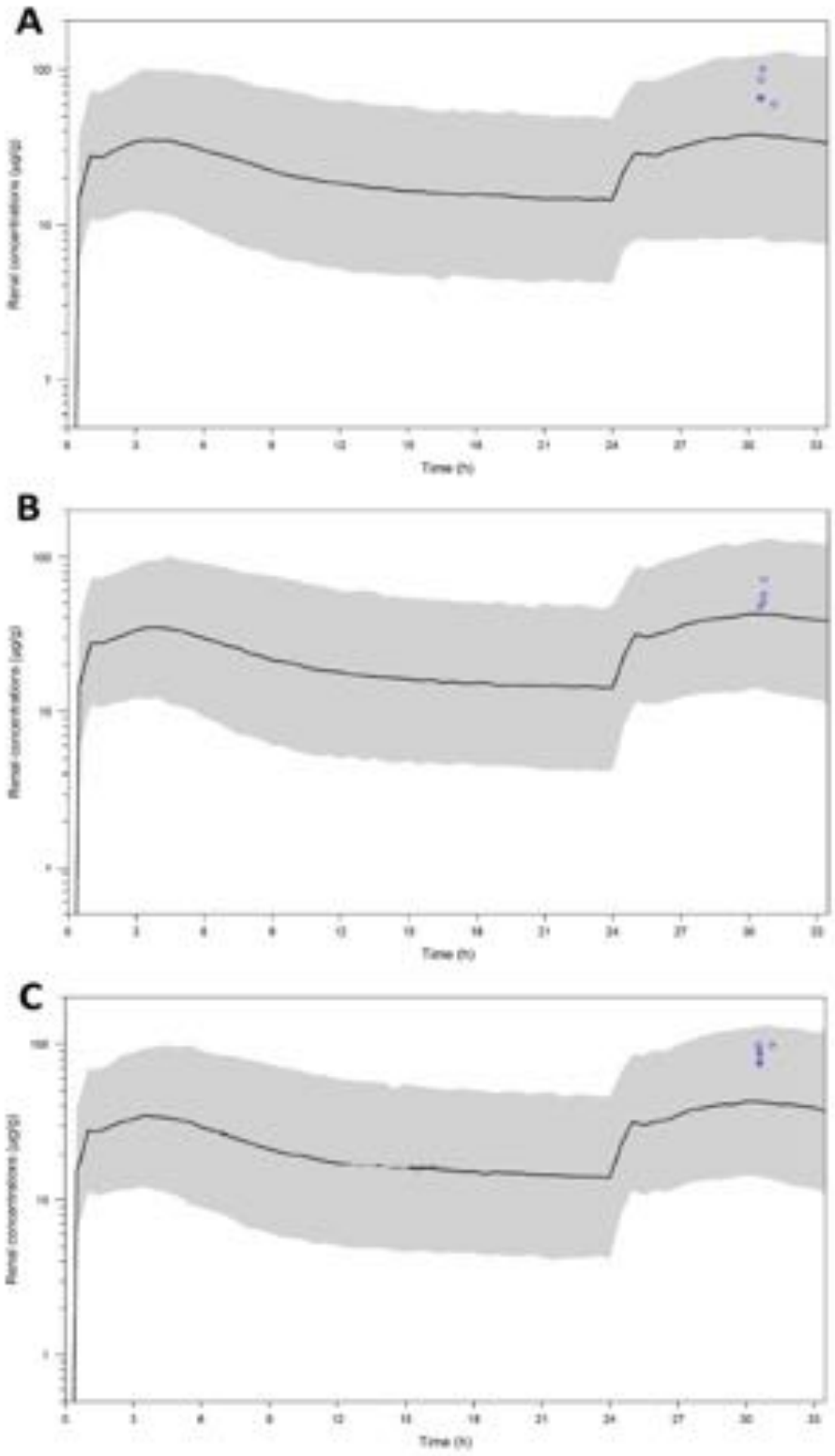

Fig 4: Model prediction of colistin renal concentrations versus observed data (blue dots) after a dosing regimen of CMS for different age/bodyweight of piglets. (A) 7kg; (B) 15kg; (C) 30kg
Grey area is the 90 % prediction interval.

CHANGES IN RETINAL VASCULATURE IN GERIATERIC CATS OF VARYING BLOOD PRESSURE STATUS

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Aims: These were to (i) determine the retinal vessels diameter at specific locations and compare this in geriatric cats according to blood pressure status; and (ii) evaluate the changes in retinal vasculature of hypertensive cats before and post treatment.
Methods: Colour fundus images centred on the optic disc were obtained bilaterally with Optibrand ClearView™ from normal cats (group [G]1, normotensive: systolic blood pressure [SBP] <140mmHg and G2, pre-hypertensive: SBP 140-160mmHg), cats with chronic kidney disease (G3, normotensive: SBP<140mmHg, G4, pre-hypertensive: SBP 140-160mmHg) and hypertensive pre-treatment (G5: SBP >160mmHg). Additionally, post treatment fundus images from hypertensive cats were available to evaluate the effect of amlodipine treatment (for 3 and 6 months). The width of the dorsal retinal venule and arteriole was manually annotated at four equidistant points from the optic disc and vascular diameter was calculated using VAMPIRE™ annotation tool. Linear mixed effects models were used to compare vessel diameters between groups and to assess treatment effects.
Results: There were total 108 cats included in the analysis (Table 1). G1 cats were significantly younger than the other groups (P ranged from 0.001 to 0.03). There was no difference in body weight between groups. Increased age significantly reduced the vessel diameters (-0.18±0.05 pixel/year, P=0.0001); but there was no effect of weight (0.13±0.11 pixel/kg, P=0.24). There were significant differences in the vessel diameters between groups (P=0.007) and between the arteriole and venule (P<0.0001) (Table 2). Overall, G1 cats had lower vessel diameters than G2 (-1.21±0.38 pixel, P=0.001) and G4 cats (-1.11±0.40 pixel, P=0.005), and slightly lower vessel diameters than G3 (-0.61±0.31 pixel, P=0.047) and G5 (-0.76±0.38 pixel, P=0.043). There was no difference between pre-hypertensive and hypertensive cats. Six of those 7 hypertensive cats with post-treatment observations had the blood pressure controlled (<160 mmHg) after 3 months. Arteriole diameter was reduced at 3 and 6 month post treatment compared to pre-treatment (-0.68±0.36, P=0.06; -1.22±0.41, P=0.003, respectively, Table 3 & Figure 1). Similarly, the venule diameter was significantly reduced post treatment (-1.77±0.36, -2.25±0.41 pixel, both P<0.0001).
Conclusions: Using Vampire annotation tool, the vascular diameters could be measured and appeared to be increased in hypertensive compared to normotensive cats. This may be due to sustained hypertension. Amlodipine treatment to control hypertension led to a reduction in retinal vascular diameters to the level of normotensive cats. Further studies are warranted to determine the prognostic value of assessment of retinal vascular architecture in the geriatric cat.

Table 1. Descriptive statistics of age, body weight and sex among the 5 groups of cats.

Group	N	Age (years) median (min, max)	Weight (kg) median (min, max)	Sex female/male
G1	40	12.2 (9.2, 17.8)	4.3 (2.6, 7.3)	20/20
G2	14	13.5 (9.8, 17.8)	3.8 (2.6, 6.1)	7/7
G3	26	15.4 (9.1, 19.1)	4.0 (2.4, 7.2)	14/12
G4	13	16.3 (10.1, 22.0)	3.9 (3.0, 6.2)	7/6
G5	15	15.3 (9.6, 20.1)	3.7 (2.6, 6.2)	7/8

Table 2. Age and weight adjusted mean and standard error of arteriole and venule diameters.

Group	Arteriole diameter (pixel) Mean ± standard error	Venule diameter (pixel) Mean ± standard error
G1	6.25±0.22	8.88±0.22
G2	7.57±0.36	10.04±0.36
G3	6.91±0.27	9.52±0.27
G4	7.41±0.38	9.95±0.38
G5	6.97±0.35	9.73±0.35

Table 3. Mean and standard error of arteriole and venule diameters among the 7 hypertensive cats with 3 and 6 months post-treatment observations.

Group	Arteriole diameter (pixel) Mean ± standard error	Venule diameter (pixel) Mean ± standard error
Pre-treatment	7.12±0.52	10.50±0.52
3 months post treatment	6.44±0.55	8.73±0.55
6 months post treatment	5.90±0.58	8.25±0.58

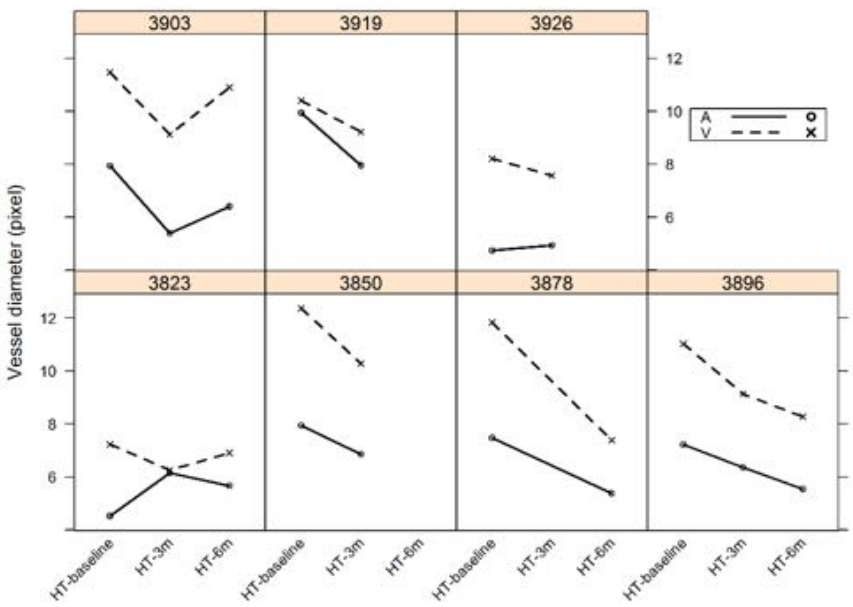

Figure 1. Vascular diameters of hypertensive cats before and after amlodipine treatment.

Does lowering blood pressure to below 140 mmHg have additional health benefits for hypertensive cats?

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Background: The empirical target systolic blood pressure (SBP) for hypertensive cats on treatment is <160 mmHg [1]. Recent evidence supports a pre-hypertensive stage (SBP between 140 and 160 mmHg)[2]. The aim of this retrospective pilot study was to determine whether there was benefit in reducing SBP below 140 mmHg.
Animals: Two groups of hypertensive cats treated with amlodipine, leading to SBP controlled below 140 mmHg (Gp1, n=13) or between 140 and 160 mmHg (Gp2, n=17) were retrospectively identified from the Royal Veterinary College clinic database.
Methods: Archived plasma and urine samples were identified at the pre-treatment and 'on treatment' (SBP stabilised) time points and submitted for urine protein to creatinine ratio (UPC) and plasma NT-pro-brain natriuretic peptide measurement (NT-proBNP; Idexx Ltd., Wetherby West Yorks).
Numerical data were summarised as mean ± standard deviation or median [minimum, maximum]. NT-proBNP below (or above) measurement limit was set as 22 pg/ml (or 1501 pg/ml). Both UPC and NT-proBNP were log transformed prior to analysis. Two samples *t*-test was used to compare SBP, UPC and NT-proBNP between groups prior to amlodipine treatment. Treatment duration was compared by Mann-Whitney U test. Linear mixed effects models were used to assess the effects of group (1 vs. 2), treatment (none vs. amlodipine) and their interaction while accounting for repeated measures (within cats); mean ± SE was used to infer treatment effect.
Results: Pre-treatment, Gp2 had significantly higher SBP than Gp1 (183.4±25.6 vs. 203.1±23.7mmHg; P=0.038). Pre-treatment UPC (Gp1: 0.18 [0.05, 0.55] vs. Gp2: 0.28 [0.05, 3.46], P=0.19) and NT-proBNP (Gp1: 201 [66, 1501] vs. Gp2: 434 [34, 1501] pg/ml, P=0.48) did not differ significantly between groups. Most cats were sampled at their first visit whilst receiving amlodipine treatment, although seven had an additional visit after dose adjustment from which the 'on treatment' samples were derived. Seventy percent of cats had their SBP stabilised within 4 weeks. On treatment, UPC tended to be reduced for Gp1 (-21±14%, P=0.08) whereas remained similar for Gp2 (6±12%, P=0.64). Plasma NT-proBNP decreased on treatment in both groups (-49±16% and -48±14%; Gp1 and 2 respectively; P<0.0001) with no difference in reduction between groups (P=0.92).
Conclusion: The limited sample size precludes definitive inferences regarding the benefits reducing SBP below 140 mmHg but the results may suggest lowering the target SBP to <140 mmHg is associated with a reduction in proteinuria. Post-treatment UPC was shown to be inversely related to survival in hypertensive cats[3], suggesting further prospective investigation of this lower SBP target is warranted.

References

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