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Federation of European Companion Animal Veterinary Associations

EJCAP ONLINE

Volume 23(4), Winter 2013

Correction of a malocclusion

Endocrine diseases in ferrets

Feline OA and NSAIDs

Responsible use of antimicrobials in companion animals

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COMMISSIONED PAPER (UK)

Feline osteoarthritis and NSAID therapy

A H Sparkes[1]

ABSTRACT

The efficacy of NSAIDs as anti-inflammatory and analgesic agents in cats is not questioned and the benefit of using a relatively COX-2 selective product in improving the safety profile is also not questioned. Fortunately there is a growing body of data supporting the long-term use of such agents in cats and demonstrating their safety when used appropriately.

Side effects do occur with NSAID use and knowledge of drug metabolism and pharmacokinetics is needed for appropriate dosing strategies. However, even where appropriate doses and frequency of drug use are known in cats, this still does not mean that side effects will not occur, as in other species. This means that when NSAID therapy is indicated (as is often the case, for example, when dealing with osteoarthritis, now recognised as a common disease in older cats) the risks and benefits of therapy need to be evaluated and strategies used that will minimise any potential risks. This applies to the use of NSAIDs in all species, not just cats. The potential dangers of NSAID use in humans are very well documented and side effects occur predictably in some groups of patients and unpredictably in others. Patients at higher risk of adverse events where more judicious dosing and more careful monitoring are required can usually be identified relatively easily and in most cases NSAIDs, when used carefully, can be of great value in cats as in other animals.

This paper was commissioned by FECAVA

Introduction

Osteoarthritis (OA) is an under-recognised condition in cats. Historically there has been a widely held opinion that cats generally either do not suffer from osteoarthritis or, that if they do, it is rarely of clinical significance. These assumptions have probably occurred for a number reasons including:

- The small size/weight of cats suggesting cats put 'less strain' on their joints.
- Decreased exercise tolerance, gait abnormalities and lameness may be difficult to appreciate in cats.
- In many cats the disease is bilateral, and along with the insidious onset of disease this means overt lameness is often not seen.
- Cats are very adaptive –joint pain may result in increased rest and sleep which may just be attributed to 'the ageing process'.

However, during the past 10-15 years, there have been a growing number of studies and publications that are helping to fundamentally change the way we think about feline OA and degenerative joint disease (DJD). Several retrospective studies have looked at the prevalence of radiographically evident DJD and OA in cats (which were being radiographed for other reasons). These studies demonstrated[1-3]:

- Limb joint OA was found in 65% of 99 cats over the age of 12 years [1] and 15 of the 64 affected cats had moderate to severe radiographic changes.
- In another study looking at all cats 1 year of age or greater, 22% of all the cats had evidence of OA, but this again was more common in older cats with the average age of affected cats being 11 years [2]

[1] Veterinary Director,International Cat Care and International Society of Feline Medicine, High Street, Tisbury, Wilts, GB- SP3 6LD
E-Mail: andy@icatcare.org

- Another study looked at cats between 3 months and 18 years of age and in that study 19% (of 191 cats) had radiographic evidence of limb OA [3] and again the affected cats were older with an average age of 10 years.
- Hip dysplasia has also been recognised in cats – in one retrospective study of cats that had undergone hip joint radiography, 7% of 684 had evidence of some degree of hip dysplasia [4]. Other studies have suggested a breed predisposition in Siamese, Persian and in particular Maine Coon cats. One study identified hip dysplasia in 50% (61/121) Maine Coon cats that were examined.

Taken together, these studies demonstrate compelling evidence for a high prevalence of OA in cats and that, as in other species, this is generally a disease of older cats. However, these retrospective studies (where full radiographic surveys of joints were often not available) almost certainly underestimate the prevalence of OA in cats and two more recent prospective studies [5,6] suggested an overall prevalence of around 60-90%.

From the studies published to date, the majority of cases of feline OA appear to be primary in origin, but with some cases secondary to recognised abnormalities such as previous fractures, infection, hip dysplasia etc. Whether cases of primary OA in cats share a similar pathogenesis to that seen in humans or dogs remains to be determined.

Published studies in cats suggest that feline OA is often (but not invariably) a bilateral disease and that the most commonly affected joints a the elbows, stifles, hips and tarsi.

How is OA diagnosed in cats?

Studies on feline OA suggest that affected cats often do not present with signs of lameness. Although further work is needed to verify these observations and to provide additional insight, it seems that the signs of OA may be much more subtle in cats and are generally much better appreciated by owners than by veterinary surgeons during a clinical examination [7,8]. Unless clinicians are 'tuned in' to looking for appropriate signs, they can be easily overlooked. There is no universal sign or collection of signs that is present in all cats with OA – the disease is variable and the clinical presentation is also variable. However, research and clinical studies suggest that overt lameness is seen in well under 50% of cases. Additionally, the challenges of performing orthopaedic examinations in cats means that assessment of signs such as joint pain and alterations to the range of joint motion, especially if subtle, is extremely difficult. From data collected it appears that so-called 'lifestyle' changes (or what some have referred to as behavioural changes) are much more common in cats with OA. These include:

- A reduced ability or reluctance to jump
- A reduction in the height to which the cat will jump.
- A reduction in overall activity levels
- Increased sleeping/lethargy
- Difficulty going up or down stairs
- Difficulty negotiating the litter tray

Other clinical signs that may also suggest the presence of OA and reduced mobility include:

- Vocalisation and/or resentment on handling
- Aggression
- Lameness.
- Stiffness and a stilted or shuffling gait (reduced stride length).
- Joint abnormalities such as swelling, pain and/or reduced range of movement.
- Constipation and/or inappropriate elimination (litter tray difficulties).
- Reduction in, or difficulty with, grooming.
- Reduced interaction with other pets and/or people

In one of the published studies of OA [9], the most common changes noted in association with arthritis were a reduced ability to jump (in 71%) and a reduced height of jump (67%), whereas a stiff gait was only identified in 32% and lameness in 46% (and were rated 'slight' or 'moderate'). Because many of the clinical signs of feline OA are subtle and associated with life-style changes rather than changes that can be readily detected on clinical examination and orthopaedic evaluation, a thorough clinical history and careful discussion with the client about these changes may be needed to identify cats potentially affected with OA. The use of a standard owner mobility questionnaire (Figure 1) may help in identifying cats potentially affected by OA that may need further evaluation and potentially trial therapy and there is good rationale in using such questionnaires in all older cats (eg, 6-7 years and older).

Radiography might be of value in some situations when looking for changes to confirm the presence of OA (such as the presence of osteophytes, subchondral sclerosis, joint space narrowing or joint effusion) or to rule out other diseases. (Figure 2) However, in most cases this is unlikely to be required. Further, although radiography may be valuable to confirm a diagnosis it is recognised that both in cats and other species, the severity of radiographic signs does not correlate well with the severity of clinical disease [10].

Although orthopaedic examinations are notoriously difficult to perform in cats and the presence of joint pain can be

	Yes	No	Not sure
Does your cat sleep more and/or is it less active?	☐	☐	☐
Is your cat less willing to jump up or down?	☐	☐	☐
Will your cat only jump up or down from lower heights?	☐	☐	☐
Does your cat ever show signs of stiffness?	☐	☐	☐
Is your cat more reluctant to greet you or interact with you?	☐	☐	☐
Does your cat play with other animals or toys less?	☐	☐	☐
Does your cat have a poor coat and/or spend less time grooming?	☐	☐	☐
Overall is your cat less agile?	☐	☐	☐
Does your cat show signs of lameness or limping?	☐	☐	☐
Does your cat have more accidents outside the litter tray?	☐	☐	☐
Does your cat have more difficulty getting in or out of the cat flap?	☐	☐	☐
Does your cat have difficulty going up or down stairs?	☐	☐	☐

Figure 1 Example of a mobility check list

difficult to assess on examination, the fact that OA can be a painful condition is indisputable. The marked improvement documented in response to analgesic and anti-inflammatory therapy in many studies confirms this. To diagnose OA then, it is not only important to conduct a thorough clinical and orthopaedic examination, but obtaining a thorough history from the owner and asking pertinent questions about the cat's mobility are essential. Radiography may be helpful in some situations, but as in many species, the diagnosis will usually be presumptive and used as a basis for trial therapy.

In recognising that OA is predominantly a disease of older cats, the presence of concomitant disease in many individuals may also complicate the clinical picture meaning that a heightened awareness of the possibility of OA is important if the disease is not going to be overlooked.

Management of feline OA

The health and welfare impact of chronic OA in cats should not be underestimated. Although many cats do not show overt lameness, significant pain and discomfort are often present and the impact on quality of life can be very significant. In the study by Clarke and Bennett [9] (2006) evaluating the effect of meloxicam on cats with OA, nearly two thirds of owners were able to perceive a marked improvement in their cats on therapy and of owners who identified a reduced ability to jump or a reduced height of the cat's jump prior to starting meloxicam therapy, 95% reported improvements in these parameters during therapy. Significant improvements were also seen in the cats' activity levels, their stiffness and their lameness. This and other studies [11-14] provide ample evidence that OA should be considered an important clinical problem that requires therapy.

There is no single solution to OA in cats, or in other species, but an increasing array of treatment options are available. In many, if not most cats, a multimodal approach to therapy is likely to be of most benefit, but non-steroidal anti-inflammatory drugs (NSAIDs) are likely to be the mainstay of therapy in the majority of cases.

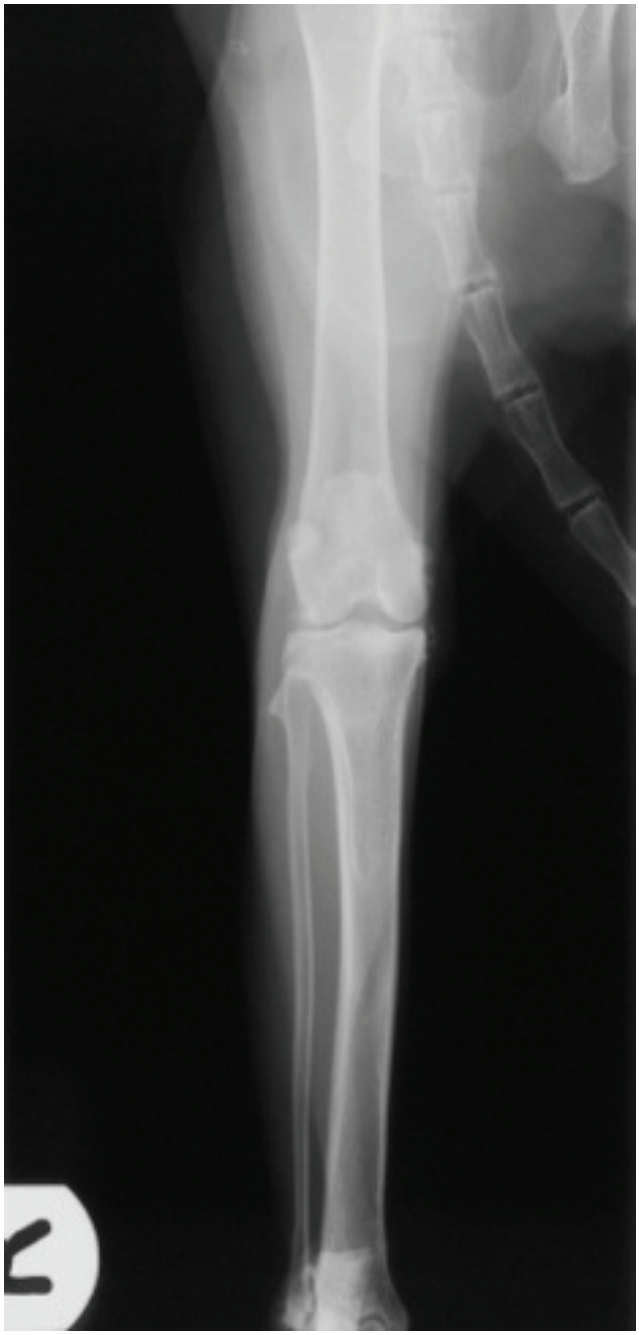


Figure 2 Radiographic evidence of OA in the right stifle joint of a cat

Considerations in the management [7,15] of feline OA include:

- ***Obesity management*** – this is important, as a reduction and normalisation of bodyweight may help ameliorate clinical signs and may help reduce further deterioration of affected joints.
- ***Environmental modifications*** – owners can help considerably by modifying the environment so that the cat has to do less jumping (up or down) thus making access to favoured sites still possible with less discomfort. Chairs, stools, ramps or other objects can be placed strategically to help a cat manoeuvre into a favoured position (e.g. on a windowsill) where it may find difficulty in jumping. High-sided litter trays can also be avoided to make getting in and out of the tray easier. Owners can also spend a greater amount of time grooming the cat.
- ***Nutrition and nutraceuticals*** – there is currently very limited evidence for the efficacy of dietary change and use of nutraceuticals (such as glucosamine and chondroitin sulphate supplements – 'chondroprotectants') in the management of feline OA [16]. This is not to say they necessarily have no efficacy, but this area has been poorly studied in cats. Based on our knowledge in other species it is possible that both diet and chondroprotectants may have some role in the management of OA but their efficacy is likely to be relatively limited and perhaps suited only to management of very mild cases or as adjunctive therapies.
- ***Glucocorticoids*** - are potent anti-inflammatory drugs and may help to manage the inflammation, pain and discomfort associated with OA. Their use has not been studied in feline OA, but based on other species, the effectiveness of glucocorticoids in management of OA is likely to be limited and their use can be associated with both systemic side effects and potentially deleterious effects on joint cartilage. Although their use may be considered in some situations, they cannot be combined with NSAIDs and they should not be regarded as a 'first line' therapy for feline OA

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be beneficial in managing feline OA and are a first-line of therapy in other species. Most NSAIDs are only licensed for short-term therapy in cats, but recently meloxicam (Metacam®, Boehringer Ingelheim) was granted a European license for long-term management of musculoskeletal pain in cats. Although there are some situations where the use of NSAIDs may be contra-indicated or where they would have to be used with particular care (eg, presence of dehydration, hypovolaemia, presence of renal insufficiency, presence of hypertension, presence of congestive heart failure, concomitant therapy with diuretics and/or ACE-inhibitors etc.), in general meloxicam appears to be extremely well tolerated and as a so-called 'COX-2 preferential' NSAID, results in less gastrointestinal side-effects. The availability of a licensed NSAID for long-term therapy in cats is an important advance, especially for cats with OA.

Rational NSAID therapy

While NSAID therapy is likely to be needed in many cases of feline OA to manage pain and inflammation, it is well recognised that as a class of drugs adverse reactions can be problematic, especially if they are used inappropriately. To address this, the International Society of Feline Medicine (ISFM) and the American Association of Feline Practitioners (AAFP) developed consensus guidelines on the safe long-term use of NSAIDs in cats [17] to help provide a framework for practitioners.

As a group, NSAIDs have a recognised profile of potential adverse effects which are encountered more commonly with some NSAIDs than with others. The prevalence of particular side effects is dictated in part by the cyclo-oxygenase (COX)-selectivity of the agent. As in other species, serious adverse reactions to NSAID therapy in cats typically involve either the gastrointestinal tract (GIT) or the kidneys, but COX-2 selective or COX-2 preferential agents (see below), such as meloxicam or robenacoxib, have a much better safety profile than non-selective agents.

COX-inhibition

The major mode of action of NSAIDs is via inhibition of cyclo-oxygenase (prostaglandin synthetase) enzymes. These enzymes catalyse the incorporation of oxygen into polyunsaturated fatty acids that are liberated from phospholipids in cell membranes under the action of phospholipase enzymes. This results in the production of prostanoids (thromboxanes, prostacyclines and prostaglandins), which serve, among other functions, as inflammatory mediators.
At least three isoforms of cyclo-oxygenase are now recognised – COX-1, COX-2 and COX-3, which have differing roles.

COX-1 expression

In general, COX-1 is an isoform that is expressed constitutively in most tissues in the body and is considered crucial for the production of prostaglandins associated with many normal physiological processes. Maintenance of normal homeostatic mechanisms by COX-1 mediated prostaglandin production is well established and researched in the GIT and the kidney. In the gastrointestinal tract this is mainly mediated by the E-series prostaglandins and their effects include:

- Reduction in stomach hydrochloric acid secretion
- Increase in bicarbonate secretion
- Increase in mucus production
- Maintenance of epithelialisation
- Maintenance of mucosal blood flow

In the kidneys, COX-1 mediated prostaglandin synthesis is also crucial for maintenance of renal blood flow. Their role may be relatively limited in the 'normal' resting state, but in the face of hypovolaemia or hypotension their role is vital. Increased prostaglandin synthesis occurs in the glomerulus and the effects include:

- Antagonism of vasoconstrictive mediators such as catecholamines, angiotensin II and vasopressin
- Vasodilation/maintenance of renal blood flow
- Promotion of sodium and water excretion by tubules
- Stimulation of renin secretion
- Maintenance of urine production.

Platelets also constitutively express COX-1 and its expression is increased in the presence of thrombin (during clot formation). This results in the production of thromboxanes (TXA2) by the platelet, which is important in mediating platelet aggregation.

With these important physiological roles it is easy to see why indiscriminate and excessive suppression of COX-1 activity can be associated with significant GIT (ulceration, vomiting, diarrhoea), haematological (increased bleeding) and renal (acute kidney injury) side effects, as well as renal sodium and water retention.

COX-2 expression

In addition to COX-1, COX-2 was identified as a separate largely inducible form of the enzyme in the early 1990s. Its structure and function is very similar to COX-1 and both are proteins integrated into the cell membrane. However, COX-2 is largely expressed (induced) in response to cellular insults, it has a somewhat different cellular distribution to COX-1, and it may be able to use a wider range of lipid substrates than COX-1. Much evidence has been accumulated to show that COX-2 expression is an integral part of the inflammatory cascade and the production of inflammatory eicosanoids. Almost all tissues under basal conditions constitutively express COX-1, and although COX-2 is generally regarded as an inducible enzyme there are exceptions to this. In mammals, some tissues (including the CNS and the kidneys) also constitutively express COX-2 and there is evidence that it may have a role in maintenance of GIT integrity in cats. In the CNS, COX-2 may have a role to play in pain signalling, while in the kidney expression in vascular, tubular and interstitial cells appears to play a similar role to COX-1 expression in maintaining blood flow and sodium/water excretion in the presence of hypovolaemia or hypotension.

Although COX-2 is an enzyme whose expression is induced during inflammatory responses and is closely linked with inflammatory processes, its physiological role is much wider than this. Nevertheless, inflammatory prostaglandins are largely produced in response to COX-2 expression (although increased COX-1 expression may have some role too), and this remains the primary target for NSAID therapy.

COX-3 expression

COX-3 is a 'splice variant' of COX-1, being produced by the same gene (a different gene encodes COX-2 expression). Expression of COX-3 has been shown to occur in the CNS, the heart and the intestinal epithelium among other tissues in some mammals, but its physiological role is still debated. It appears that COX-3 may have a role in mediating pain and pyrexic responses in the CNS and may also have a role in modifying the expression of COX-1 and COX-2 in other tissues.

NSAID therapy and COX-selectivity

It is undoubtedly true that using NSAID drugs which have a greater COX-2 selectivity (such as meloxicam and robenacoxib), because of the differing physiological roles of COX-1 and COX-2, target anti-inflammatory therapy better while reducing the prevalence of side effects (which are often, but not invariably, mediated by COX-1 inhibition). However, as has clearly been demonstrated in human medicine, using COX-2 selective drugs does not completely abrogate side effects associated with NSAID therapy and highly selective COX-2 suppression can lead to other side effects developing (such as thromboembolic disease).

Practical NSAID therapy in cats

The efficacy of NSAIDs as anti-inflammatory and analgesic agents in cats is not questioned, and the benefit of using a relatively COX-2 selective product in improving the safety profile is also important. Fortunately there is also a growing body of data supporting the long-term use of such agents in cats and demonstrating their safety, when used appropriately.

Adverse events do occur with NSAID use in cats and these will occur more frequently with inappropriate drug dosing. Metabolism of many drugs in cats is different to other species, and in particular the relative lack of glucuronyl transferase in cats means that many drugs metabolised in this way need to have adjustments to dosing quantity and frequency for their appropriate use. Although many NSAIDs are metabolised via the glucuronyl transferase, others are partially or exclusively metabolised via oxidative pathways. Evidence supports that the latter is true for meloxicam, with pharmacokinetic studies suggesting its half-life in cats is similar to that in dogs and that once daily dosing is appropriate [18].

However, even where appropriate doses and frequency of drug use are known in cats, this still does not mean that side effects will not occur. Again, this is not a reason not to use drugs if and when their use is indicated, it simply means that risks and benefits need to be weighed up, that the benefits should outweigh the risks, that owners need to give informed consent and that appropriate monitoring should be performed. All this is true with the use of NSAIDs in cats and equally it is true of NSAID use in other species too. The potential dangers of NSAID use in humans are very well documented and side effects occur more predictably in some groups of patients and less so in others. This does not stop the extremely widespread prescription of NSAIDs, but it does alter the way in which they are used. The same should also be true in feline medicine.

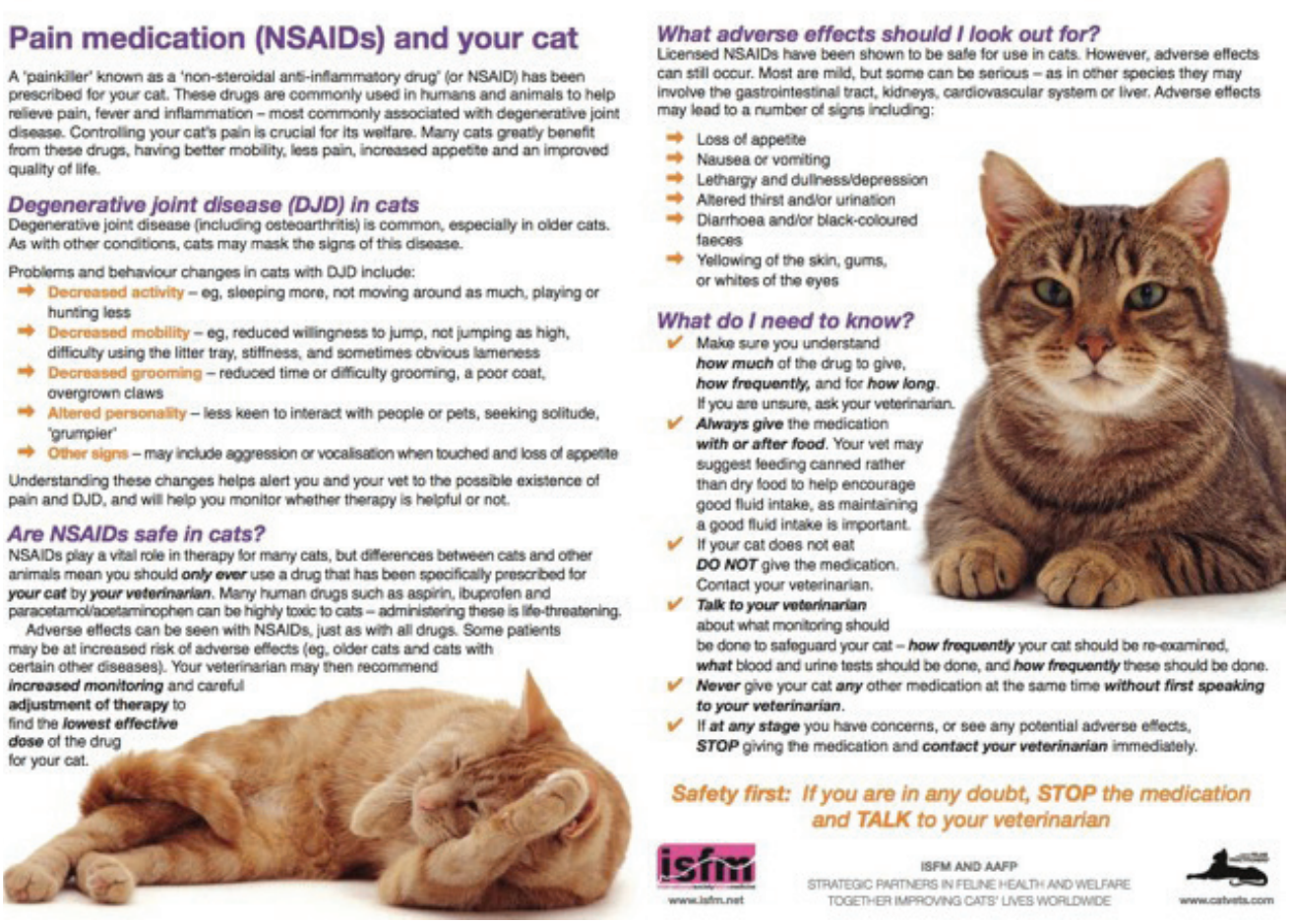
Considerations in the use of NSAIDs

In otherwise healthy cats, there is growing evidence of the good safety profile of drugs such as meloxicam and robenacoxib when used appropriately. However, it is prudent to inform owners of clinical signs to watch out for which may suggest an adverse drug reaction and indicate temporary or permanent cessation of therapy, for example:

- Development of anorexia
- GI disturbances such as vomiting, diarrhoea or presence of melena
- Increased thirst and/or increased urination

A simple owner leaflet (Figure 3) explaining the nature of the treatment, the warning signs to watch out for, and when to contact the clinic can do much to ensure the safe use of NSAIDs.

Accurate and careful dosing of the drug is also important as it is clear from accumulated data that severe side effects are much more likely to occur with over-dosage of NSAIDs. The use of an oral solution for dosing (Figure 4), rather than tablets, clearly allows for much more accurate and individualised dosing which is considered an advantage in cats. An important concept in this respect is the 'lowest effective dose'. In many (although not all) situations it



Pain medication (NSAIDs) and your cat

A 'painkiller' known as a 'non-steroidal anti-inflammatory drug' (or NSAID) has been prescribed for your cat. These drugs are commonly used in humans and animals to help relieve pain, fever and inflammation – most commonly associated with degenerative joint disease. Controlling your cat's pain is crucial for its welfare. Many cats greatly benefit from these drugs, having better mobility, less pain, increased appetite and an improved quality of life.

Degenerative joint disease (DJD) in cats

Degenerative joint disease (including osteoarthritis) is common, especially in older cats. As with other conditions, cats may mask the signs of this disease.

Problems and behaviour changes in cats with DJD include:

- **Decreased activity** – eg, sleeping more, not moving around as much, playing or hunting less
- **Decreased mobility** – eg, reduced willingness to jump, not jumping as high, difficulty using the litter tray, stiffness, and sometimes obvious lameness
- **Decreased grooming** – reduced time or difficulty grooming, a poor coat, overgrown claws
- **Altered personality** – less keen to interact with people or pets, seeking solitude, 'grumpier'
- **Other signs** – may include aggression or vocalisation when touched and loss of appetite

Understanding these changes helps alert you and your vet to the possible existence of pain and DJD, and will help you monitor whether therapy is helpful or not.

Are NSAIDs safe in cats?

NSAIDs play a vital role in therapy for many cats, but differences between cats and other animals mean you should ***only ever*** use a drug that has been specifically prescribed for ***your cat*** by ***your veterinarian***. Many human drugs such as aspirin, ibuprofen and paracetamol/acetaminophen can be highly toxic to cats – administering these is life-threatening.

Adverse effects can be seen with NSAIDs, just as with all drugs. Some patients may be at increased risk of adverse effects (eg, older cats and cats with certain other diseases). Your veterinarian may then recommend ***increased monitoring*** and careful ***adjustment of therapy*** to find the ***lowest effective dose*** of the drug for your cat.

What adverse effects should I look out for?

Licensed NSAIDs have been shown to be safe for use in cats. However, adverse effects can still occur. Most are mild, but some can be serious – as in other species they may involve the gastrointestinal tract, kidneys, cardiovascular system or liver. Adverse effects may lead to a number of signs including:

- Loss of appetite
- Nausea or vomiting
- Lethargy and dullness/depression
- Altered thirst and/or urination
- Diarrhoea and/or black-coloured faeces
- Yellowing of the skin, gums, or whites of the eyes

What do I need to know?

- Make sure you understand ***how much*** of the drug to give, ***how frequently,*** and for ***how long***. If you are unsure, ask your veterinarian.
- ***Always give*** the medication ***with or after food***. Your vet may suggest feeding canned rather than dry food to help encourage good fluid intake, as maintaining a good fluid intake is important.
- If your cat does not eat ***DO NOT*** give the medication. Contact your veterinarian.
- ***Talk to your veterinarian*** about what monitoring should be done to safeguard your cat – ***how frequently*** your cat should be re-examined, ***what*** blood and urine tests should be done, and ***how frequently*** these should be done.
- ***Never*** give your cat ***any*** other medication at the same time ***without first speaking to your veterinarian***.
- If ***at any stage*** you have concerns, or see any potential adverse effects, ***STOP*** giving the medication and ***contact your veterinarian*** immediately.

Safety first: If you are in any doubt, STOP the medication and TALK to your veterinarian

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Figure 3 NSAID leaflet for owners - available from http///www.icatcare.org/sites/default/files/PDF/client_leaflet(English).pdf

Figure 4 Use of a liquid formulation allows accurate dosing and dose titration in cats

may be possible to go below the data sheet recommended dose of a NSAID and still maintain efficacy. This appears to be particularly true with feline OA as a number of studies have suggested good clinical effects from using meloxicam doses of around 0.02 mg/kg/day, which is only 40% of the datasheet recommended dose of 0.05 mg/kg/day. Where possible, using lower doses of NSAIDs with maintained clinical efficacy is an excellent way to reduce risks of side effects.

Involving owners in the assessment of efficacy by getting them to keep a daily diary of clinical signs (based around mobility levels, activity levels, grooming and temperament) may allow for better dose-adjustment and titrating down to the minimum effective dose. Using a liquid drug preparation also facilitates this. Although somewhat controversial, some clinicians also use drugs like meloxicam on an 'every other day' basis in some cats. Although pharmacokinetic studies suggest daily dosing would be optimal, it is possible that (because NSAIDs are highly protein bound) there may be persistence of the drug at the site of inflammation permitting less frequent dosing. If this is attempted, careful clinical monitoring is suggested to try to ensure adequate pain relief is being maintained.

While appropriate NSAID use in many cats should carry a low risk of significant side effects, it is clear from clinical use and from experience in other species that greater care and caution is warranted with the use of certain other medications and the presence of certain concomitant diseases. This list should include:

- Cats receiving diuretic therapy
- Cats receiving ACE inhibitor therapy
- Cats receiving corticosteroids
- Cats with pre-existing GI disease
- Cats with renal insufficiency
- Cats with hypertension
- Cats with hepatic impairment

- Cats with asthma
- Cats with congestive heart failure
- Cats undergoing anaesthesia /sedation (especially where blood pressure is not monitored)
- Cats with dehydration or volume depletion
- Cats with pre-existing bleeding disorders

While the presence of some conditions or concomitant therapies may make NSAID therapy absolutely contraindicated (eg, concomitant corticosteroid therapy) because of the very high risk of significant side effects, in other situations, a knowledge of disease and drug interactions with NSAID therapy should prompt caution with NSAID use, perhaps a reduction in dosage, and the increased risks may dictate more careful monitoring of patients (see below).

It may also be appropriate to suggest that patients in certain categories should not be administered NSAIDs without appropriate pre-therapy investigations (eg, blood and urine tests) and follow-up monitoring. At the very least, owners need to be made aware of the increased risks that may sometimes exist and be warned to be extremely vigilant about monitoring their cat and seeking advice should changes occur that cause any concern.

NSAIDs and GI adverse events

Gastrointestinal disturbances appear to be the single most common adverse event associated with NSAID use in cats, as in most other species. This can range from mild GI irritation through to ulceration and perforation of the GI tract. Simple measures however can minimise the risks of GI adverse events including:

- Using COX-1 sparing NSAIDs (COX-2 preferential or selective agents such as meloxicam and robenacoxib)
- Using only the lowest effective dose
- Only administering the drug with or after food – inappetence may be the earliest sign of GI irritation and it is probably best to withhold therapy in an inappetent/ anorexic cat until veterinary attention is sought
- Avoid using NSAIDs with glucocorticoids

NSAIDs and renal adverse events

Perhaps of greatest concern to many clinicians is the potential for NSAIDs to adversely affect renal function and certain risk factors for this are recognised in human medicine. The greatest risk with NSAID use is the induction of acute kidney injury (AKI) and the increased risks mainly relate to hypovolaemia or hypoperfusion of the kidneys, a situation where both COX-1 and COX-2 enzymes are recognised to be important in maintaining renal perfusion. Concomitant use of NSAIDs with diuretics and/or ACE-inhibitors also increases the risk of AKI.

The risk of AKI in cats treated with NSAIDs is thus more likely, for example, with:

- Dehydration
- Low blood pressure
- Congestive heart failure
- Use of diuretics and/or ACE-inhibitors (the so-called 'double whammy' or 'triple whammy')

In most cases, AKI is an adverse event that occurs early after starting NSAID therapy, often within 5-7 days and as with other causes of AKI is reversible if diagnosed early and managed properly. Monitoring cats carefully during the first week and making owners aware of signs to look out for (loss of appetite, change in thirst etc.) are important safety measures.

As with GI adverse events, the risks of AKI can be reduced by following some simple recommendations, including:

- Managing dehydration and hypoperfusion
- Using the lowest effective dose
- Monitoring cats carefully
- Where there are higher risks of dehydration, administering NSAIDs with (or after) 'wet' foods (tins or sachets) and not administering the drug if the cat does not eat.

There is some evidence that prolonged use of high doses of NSAIDs in humans may, in some situations, contribute to the progression of chronic kidney disease (CKD) although not all studies support this finding. In cats, at least three studies have been published where the risks of cats developing CKD while on NSAIDs have been evaluated and/or the risks of CKD worsening have been evaluated [11-13,19]. In these studies, no evidence has been found for a role of NSAIDs in either causing overt CKD in cats or worsening pre-existing CKD. The studies in contrast showing, that prudent use of low doses of NSAIDs appears to be safe in this situation. The presence of CKD is thus not a reason to withhold needed NSAID therapy, just a situation where again their use requires more caution and monitoring.

Monitoring cat on NSAID therapy

Strict guidelines on the use of NSAIDs in cats are difficult to establish, in part because there is still insufficient clinical data about their use in many situations. However, a prime concern should always be the relief of pain and suffering and while other drugs may also be used to achieve this purpose or as adjunct therapy, NSAIDs remain an extremely

Parameter		Always	Suggested minimum	Ideal if possible
Review history		✓	✓	✓
Full physical examination (including blood pressure measurement if possible)		✓	✓	✓
Heamatology	Heamatocrit		✓	✓
	Complete Blood Count			✓
Biochemistry	Urea/Creatine		✓	✓
	ALT/ALP		✓	✓
	AST/GGT/Bile acids			✓
	TP/Albumin			✓
	Na/K			✓
Urinalysis	Specific gravity		✓	✓
	Dipstick biochemistry		✓	✓
	Urine protein: creatinine ratio			✓
	Sediment analysis			✓

Figure 5 Suggested monitoring of cats on NSAID therapy (from Sparkes et al)[17]

important class of drugs. Their use should not be avoided due to irrational fears, but rather a logical approach should be sought to their risk assessment and as to how to handle increased risks through lower doses of NSAIDs, careful choice of NSAIDs, adjuvant therapy and careful monitoring.

In an ideal situation a physical examination would be accompanied by routine blood and urine screening prior to the use of NSAIDs and whilst on therapy. This would help to identify the presence of pre-existing disease that may mean more careful monitoring is required (eg, hypertension, congestive heart failure or kidney disease) and may allow the early detection of adverse reactions. However, the extent of such screening tests will be dependant in part on owner willingness and financial abilities – nevertheless, even limited screening tests (Figure 5) can be extremely valuable, and should be possible in the vast majority of circumstances.

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REPRINT PAPER (A)

Case presentation: Correction of malocclusion in a dog using an expansion screw

Camil Stoian[1]

INTRODUCTION

Orthodontics is the specialty of dentistry that is concerned with the study and treatment of malocclusions or improper bites. Malocclusions may be a result of tooth irregularity, disproportionate jaw relationships, or both conditions. Orthodontic treatment can focus on dental displacement only, or can deal with the control and modification of facial growth.
Orthodontic treatment can be carried out for purely aesthetic reasons with regards to improving the general appearance of patients' teeth or it can be focused on the functionality of the stomatognathic system.
The large number of species and breeds that come in various sizes encountered in veterinary dentistry makes the choices used for each orthodontic correction a unique situation. Not only morphological characteristics influence the outcome but also the temperament of the dog and quite importantly the owner's compliance and willingness to offer proper and special care for the duration of the treatment.

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Case presentation

In this case a Cavalier King Charles, female, 8 months of age, weighing 6.5 kg was presented to our dental service with a class I malocclusion (neutrocclusion) with palatoversion or palatal inclination (tipping) of the upper (maxillary) central and lateral incisors 101, 102 and 201, 202 in Triadan nomenclature. This malposition of the upper four incisors is also referred to as anterior cross bite.

We can see this malposition from a frontal view in two different angles in Figure 1 and Figure 2 as well as palatal view in Figure. 3 where the red arrows show the central upper incisors (101, 201) that are tipped or tilted palatally by 2 mm and with black arrows the second incisors (102, 202) that are tipped 1 mm palatally.

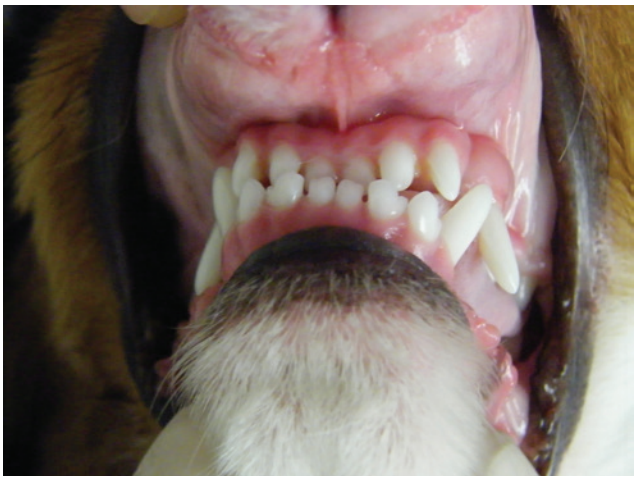

Figure 1

1 Veterinary Dental Referral Practice, Marktstraße 19, A-2331 Vösendorf, Austria
E-mail: ordination@tierzahnarzt.at

* Presented by VÖK (A)

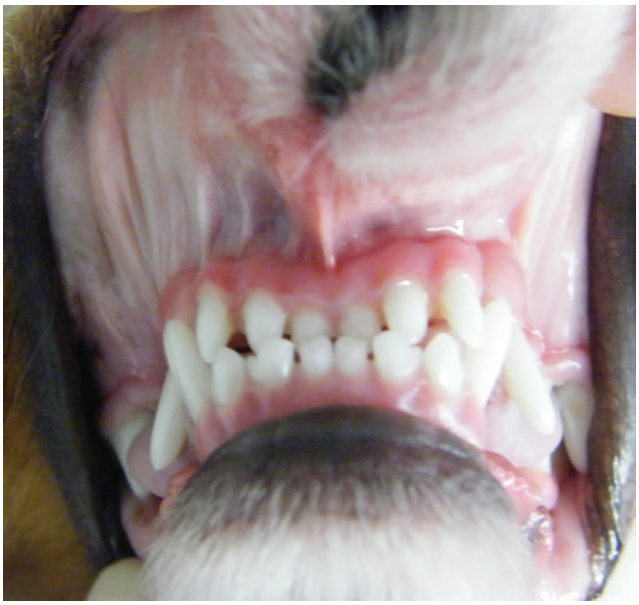

Figure 2

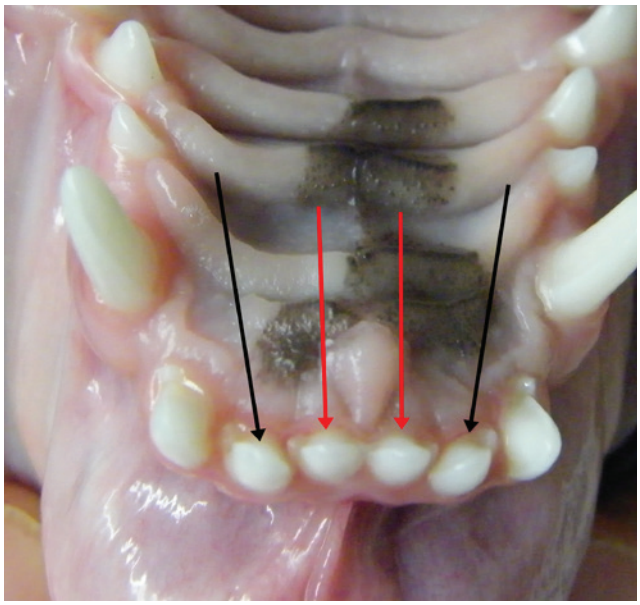

Figure 3

In order to correct this condition we must properly assess all options. There are two basic types of appliances that can be used in orthodontics: removable and fixed. An orthodontic appliance means any kind of material or device capable of exerting continuous or intermittent forces against the tooth in order to mobilise and change the position of this tooth in relation to other teeth or with the jaws. Sometimes orthodontic devices are referred to as dental braces.
Removable orthodontic appliances are rarely used in veterinary dentistry due to obvious reasons related to the temperament of the dog, difficulty of application and owner compliance. A fixed device can be used in this case. There are still a number of options that might be applied. A so called labial maxillary arch bar combined with an elastic chain or with brackets (lingual buttons) and elastic chain may be used. However due to the size and bulkiness of this device the upper lip is constantly irritated and there is a risk that the dog might remove the device with the paw. Another option might be a palatal maxillary arch bar with kick springs or coils. It is an acceptable solution, but the continuous forces exerted by the tension in the coils or kick springs might cause the dog a continuous irritation and discomfort.

Finally, a maxillary expansion screw was the choice we decided to use in this particular case. There are two types of expansion screws: acrylic-base and metal-cast. The acrylic base has the disadvantage that food and debris may accumulate and irritate the soft tissues, the metal base expansion screw however is not so bulky but it is much more expensive and necessitates the intervention of the dental laboratory and, of course, a supplementary anaesthesia session.

In order to understand the principle of tooth movement we must be aware of the 3 stages of tooth movement (according to Burstone):

- Initial phase
- Lag phase
- Post-lag phase.

The initial phase of tooth movement is immediately seen following the application of a force on a tooth. The phase is characterised by a sudden displacement of the tooth within its socket. The movement of the tooth into the periodontal space and the change of architecture in the alveolar bone will determine the displacement. The extent of movement achieved is nearly the same for both light and heavy forces. The lag phase is characterised by very little or no tooth movement. It is the phase where the cellular components around the area of interest get activated to allow tooth movement. The lag phase is longer if high forces are applied, as the area of hyalinization created is large and the resorption is rearward.

Shorter duration of the lag phase is noticed for lighter forces. There is very little, if any area of hyalinization and frontal resorption of the alveolar bone is noticed.
The post-lag phase is characterized by the removal of the hyalinized tissue and tooth movement. The movement is mediated by osteoclasts and there is either direct resorption of the bony surface facing the periodontal ligament or rearward bone resorption.

Bone resorption means that the bone is being removed by the various cellular activities at the site of pressure. Two types of bone resorption are seen depending upon the magnitude of the applied force: direct-frontal and undermining-rearward.

Surgical treatment

Now in our case, in order to correct the malocclusion we used a Hyrax® Mini-7 special expansion screw (Dentaurum) with a maximum expansion range of 7 mm. We intimately formed the expansion screw intra-operatively according to the dog's tooth morphology and occlusion and bent the 2 arms to act primarily on the 2 central incisors (101, 201) that were more tipped palatally and secondarily on the 2 second incisors (102, 202).

After forming the shape of the expansion screw we fitted the 2 distal arms around the 2 maxillary canines (104 and 204) with 1 loop for each canine tooth and the 2 rostral arms were bent in the shape of a bow that rests on the 4 upper incisors, (Figure 4 and Figure 5).

In order to prepare the device for cementation or final fixation we proceeded to acid-etching. We used for this purpose a 37.5 % orthophosphoric acid that was applied on the surface of the enamel for 120 seconds (Figure 6). Acid-etching is used to dissolve some of the dental or restorative surfaces. This leaves a surface with more microporosities in which material such as resins can enter and provide a greater micromechanical interlock or bond. In the bonding process of a composite resin to a dental cavity or surface preparation, the acid-etching provides greater bonding strength and margins more resistant to leakage. Phosphoric acids are the most commonly used in a 35 to 38% gel or solution for enamel and 10 to 38% solution for dentin etching.

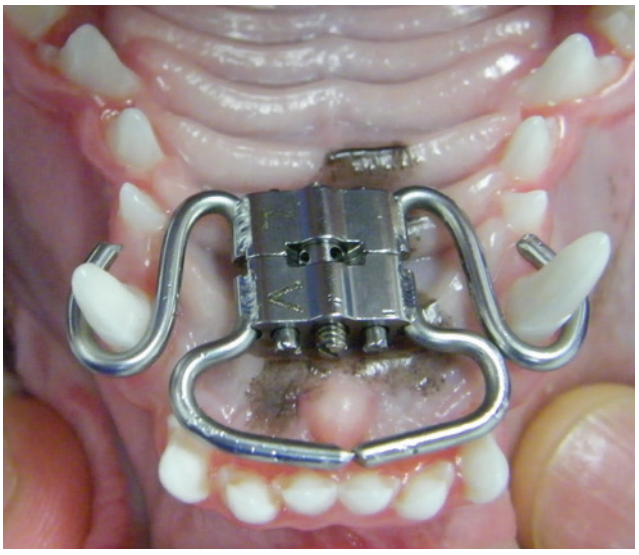

Figure 4

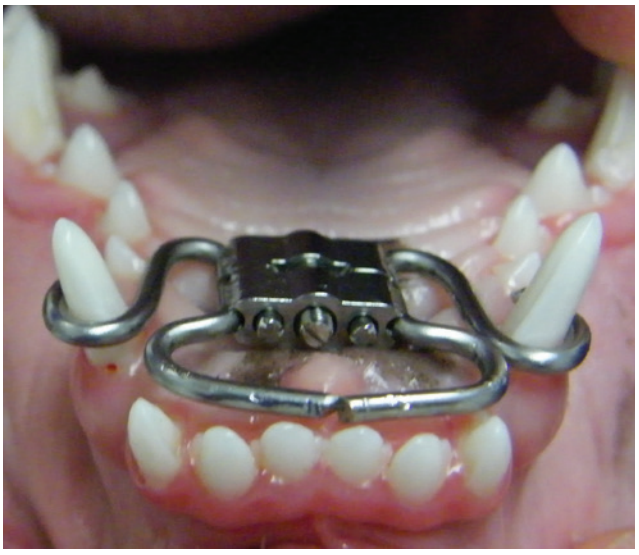

Figure 5

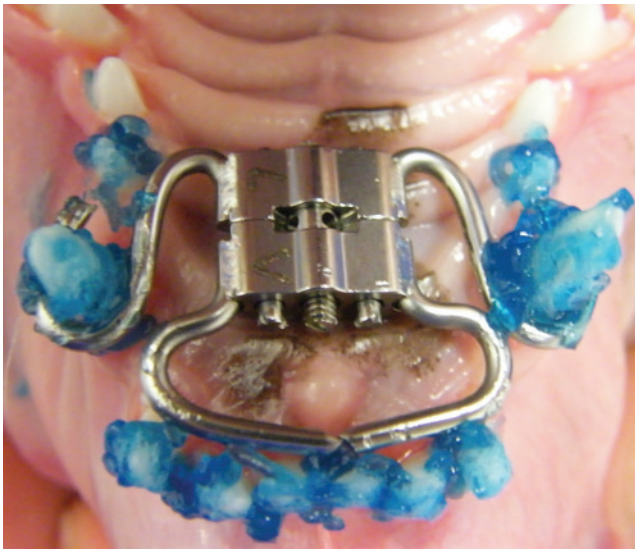

Figure 6

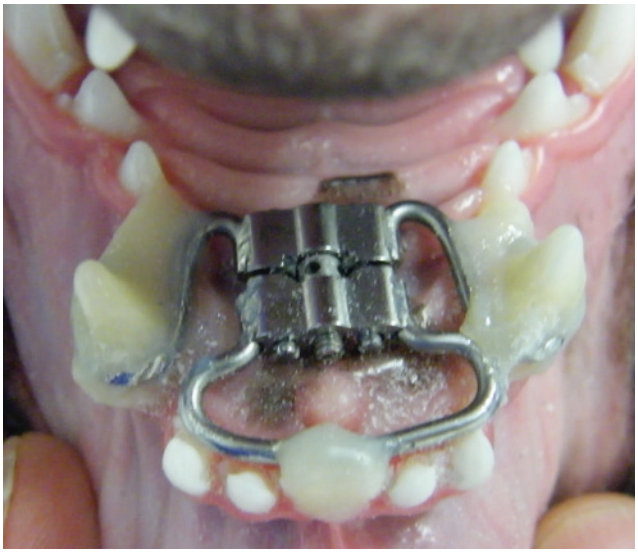

Figure 7

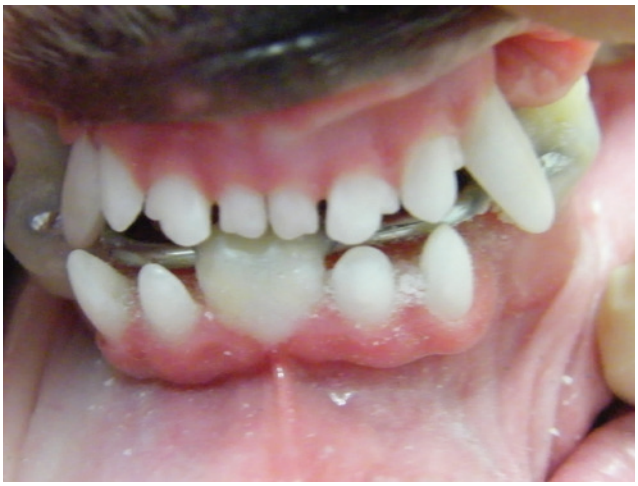

Figure 8

After 2 minutes we rinsed the orthophosphoric acid away with the air-water spray than we air dried it leaving a chalk white matt surface just ready to receive the fixation material. In this case we used Protemp™ 4 temporization material (3M ESPE) applied with an application gun provided with single use application tips. Protemp™ 4 is a two-component composite with a new generation of fillers for fabrication of interim restorations. It is indicated for temporisation of single- and multiple-unit crowns, bridges, inlays/onlays and veneers, including long-term provisional restorations. After application we formed the material with the use of a tungsten-carbide flame shape burr (Figure 7), and verified that our device did not interfere with the normal occlusion or bite pattern of the dog (Figure 8).

We decided to perform weekly activations of the expansion screw using one and a half turns each week. The activation is performed with a special activation key that enters the slot/hole of the screw. The turn is performed in the direction of the arrow stamped on the rostral portion of the screw. Our patient had a quite balanced and calm temperament that allowed us to activate the screw without using sedation. Sometimes in temperamental dogs a short sedation might be necessary in order to be able to perform the activation. We continued with weekly activations for 3 months, then for one month we maintained the expansion screw for the post-lag phase as a retainer to prevent the upper incisors to recidivate (return to their original position). During this time the owner was instructed to maintain strict oral hygiene including flushing the device with diluted chlorhexidine digluconate solution several times a day to prevent packing of food and debris underneath the expansion screw. Also the dog should not play with any hard materials such as toys, chewing bars or any other materials that might displace or break the fixation composite material.

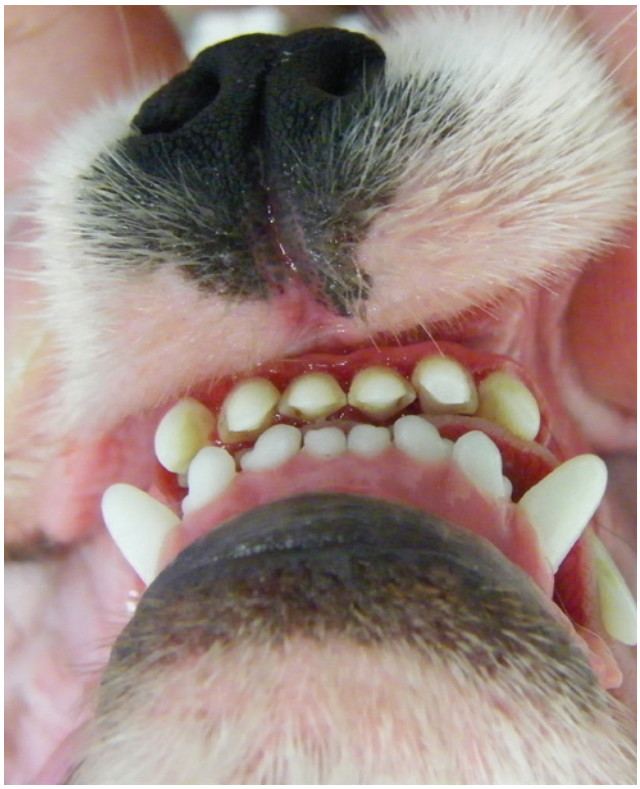

Figure 9

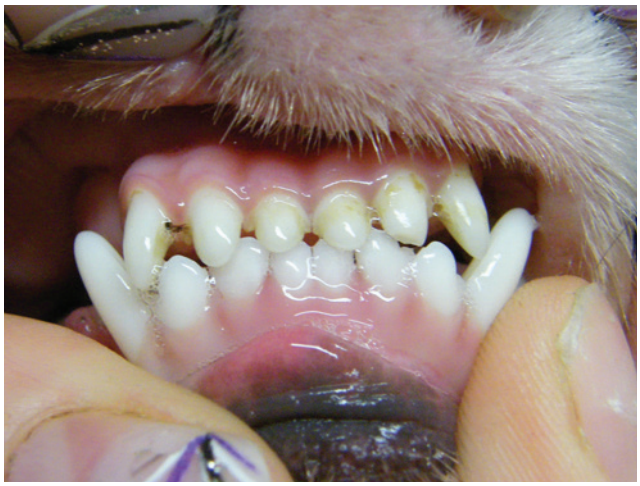

Figure 10

After 4 months we finally removed the device with the aid of a metal round burr and special orthodontic pliers.

A transient gingivitis was present at the contact points between the temporization material and soft tissues (Figure 9). This is a normal reaction of the soft tissue to the foreign material applied, however this subsides in within one week of removal of the material and proper oral hygiene. After a final assessment one month later we could see not only did the gingivitis heal completely, but also that we achieved a normal occlusion and the 4 incisors (101,102,201,202) were in the desired position (Figure 10).

Orthodontic corrections can be applied successfully after

proper patient and method selection. Not all patients are suitable for this kind of procedure: patients with periodontal disease, immune conditions or chronic heart disease, diabetes etc. are not suitable candidates.
Since any malocclusion might have hereditary involvement, genetic counselling is advisable, thus the patient should not be used for breeding purposes in order to prevent further transmission of this condition.

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COMMISSIONED PAPER (NL)

Endocrine diseases in ferrets

Nico J. Schoemaker[*1], *Yvonne R.A. van Zeeland*[1]

SUMMARY

Endocrine diseases are among the most commonly seen conditions in ferrets. Tumours of the islet cells in the pancreas, referred to as insulinomas, and tumours of the adrenal glands, referred to as hyperadrenocorticism, are more commonly described in this species than in any other species. Insulinomas are predominantly benign, insulin-producing tumours which cause hypoglycaemia and associated clinical signs, such as weakness of the hind limbs, a glazed look in the eyes and/or coma. Due to their small size, visualisation of insulinomas is difficult, rendering measurement of blood glucose as the primary diagnostic tool. The condition can be managed both surgically as well as medically. After diagnosis, the average survival is one year due to the appearance of new islet cell tumours.

Hyperadrenocorticism is even more common than insulinomas. The clinical signs, which result from increased plasma concentrations of androgens and oestrogen, are most frequently seen in neutered animals and include return of sexual behaviour, signs of oestrous in females and difficulty urinating in males due to the pathology of the prostate. Diagnosis is based on clinical signs in combination with identifying the affected gland during an ultrasonographic examination. Surgery as well as hormonal therapy are treatment options which are discussed.

Keywords: Insulinoma, hypoglycaemia, hyperadrenocorticism, adrenal gland, Mustela putorius furo, androgen

This paper was commissioned by FECAVA

Introduction

Endocrine diseases, especially neoplastic conditions, are commonly seen in ferrets. Insulinomas or islet cell tumours, and adrenocortical tumours constitute the majority of these neoplasms and are particularly common in middle-aged to older ferrets, although they may be occasionally seen in younger ferrets as well. Both of these diseases will be addressed later.

Aside from these two endocrine disorders, persistent oestrous is also a well-known endocrine condition that affects non-neutered female ferrets. Female ferrets are induced ovulators and therefore remain in oestrus until they are mated, or for as long as daylight lasts longer than 12 hours. The prolonged oestrous may subsequently result in an oestrogen-induced bone marrow suppression, and thus pancytopenia (Fig 1)[1]. Neutering is therefore recommended in any ferret which is not bred. Surgical intervention may however, potentially result in the development of adrenal neoplasms, hence explaining the high incidence of hyperadrenocorticism in pet ferrets.

[1] Division of Zoological Medicine, Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University,Yalelaan 108, NL-3584 CM, Utrecht

* Corresponding author E-Mail: N.J.Schoemaker@uu.nl;

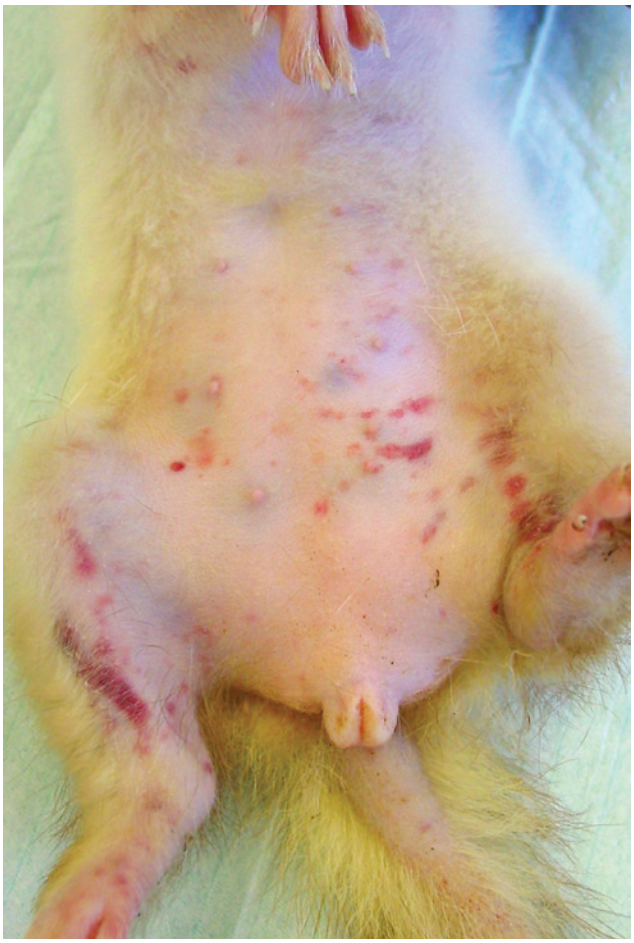

Figure 1 Petechiae due to thrombocytopaenia in a ferret with persistent oestrous

(Spontaneous) diabetes mellitus has been reported in ferrets, but is a relatively uncommon and difficult to treat disease in ferrets [2]. The clinical signs are identical to those in the more common companion animal species and include polyuria/polydipsia, lethargy and weight loss despite good appetite. Glucosuria combined with plasma glucose concentrations over 21 mmol/L are suggestive of the diagnosis, although repeated measurements are advised. A reference interval has been determined for fructosamine in ferrets (101 – 202 µmol/L [3]), but to date, no measurements have been performed in cases of (confirmed) diabetes mellitus. Although treatment with insulin is considered challenging [2], treatment with twice daily SC injections (0.5 U) of the long-acting peakless insulin glargine has been reported to be successful [4]. Since the type of diabetes mellitus is undetermined in ferrets, the use of oral hypoglycaemic drugs, such as glipizide, is questionable [5].

A few cases of hypothyroidism have been reported [6]. Clinical signs observed in these ferrets included obesity and lethargy. After finding low thyroid hormone levels, hypothyroidism was suspected, but similar to dogs and cats, confirmation of the diagnosis required the use of a TSH-stimulation test [6]. Oral treatment with 50 – 100 µg levothyroxine, twice daily has been found effective [6].
Of the endocrine diseases described in companion animals, the following have never been documented in ferrets: growth hormone deficiency or growth hormone excess, diabetes insipidus, hyperthyroidism, hypo- and hyperparathyroidism and spontaneous hypoadrenocorticism (Addison's disease). These diseases would therefore not be placed high on the differential diagnosis list. A single case report of a C-cell carcinoma [7] and a case of pseudohypothyroidism [8] have been described, however. Despite the lack of reported cases, the above mentioned differentials should not be ruled out, and further diagnostic work-up for such diseases is warranted when confronted with a ferret with clinical signs corresponding to symptoms seen in dogs and/or cats with the aforementioned endocrine diseases.

Due to the relatively infrequent occurrence of endocrine diseases other than insulinoma and hyperadrenocorticism, this review will further focus on the latter two conditions, and give an overview of the currently available information on their respective aetiology, clinical signs, diagnostic work-up, therapeutic intervention and prognosis.

Insulinoma

Insulinomas or islet cell tumours are small tumours (Fig 2) of the pancreatic beta cells which results in the production of excessive amounts of insulin and subsequent hypoglycaemia. The distribution of these adenomas, which are usually between 0.5 and 2 mm, is equal among the sexes. With a reported prevalence of 20-25% of the diagnosed neoplasms in ferrets, insulinomas are one of the most commonly diagnosed tumours in middle-aged to older ferrets, with a

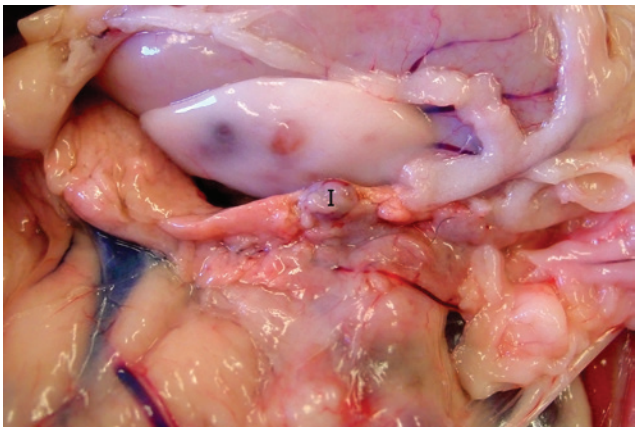

Figure 2 A relatively large tumour within the pancreas of a ferret is seen at (I). Histological examination of this tumour proved it to be of islet cell origin.

median age of 5 years (range 2 - 8 years) [2,9,10,11,12].

Aetiology

The aetiology of the development of insulinoma in ferrets is unknown. The limited genetic diversity of ferrets, which stem from a limited number of breeder farms, has led to the suggestion that a genetic component may be involved [5]. Another theory suggests that, based on the natural carnivorous diet of mustelids, diets high in carbohydrates may contribute to the development of these tumours [13]. A diet high in protein (42–55%#), high in fat (18–30%#1), low in carbohydrates (8-15%#1), and low in fibre (1–3%#1) has therefore been advised to reduce the incidence [13]. Alternatively, feeding commercial balanced diets based on entire prey animals has been recommended. No scientific evidence, however, is available to back up any claims on the aetiology of insulinoma, nor has it been proven that the incidence is reduced when ferrets are fed prey based diets or low-carbohydrate kibble.

Clinical signs

Clinical signs vary from lethargy, slight incoordination and weakness in the hind limbs to complete collapse and coma [2]. In humans, an overdose of insulin may result in stimulation of the autonomic nervous system resulting in nausea. The nausea, which is commonly seen in ferrets with an insulinoma, but not in dogs and cats, often manifests itself in the form of ptyalism and pawing at the mouth. In addition, owners may notice a glazed look in the eyes of their ferrets. Signs are most evident when the ferret has not eaten for some time, and will often resolve spontaneously after providing the ferret with some food (Fig 3) or a calorie-rich beverage. If the waxing and waning of the signs are not seen, other diseases affecting the hind limbs should also be considered [2,11].

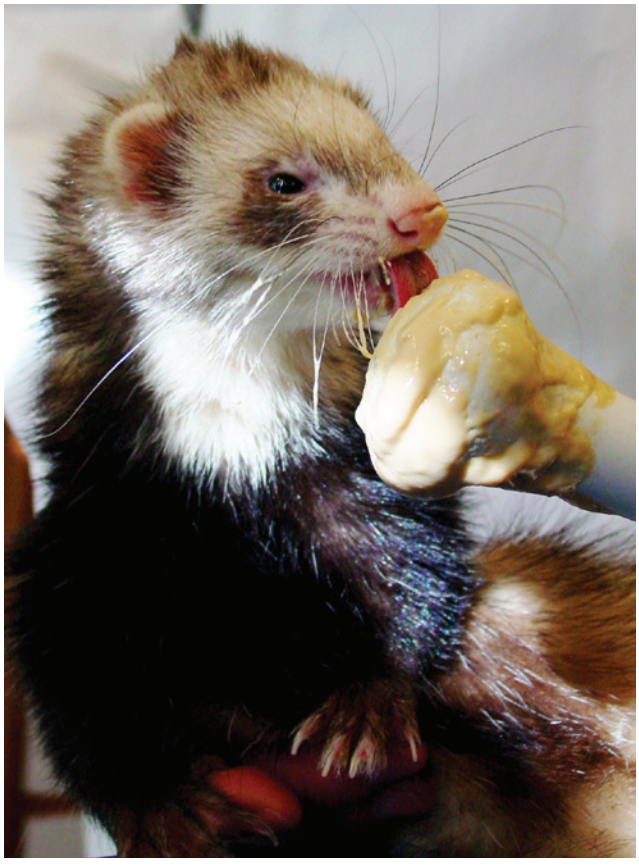

Figure 3 A ferret in a hypoglycaemic crisis may be fed a protein rich diet to quickly correct the energy balance

Differential diagnosis

The differential diagnosis of hind limb weakness consists of: neurological diseases (e.g. trauma, intervertebral disc disease, Aleutian disease), cardiac disease, generalized weakness and metabolic disorders, such as hypoglycaemia [14]. In ferrets, hypoglycaemia is considered the most commonly seen cause of hind limb weakness.
Within the differential diagnosis of hypoglycaemia, excessive glucose consuming conditions, such as rapid multiplying neoplastic cells, severe hepatic disease and sepsis should be considered#[2]. These conditions can usually be ruled out based on the results of the history, physical examination and/or the diagnostic work-up.

Diagnostic work-up

Blood chemistry – Blood glucose concentrations lower than 3.8 mmol/l (reference range: 5.0 – 6.9 mmol/l), after withholding food for 4 hours, are highly suggestive of an insulinoma when ferrets display the above mentioned signs [9]. In ferrets with blood glucose concentrations between 3.9 and 5.0 mmol/l, the authors advise to prolong the fast with another 2 hours. In many cases, the blood glucose will then drop to below 3.8 mmol/l confirming the tentative diagnosis. Portable blood glucose meters (PBGM) seem very practical for obtaining quick results. They only need one drop of blood which can be collected from any vein (Fig 4), but also from a puncture of a footpad. Due to the method of analysis, heparinized blood should not be used. In a comparison study evaluating the agreement between glucose concentrations measured with a laboratory analyser and 3 different PBGMs it became clear that the human PBGMs severely underestimate the actual glucose concentrations [15]. The veterinary PBGM had 2 settings in which the canine setting produced the most agreeable values. If one wants to use a PBGM in practice, it is good to realize that underestimation is possible and that accurate values can only be obtained with a laboratory analyser. Plasma insulin concentrations can also be measured and are usually

based on dry matter base

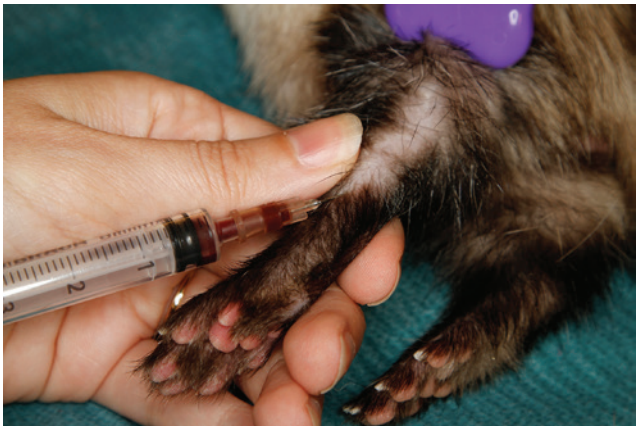

Figure 4 In ferrets suspected of having an insulinoma, blood may be collected from the lateral saphenous vein

increased, but concentrations within the reference range may also be seen [2]. The latter should still be considered increased, as insulin plasma concentrations should decrease during a hypoglycaemic event [2].

Diagnostic imaging – As insulinomas are usually very small in size (0.5–2 mm), it is extremely difficult to visualize the primary tumour by use of ultrasound [16]. In the experience of the authors, insulinomas may occasionally be visualized by ultrasound, but they are also frequently missed. In dogs, insulinomas have a poor prognosis due to the high rate of metastasis, which frequently occurs to the liver. These metastases can be visualized on ultrasound. Adenocarcinomas of the pancreas have been reported in ferrets, and metastases have been found on ultrasound [16]. The great majority of insulinomas, however, are benign and do not metastasise [11]. Diagnostic imaging in the form of radiography or ultrasound examination is therefore not routinely advised. Computed Tomography, MRI and nuclear scintigraphy with octreotide or indium-111 have, to the authors' knowledge, not been used in ferrets to diagnose insulinomas. The expense of the nuclear scanning and the lack of sensitivity in finding insulinomas in dogs and humans with CT and MRI make these advanced diagnostic imaging tools less promising for future use in practice [2].

Treatment

Insulinomas may be managed surgically and/or medically. Many factors, such as age of the ferret, desire of the owner to have an instant solution and/or financial restrictions, may play a role in the decision-making process. It is recommended by the authors that a veterinarian presents all facts, in order to allow the owner to make an informed decision based on the pros and cons of each method.

Surgical treatment – To fully eliminate the source of excess insulin production, surgical removal is seemingly the best therapeutic option. Due to the limited ability to visualize the tumours, the possibility to excise the insulinoma(s) can only be evaluated upon explorative surgery. Surgical excision may not be successful in alleviating the clinical signs as some tumours may remain undetected during surgery due to their small size. A partial pancreatectomy has therefore been recommended over pancreatic nodulectomy in order to remove as much undetectable islet cell tumours and thus increase the survival time after surgery [11]. In addition, if the neoplasm is located in the body of the pancreas, it is often difficult to remove, as resection of this part of the pancreas is not possible due to the presence of the pancreatic duct. A mean disease free state after surgery of about 1 year, and survival times of over 3 years have been reported [2,11]. Recurrence of clinical signs are mainly due to the occurrence of new insulinomas and not due to metastasis of the removed tumour. If too much of the pancreas is removed, complications such as diabetes mellitus may occur. It should be stressed that every effort should be taken to avoid this condition from occurring, since the medical management of insulinoma is far easier than that of diabetes mellitus. It could also be speculated that an exocrine pancreatic insufficiency could occur when too large a portion of the pancreas is removed. However, this has not been reported.

Medical treatment – Prednisolone and diazoxide are the most commonly used drugs for treating insulinomas. Somatostatin, which inhibits the synthesis and secretion of insulin by normal and neoplastic beta cells, has also been incidentally used in ferrets, but no clear beneficial effects were seen over the other two modes of treatment [2]. In private practice, prednisolone and other glucocorticoids, which induce gluconeogenesis, are frequently used as the drug of first choice. Although these drugs commonly induce side-effects in other species, ferrets seem relatively refractory to developing side-effects due to glucocorticoid administration, and generally respond well to the treatment protocol [2]. Weight gain and impaired hair growth (suggestive of iatrogenic Cushing's disease), however, has been reported in ferrets that have received glucocorticoids for prolonged periods of time [9]. In addition, the gluconeogenic mode of action of glucocorticoids results in an increase of glucose, which may be contraindicated in ferrets with insulinomas due to the risk of stimulating the secretion of insulin.

Diazoxide, which is registered for treating human insulinoma patients, inhibits insulin release [2]. The authors therefore prefer this drug over the use of glucocorticoids. The drug, however, is more expensive than prednisolone, which may also explain why prednisolone is frequently chosen over diazoxide. Although this is a factor to be considered in dogs (especially larger breeds), the ferret's low body weight results in limited daily requirements of the drug, thereby making diazoxide an affordable alternative for ferrets. Compounding the drug is, however, necessary to allow accurate dosing. Treatment is started at an oral dose of twice daily 5 mg/kg diazoxide. Based on the response to treatment (as judged by disappearance or continuation of clinical signs), the dose may need to be increased gradually. When using plasma glucose concentrations to monitor the effect of treatment, blood should always be collected 4 hours after giving the diazoxide. During this period food should be withheld from the ferret. Once the dose of diazoxide has been increased to 15 – 20 mg/kg q12h and clinical signs still have not resolved, prednisolone may be added to the treatment protocol in a concentration of 0.2 – 1 mg/kg PO, q24h. For both drugs, doses may be increased further if necessary, with no real upper limits existent. The only limiting factor may therefore be the development of side-effects such as vomiting and anorexia [2]. Medical management based on the aforementioned protocol is usually sufficient to control hypoglycaemia for a period up to 18 months, with some ferrets in the authors' clinic even surviving up to 2 years on medical treatment.

Prognosis

In ferrets, the prognosis is better compared to dogs, in which metastases are very common. Although metastases are rare in ferrets, multiple tumours and recurrent signs are common. Recurrent signs are probably due to the development of new tumours rather than metastasis of the earlier tumour [2].

Hyperadrenocorticism

Hyperadrenocorticism is most commonly seen in neutered pet ferrets that are older than 3 years of age. An exact incidence of the disease is not known, but some have reported that up to 95% of ferrets presented for post mortem examination have adrenal pathology [9]. In the United States, however, some ferrets are already diagnosed with the disease at the age of 2 years. The disease affects males and females equally [17].

In contrast to dogs (in which excessive production of glucocorticoids [hypercortisolism or Cushings' syndrome] is most common) and cats (in which excessive production of mineralocorticoids [hyperaldosteronism or Conn's syndrome] is most common), hyperadrenocorticism in ferrets most commonly results in hyperandrogenism. In rare cases, hypercortisolism [18] or hyperaldosteronism [19] may be seen in ferrets as well.

Hyperadrenocorticism in ferrets is characterized by elevation of plasma levels of plasma androstenedione, 17∝-hydroxyprogesterone and/or oestradiol concentrations [18]. In ferrets with hyperadrenocorticism, a unilateral or bilateral enlargement of the adrenal glands may be present. A unilateral enlargement (without atrophy of the contralateral adrenal gland) appears to be most common (present in approximately 85% of ferrets) [20]. In these cases, however, disease may develop in the contralateral adrenal gland after surgical removal of the initially affected gland, thereby leading to recurrence of the disease [21]. Bilateral enlargement may be found in a small percentage of cases (approximately 15% of ferrets with adrenal gland disease) [20]. The adrenal tumours have been histologically classified as (nodular) hyperplasia, adenoma and adenocarcinoma [20]. This histological diagnosis, however, does not provide any prognostic information, nor does it say anything about functionality of the tumour. In contrast to dogs with Cushing's disease, no relationship has been found between pituitary and adrenal tumours in ferrets [22].

Aetiology

Different aetiologies have been suggested for the high incidence of hyperadrenocorticism in ferrets. These include (early) neutering of ferrets, housing ferrets indoors, and genetic background.

(Early) neutering – In previous years, it has been hypothesized that a castration-related increase of gonadotrophins, which develops as a result of a loss of negative feedback from the gonads, stimulates the adrenal cortex, eventually leading to the development of an adrenocortical neoplasm (Fig 5) [17,20]. Findings in support of this hypothesis include 1) initial signs of hyperadrenocorticism occur only during the breeding season, when plasma concentrations of gonadotrophic hormones are high [23]; 2) adrenal tumours are more frequently seen in countries where ferrets are routinely neutered (USA), compared to countries where ferrets were not routinely surgically castrated in the past (UK) [24]; 3) a significant correlation has been found between the age at neutering and age at onset of hyperadrenocorticism [17]; 4) the successful use of the depot gonadotrophin-

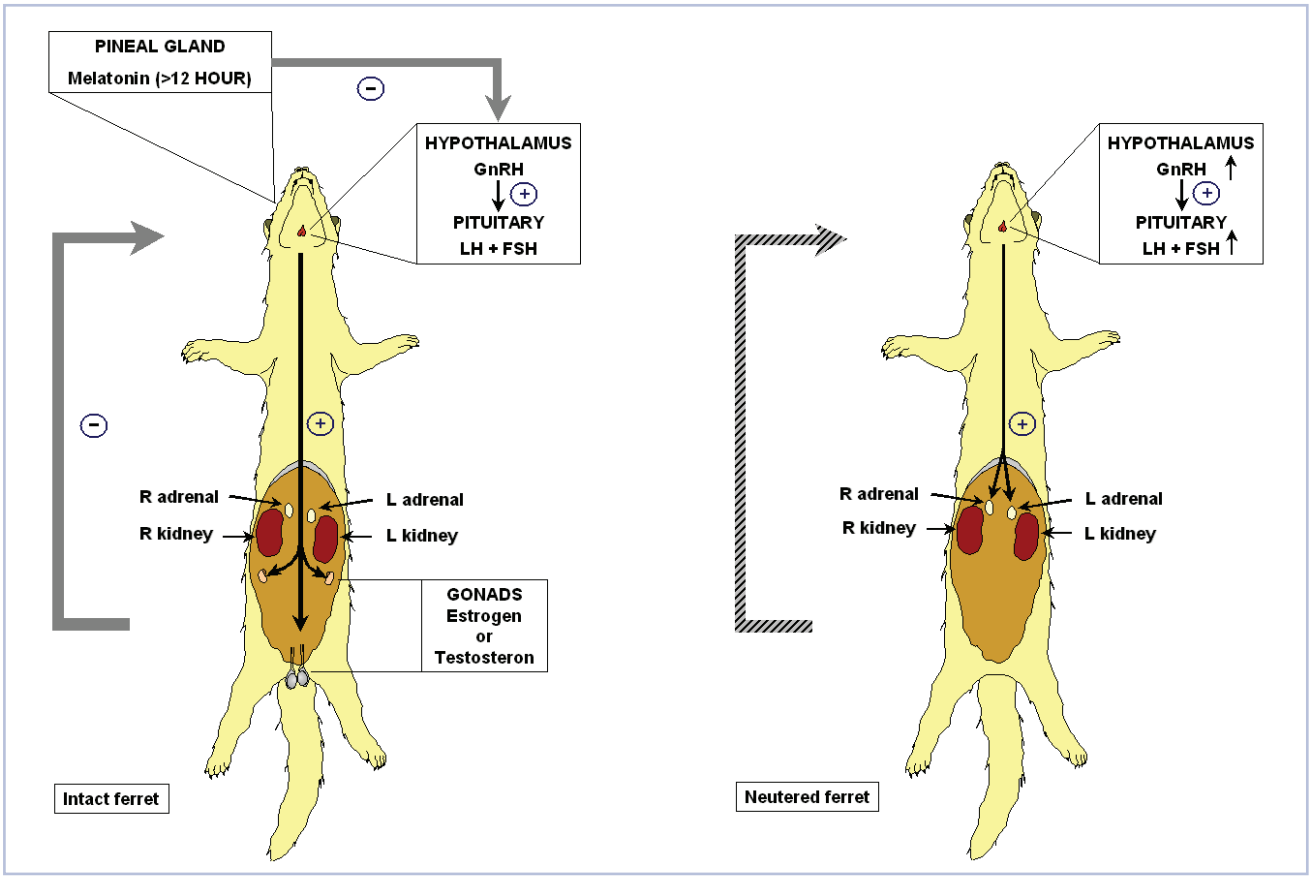

Figure 5 Diagram illustrating the regulation of reproductive endocrinology in intact ferrets, the consequences of neutering on this process, and the possible role it plays in the development of hyperadrenocorticism in this species. In short; high melatonin concentrations for more than 12 hours per day suppress the release of GnRH. When this suppression is lost, GnRH is released in a pulsatile fashion, resulting in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the release of estrogen and testosterone. This exerts a negative feedback on the hypothalamus and pituitary gland. When ferrets are neutered this negative feedback is lost, resulting in an increased release of the gonadotrophins, which may activate their respective receptors in ferret adrenal glands if they are present.

releasing hormone (GnRH)-analogues leuprolide acetate and deslorelin, which lead to a decrease in gonadotrophins, in the treatment of hyperadrenocorticism [25,26]; and 5) the increased plasma androgen concentrations seen after an intravenous injection of a GnRH-agonist, as a result of the presence of functional luteinizing hormone (LH) receptors in the adrenal cortex of ferrets [24]. Although a correlation has been found between neutering and occurrence of adrenal tumours in ferrets, it is questionable whether the age of neutering is of influence as the prevalence of hyperadrenocorticism in Dutch ferrets (which are usually neutered between 6 and 12 months of age) appears to be more or less similar to the prevalence in the USA ferrets (which are commonly neutered at an age of 6 weeks) [17]. The age of neutering may thus be of less importance for the development of adrenocortical tumours in ferrets than neutering itself.

Housing ferrets indoors – Similar to the hypothesis that increased gonadotrophin levels induced by neutering pose an increased risk for developing adrenal gland tumours, indoor housing may also pose as a risk factor for developing increased gonadotrophins and subsequent hyperadrenocorticism [27]. As ferrets that are kept indoors will be exposed to longer daylight periods (i.e. owners will have lights on inside when it is already dark outside), melatonin will be longer suppressed, resulting in prolonged periods of elevated gonadotrophin plasma concentrations in comparison to ferrets that are housed outdoors. This hypothesis is further supported by the lower incidence of adrenal gland disease in the UK, where many ferrets are kept outdoors [28]. Lack of neutering in these ferrets may, however, (partially) bias these findings [28].

Genetic background – In addition to the previous two hypotheses regarding the aetiology of hyperadrenocorticism in ferrets, a genetic background has also been suggested. As ferrets have a high incidence of both insulinomas and adrenal gland tumours, it has been hypothesized that the hereditary changes causing multiple endocrine neoplasms

in humans (MEN1, MEN2a and MEN2b), could also play a role in the aetiology of the formation of adrenal tumours in ferrets [29]. Since many of the ferrets in the USA come from the same breeding facility, thereby sharing a similar genetic background, it is possible that in the USA the limited genetic variation of ferrets poses an explanation for the high incidence of the disease. Ferrets in the Netherlands, however, do not share this similar background. It therefore remains questionable if the MEN genes are involved. Further research is needed to identify whether genetic abnormalities are involved.

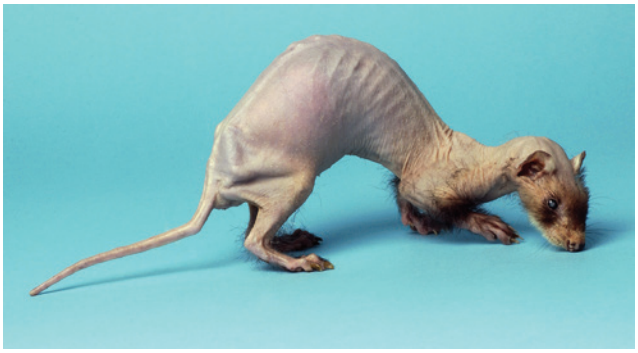

Figure 6 Severe alopecia seen in a 7-year-old, neutered female ferret with hyperadrenocorticism

Clinical signs

The most common clinical signs in ferrets with hyperadrenocorticism include symmetrical alopecia (Fig 6), recurrence of sexual behaviour after neutering, and pruritus [17,20,21]. Skin lesions are usually absent, unless scratching results in excoriations. In (neutered) female ferrets, vulvar swelling and occasional mammary gland enlargement may furthermore be noted [17,20,21], whereas in the male ferrets dysuria, pollakisuria and/or anuria may be encountered due to the development of secondary peri-prostatic or peri-urethral cysts causing urethral obstruction [30,31].
Polyuria and polydipsia has also been documented in ferrets with hyperadrenocorticism [20,21]. Whether this is due to concurrent kidney disease occurring in (elderly) ferrets, or the adrenal hormone production is not known. In a case of LH-dependent hypercortisolism (Cushing's disease) in a ferret, PU/PD was the primary clinical sign, while the other common signs of hyperadrenocorticism in ferrets, such as alopecia, were only minimally present [18].

Differential diagnoses

The most important differential diagnoses for the female ferrets with signs of hyperadrenocorticism is the presence of an active ovary, either due to a remnant of the removed ovary, or an animal which was not ovariectomized at all [2]. Food intolerance should be considered in both sexes which show signs of severe alopecia and pruritus. Infectious skin diseases should also be considered in those cases. In the latter cases, however, the skin itself will be affected. Seasonal alopecia is also commonly mentioned as a differential diagnosis. As indicated by its name, this condition is characterized by a seasonal occurrence of alopecia, with hair loss predominantly occurring on the tail. Although the actual cause for this condition is not known, the authors suspect that it may be an early sign of hyperadrenocorticism as well [2].

Diagnostic work-up

Physical examination – The diagnosis of hyperadrenocorticism can be made based on the presence of the typical signs of hyperadrenocorticism combined with the exclusion of the other differential diagnoses. During abdominal palpation, a (tiny) firm mass, representing the (enlarged) adrenal tumour, may be palpated craniomedial to the cranial pole of the kidneys [2]. The left adrenal tumour is more easy to palpate compared to a tumour located in the right adrenal gland. The right adrenal gland, on the other hand, is located more cranial, with the caudal part of the caudate liver lobe located ventral to the gland, thereby obscuring it from palpation [2].

Blood chemistry – Hormone analysis is most commonly recommended in the diagnostic work-up of ferrets suspected of hyperadrenocorticism [2,32]. For this purpose, EDTA plasma may be collected and sent to an external laboratory for analysis of androstenedione, oestradiol, and 17α-hydroxyprogesterone. This laboratory should have established reference values for these hormones in ferrets, as laboratories may use different methods to analyse these hormones, which may greatly influence the concentrations that are measured. Elevated plasma levels of one or more of the aforementioned hormones have been considered as diagnostic for hyperadrenocorticism in ferrets [32]. Plasma concentrations of androstenedione, oestradiol, and 17 α -hydroxyprogesterone in intact female ferrets, however, are identical to those in hyperadrenocorticoid ferrets [2]. The authors therefore do not consider the analysis of these hormones to help differentiate between the differential diagnoses. The measurement of these hormones may, however, be useful for monitoring the effect of treatment.

Urine analysis – The urinary corticoid-creatinine ratio (UCCR), in combination with a high dose dexamethasone suppression test (HDDST), is a common diagnostic test

for Cushing's disease in dogs [33]. This test has also been performed in ferrets and resulted in the finding of increased urinary cortisol concentrations in ferrets with hyperadrenocorticism [34,35]. As the test does not distinguish between the ferret with an adrenal tumour and an intact ferret, it is however, not considered diagnostic [35].

Diagnostic imaging – Abdominal ultrasonography is considered the most useful tool in diagnosing hyperadrenocorticism in ferrets by the authors [36]. It should be emphasized, however, that ultrasound only allows establishment of the size and morphology of the organs and does not provide any information on the functionality of the tumour. Ultrasound is, however, useful when surgical intervention is considered as it allows identification of a ovarian remnant and/or the affected adrenal gland(s). During the ultrasonographic exam, adrenal glands have a similar appearance as (abdominal) lymph nodes. Specific landmarks are therefore needed to accurately detect the adrenal glands [36]. For the left adrenal gland, which is located lateral to the aorta, the cranial mesenteric and celiac arteries branch of the aorta may be used as landmarks (Fig 7). The right adrenal gland, in contrast, is more difficult to locate as it is located dorsally to the caudomedial aspect of the caudate process of the caudate liver lobe, and attached to the dorsolateral surface of the caudal vena cava (Fig 8A). To locate this gland, the aorta, portal vein and caudal vena cava may be used as landmarks. First, these vessels are located in the region of the caudate process of the liver, of which the portal vein is the most ventral of the three, and the one with the widest diameter. The aorta is the most dorsal of the three, and pulsates. After identifying the different vessels, the right adrenal gland may be located at the level of and/or immediately cranial to the origin of the cranial mesenteric artery (Fig 8B). The ultrasonographic changes of a healthy adrenal gland to that of an adrenal tumour are the significantly increased thickness, rounded appearance, heterogeneous structure, increased echogenicity, and/or the presence of signs of mineralization [36]. Finding an extremely large adrenal gland may be suggestive of an adrenal carcinoma, which usually does not respond (well) to hormone therapy. Establishing the size of the adrenal gland may thus also be of use in non-surgical cases.

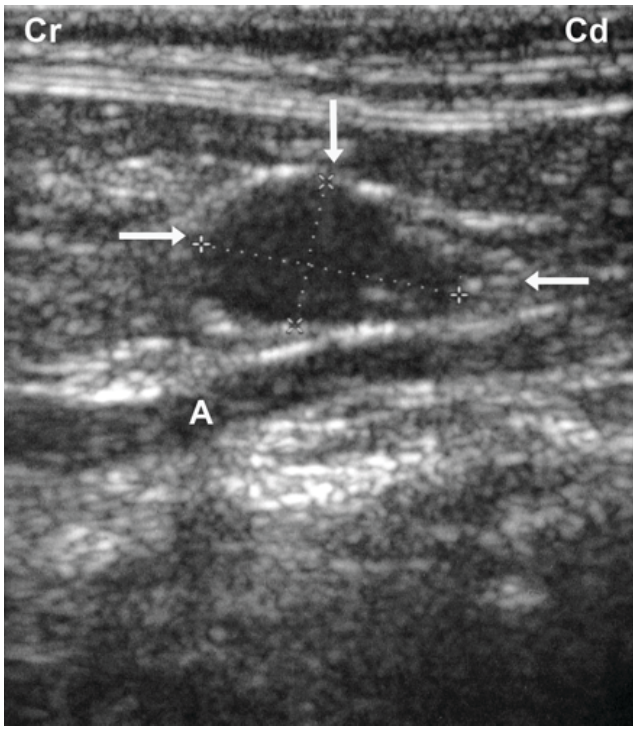

Figure 7 A longitudinal sonogram of a left adrenal gland (between the arrows) of a 3.5-year-old spayed female ferret with hyperadrenocorticism. The cranial pole is enlarged. Adrenal length is 10.4 mm and thickness is 6.4 mm. Histopathological diagnosis was adrenocortical hyperplasia. Note the location of the adrenal gland ventrolateral to the aorta (A). The top of the image is ventral, Cr= cranial, Cd= caudal (previously published [36]).

In addition to ultrasonography, computed tomography may be useful when evaluating the adrenal glands in ferrets. When using this technique, intravenous contrast medium will be needed to delineate the adrenal gland better from the caudal vena cava and enable better visualisation of the size of this gland (Fig 9).

Treatment

The most commonly used modalities for treating ferrets with hyperadrenocorticism are surgery and/or the use of long-acting GnRH analogues. The choice of treatment is influenced by many factors. Criteria such as the age of the ferret, presence of concurrent disease (e.g., renal failure, lymphoma and/or cardiomyopathy), risk of surgery (which is higher when the right or both adrenal glands are involved), and/or financial limitations may lead an owner to decline surgery. When surgery is chosen, however, it is important to realise that gonadotrophin release will persist, thereby resulting in a continued stimulation of the remaining adrenal gland. This gland may subsequently become affected at a later stage. The use of hormonal therapy (the placement of a long-acting implant containing deslorelin) may therefore also be recommended when a surgical intervention has been performed. The extra costs for the medication, may, however result in an owner opting for surgery alone.

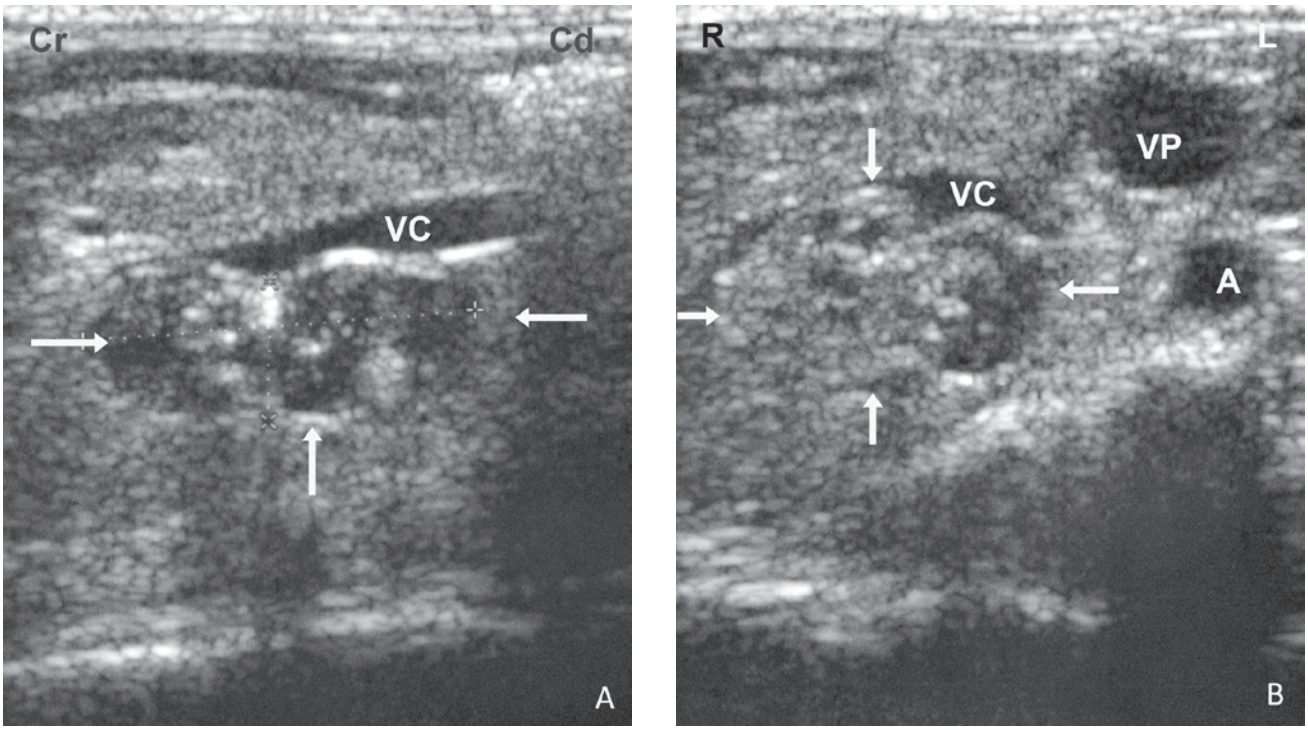

Figure 8 A longitudinal (A) and transverse (B) sonogram of the right adrenal gland (between the arrows) of a 6.5-year-old castrated male ferret with hyperadrenocorticism. The adrenal gland is hyperechoic, heterogeneous, and contains mineralizations (hyperechoic spots). The adrenal gland length is 15.6 mm and thickness is 5.5 mm. The right adrenal gland is located dorsolateral of the Vena cava (VC). The top of the image is ventral. A=aorta, VP= Vena porta, R=right, L=left, Cr=cranial, Cd=caudal (previously published [36]).

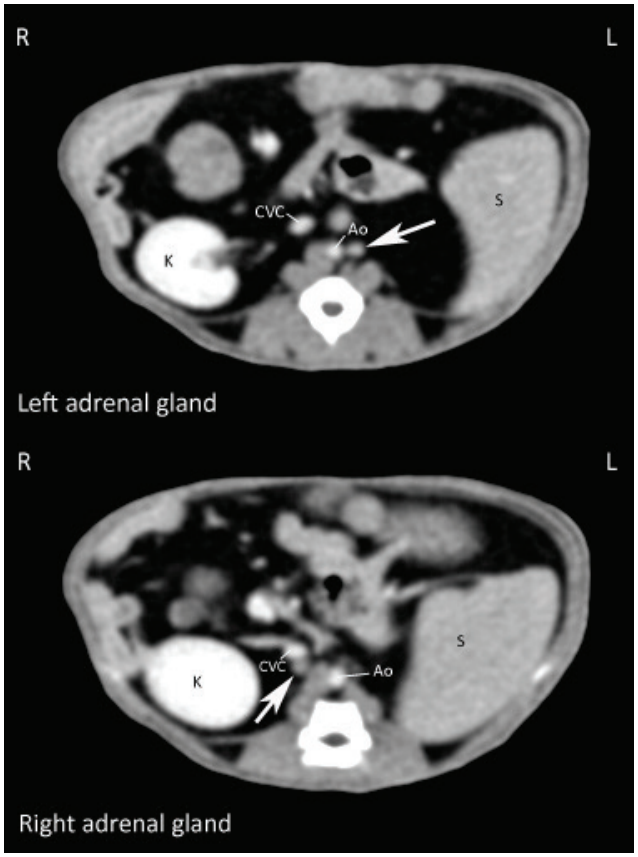

Figure 9 Computed Tomography images of a 3-year-old female ferret after IV administration of 2 ml contrast medium. The left adrenal gland (top arrow) is located in close proximity of the aorta (Ao). The right adrenal gland (bottom arrow) is located dorsal of the caudal vena cava (CVC), medial to the right kidney (K). The spleen (S) in this ferret is large, which is not uncommon in ferrets.

Surgical treatment – Compared to removal of the right adrenal gland, surgical removal of the left adrenal gland is considered fairly easy and straightforward [2,37]. The anatomical location of the right adrenal gland, however, hinders its accessibility during a standard ventral abdominal approach. In addition, surgery may be complicated further as complete removal of the adrenal gland involves removal of part of the wall of the caudal vena cava. Due to the difficulty of this procedure, many surgeons prefer to remove only part of the adrenal gland, thereby posing a risk for recurrence of the problems. Upon removal of both adrenal glands, one should also be aware of the risk for developing hypoadrenocorticism (Addison's disease). This complication, however, is rarely seen, most likely due to the fact that the right adrenal is seldom removed completely, with the remnant tissue preserving sufficient function, thereby minimizing the chance of the development of iatrogenic Addison's disease.

Medical treatment – The most effective drugs currently used for the hormonal treatment of hyperadrenocorticism are the depot GnRH-agonists leuprolide acetate and deslorelin [38,39,40,41].

Depot GnRH-agonists suppress the release of gonadotrophins by continuously releasing GnRH into the circulation, which

overrides the pulsatile release of GnRH that is needed for the release of gonadotrophins (LH and FSH). Thus, initially the administration of a depot GnRH agonist will result in short-lived release of gonadotrophins (due to the initial increase of GnRH in the circulation), which is soon followed by a drop in gonadotrophin concentrations to baseline levels (due to the reaching of a plateau phase which lacks a pulsatile release of GnRH). Initially leuprolide acetate, which is registered for use in people, was the only drug available. Since deslorelin, which is now registered for use in dogs and ferrets, has become available on the market leuprolide acetate is no longer the drug of first choice. The deslorelin containing implants can be given subcutaneously (Fig 10). The implant containing 4.7 mg deslorelin will generally be effective for approximately 8 to 30 months [40]. In a study in which a 3 mg containing implant was used in 15 ferrets with hyperadrenocorticism, five developed adrenal tumours greater than 2 cm in size within 2 months after the activity of the implant had worn off [39]. Since this publication, however, this high incidence has not been seen in practice. More research will therefore be necessary to determine why these tumours developed, and how high the actual frequency is. In addition, it should be considered that autonomous production of steroids by the adrenal gland may occur, leading to a lack of or loss of response to the hormonal treatment [40,41].

Other medical treatment options – Other medications have been proposed for the treatment of hyperadrenocorticism in ferrets. These include melatonin, mitotane (o,p'-DDD) combined with ketoconazole, and trilostane (a 3β-hydroxysteroid dehydrogenase blocker [HSD]). Although the treatment with mitotane and/or ketoconazole is well-known for treating hypercortisolism in dogs and humans, this combination was found to be insufficiently effective in ferrets [2]. Melatonin, given in a dose of 0.5 mg/kg daily PO or in the form of an implant (containing 5.4 mg melatonin), did result in clinical improvement [27,42]. However, upon receiving melatonin, tumours continued to grow, thereby posing a risk for deterioration of the ferret's condition without the owner noticing it [27]. Trilostane, a 3β-HSD-blocker that is commonly used to treat pituitary-dependent hyperadrenocorticism in dogs [33], has been used only incidentally in ferrets. Although the drug theoretically may be effective for treatment of hyperadrenocorticism in ferrets (as 3β-HSD is necessary for the synthesis of androstenedione and 17α-hydroxyprogesterone), a pilot study in ferrets with hyperadrenocorticism given 5 mg trilostane PO once daily showed deterioration or no effect rather than improvement of the clinical symptoms. More research is therefore necessary to determine whether this drug is effective and safe for use in ferrets with hyperadrenocorticism.

Figure 10 A deslorelin containing implant is placed subcutaneously in an awake ferret. The ferret is so distracted by the food provided that is does not mind the placement of the implant.

Prognosis

The prognosis of a ferret with hyperadrenocorticism in general is good. An average disease free period of 16.5 months and 13.6 months has been reported in ferrets treated with a deslorelin implant or ferrets that were surgically treated, respectively [41]. In another study, 1- and 2-year survival rates after surgery were 98% and 88% [43]. Since metastases rarely occur, this hardly influences the overall prognosis [2]. In male ferrets, however, prostate involvement may result in a life threatening urinary blockage, thereby influencing chances of survival if not treated promptly [2].

Future perspectives

Despite the frequent occurrence of insulinomas and adrenal neoplasms in ferrets, the exact aetiological cause for this high incidence has yet to be determined. If the incidence of adrenal tumours indeed is related to increased gonadotrophin release induced by surgical castration, the incidence of adrenal gland tumours should decrease when using deslorelin containing implants as alternative for surgical castration. Currently, a study is ongoing with ferrets to determine whether this indeed is the case.
In addition, molecular studies are being performed to identify the potential genes and pathways involved in the development of adrenal gland tumours [44] and (ab)normal adrenal steroid synthesis. Similarly, molecular studies may be helpful to unravel the pathophysiology of insulinomas in ferrets. Recently, a cell-line of a ferret insulinoma

was established in the endocrine laboratory at Utrecht University, which is currently being characterized and may help to determine which cellular-molecular processes and/or mutations play a role in the development of this tumour. In addition to gaining further insight into the aetiology and pathophysiology of the conditions, these molecular studies may also be useful to help identify potential new targets for preventive and therapeutic intervention.

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THE FECAVA SYMPOSIUM 2013*
The proper use of antimicrobials in companion animal practice

Antimicrobial FECAVA Initiative – Making the responsible use of Antimicrobials work in Clinical Practice!

Alexandra Vilén[1]

SUMMARY

Nosocomial infections and multiresistant infections are growing problems in small animal practice throughout Europe. As a reaction to this in 2007, FECAVA decided to initiate a working group addressing these issues. The Working Group on Hygiene and the Use of Antimicrobials in Veterinary Practice has since then developed tools for clinicians that provide essential steps in decision making on the use of antimicrobials and an eight step system for the establishment of proper hygiene measures in practice. The group has also provided related advice to pet owners in collaboration with the Bella Moss Foundation. The work is presented as four posters that can be displayed in the clinic. They are free to download from the FECAVA webpage. In conjunction with these posters, this year's FECAVA symposium is dedicated to antimicrobial resistance.

Nosocomial infections

The term "nosocomial" refers to any infectious disease contracted by a patient while under medical care in a clinic or hospital [1]. A nosocomial infection is not present or incubating prior to the patient being admitted to the clinic or hospital, but has occurred within 72 hours after admittance. Nosocomial infections have a clear association with higher costs, and higher mortality and morbidity in human care.

There are many reports from human hospitals demonstrating the importance of hospital hygiene in preventing nosocomial infections in humans [2, 3, 4]. Even though corresponding studies in veterinary clinics and hospitals currently are lacking, the evidence from human hospitals should not be ignored. There have been several reports that veterinary practices and hospitals are contaminated by pathogenic organisms [5 ,6], which could act as a source of nosocomial infection [7].

Infection control is a well-known and accepted concept in human health. There are today well-established recommendations in human health care on how to achieve good hygiene and many of these recommendations can be extrapolated to veterinary medicine. Hand hygiene has been shown to be one of the most important factors in the prevention to prevent nosocomial infections [8].

Multiresistance

Multiresistant Staphylococcus is a growing problem in small animal practice as well as ESBL (Extended Spectrum Beta-Lactamase) producing bacteria. As clinicians we are used to treating bacterial infections with antimicrobials. As antimicrobial resistance is growing our treatment

1 Helsingborg Referral Small Animal Hospital, Box 22097, Bergavägen 3 S-250 23 Helsingborg.
E-mail: alexandra@vilen.se

* Held during the 19th FECAVA /VICAS/BSAVA Eurocongress, Dublin October 2013

options are getting fewer. There are no new drugs available at this point and many of those that could be effective are considered to be of critical importance to humans i.e. should not be used in companion animals. In some European countries, there is legislation restricting the use of some substances [9,10]. Antimicrobial resistance has a clear correlation with the use of antimicrobials. Almost as soon as antibiotic use became widespread in the 1940s, the first evidence of bacteria resistant to antimicrobial therapy emerged. And now less than a century after the discovery of penicillin, some authors state that we are beginning to lose the fight [11].

A survey performed by the Working Group on Hygiene and the Use of Antimicrobials in Veterinary Practice among FECAVA directors in 2008 showed that only three member countries had national guidelines on infection control and guidelines on the use of antimicrobials.

The initiative

There is a clear need for increased awareness, regarding antimicrobial resistance and the prevention of nosocomial infection, among small animal clinicians throughout Europe as well as globally. As we aim to reduce the use of antimicrobials it is valuable to work in a close relationship with pet owners. If we could increase their awareness of antimicrobial resistance to the point where they begin to question the need for antimicrobials, make them ask for alternatives and not to expect antimicrobials at all times, this would have a positive impact on the relationship between the clinician and pet owner.

FECAVA Posters

The FECAVA posters are designed to give the clinician easy access to current recommendations in hygiene and responsible use of antimicrobials.

The first poster (Figure 1) "FECAVA Key Recommendations for Hygiene and Infection Control in Veterinary Practice" was presented at the FECAVA/WSAVA congress in Geneva in 2010 during the FECAVA symposium. Since then the poster has been translated into 10 different languages, including Chinese. As FECAVA is a member-based organisation, the current issue is an updated version where the content

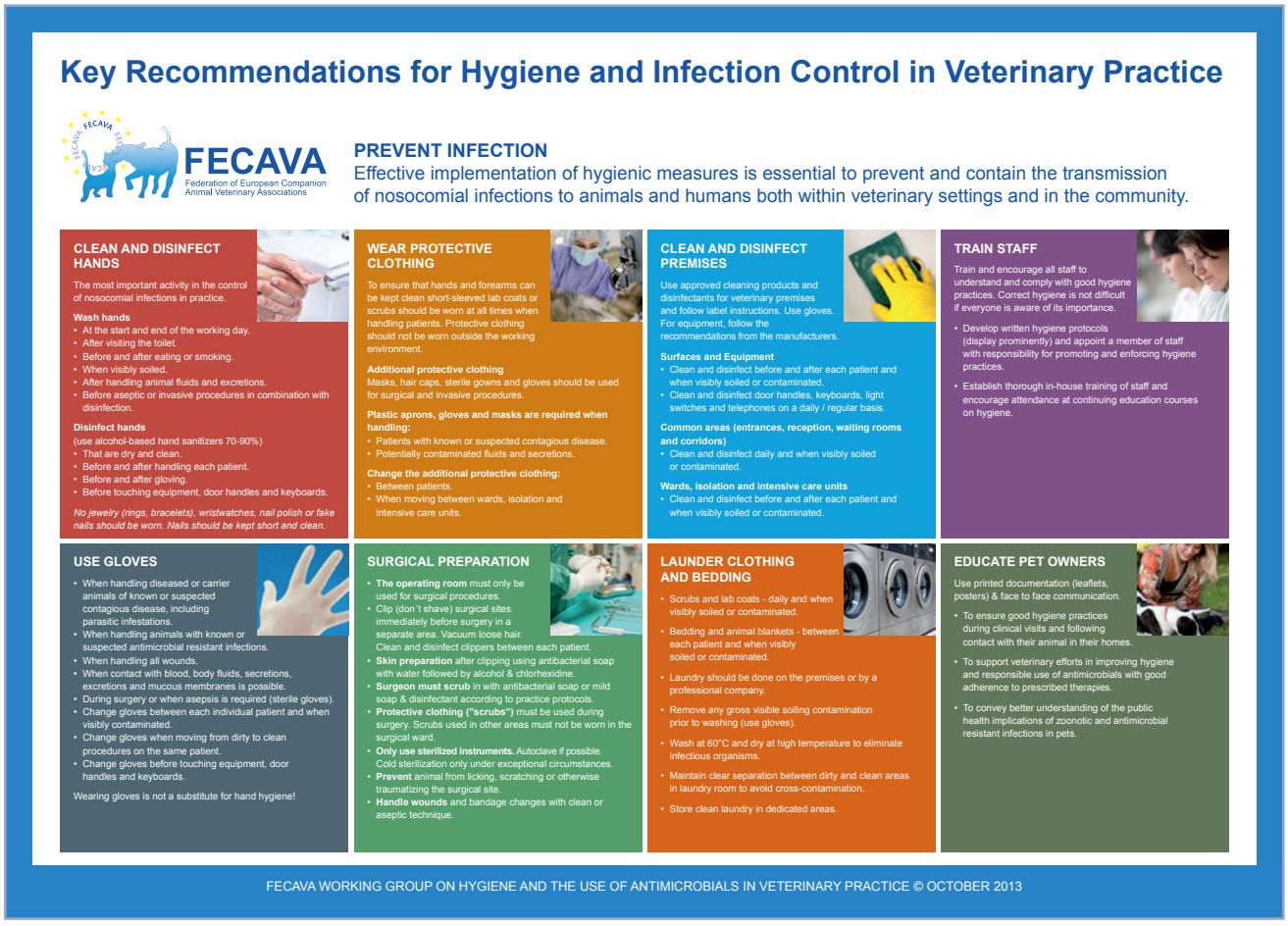


Figure 1) The revised version of the poster FECAVA Key Recommendations for Hygiene and Infection Control in Veterinary Practice designed to give the clinician easy access to current recommendations in hygiene.

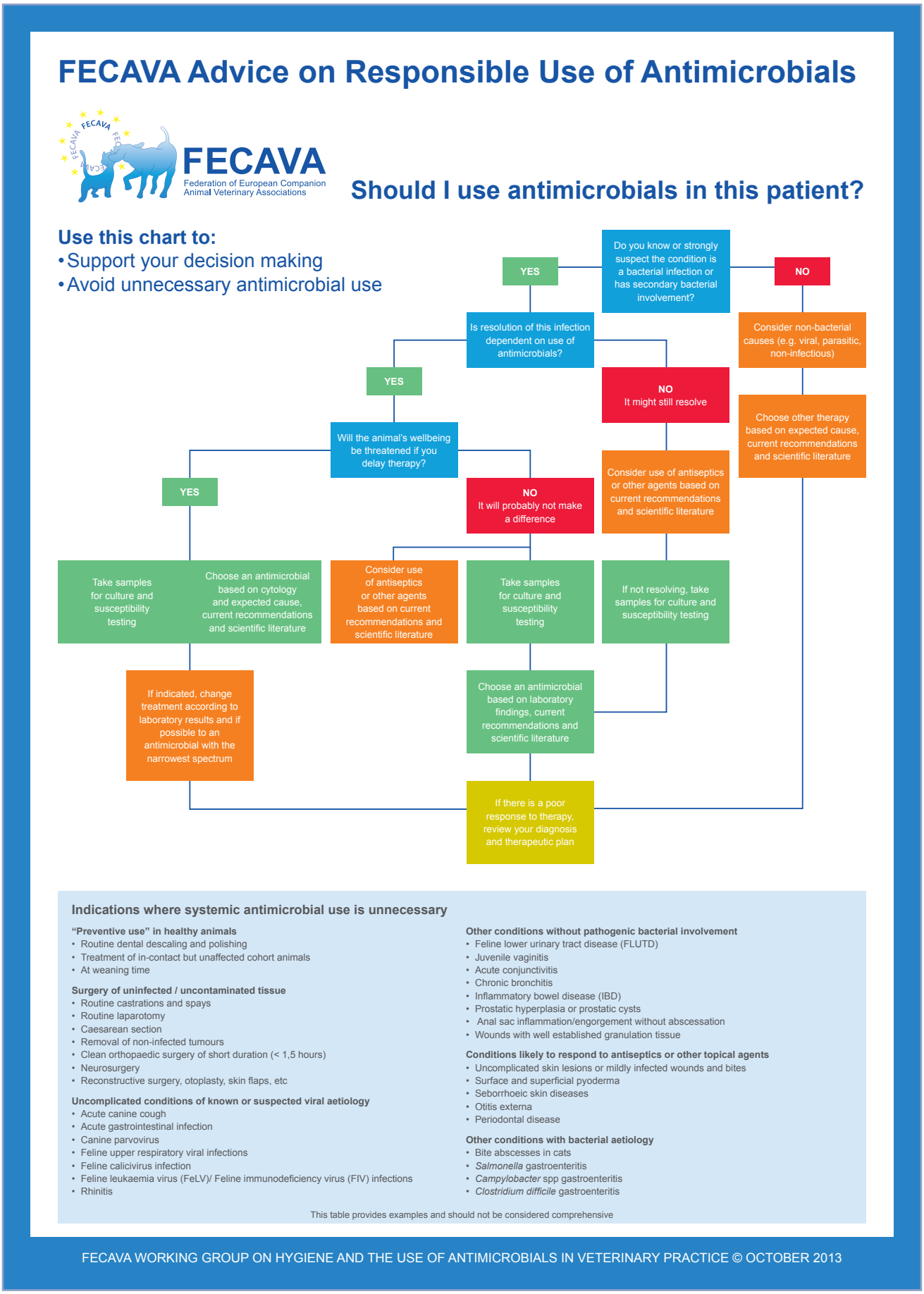


Figure 2) FECAVA Advice on Responsible Use of Antimicrobials in Companion Animals challenges the practitioner to ask the question "Should I use antimicrobials in this patient?", as not all bacterial infections require antimicrobial therapy

has been revised to better serve clinicians. The section on surgical preparation has replaced information on management of waste as this differs between countries. The second poster, (Figure 2) "FECAVA Advice on Responsible use of Antimicrobials in Companion Animals", might be considered the more important as it challenges the practitioner to ask the question "Should I use antimicrobials in this patient?" For many practitioners just the possibility that an animal may be suffering from a bacterial infection would persuade them to prescribe antimicrobials without delay. This poster gives advice to the practitioner on how to decide on the proper choice of treatment. It is a reminder that not all bacterial infections require antimicrobials and that, even if antimicrobials are required, there is often time to wait for the culture and susceptibility report and thus be more precise in the final choice of drug.

The third poster, (Figure 3) "FECAVA Recommendations for Appropriate Antimicrobial Therapy in Companion Animals" deals with the most appropriate empirical choice in different conditions. The poster also gives recommendations on the most suitable way to identify or diagnose bacterial infection and determine if there are any other specific aspects that should be addressed when initiating treatment.

The fourth and final poster, (Figure 4) "FECAVA Advice to Companion Animal Owners on Responsible Use of Antibiotics and Infection Control" is designed to be placed in the waiting room or other client area. It serves as information to pet owners to be more aware of the problem of antimicrobial resistance and not to always expect antimicrobials when visiting the veterinarian. It also aims to give an understanding why the veterinarian might not prescribe antimicrobials and to make owners aware of the importance of hygiene in practice. To have a clean practice and a proper infection control program should be as important as having well-qualified veterinarians and good equipment. Promoting the practice Infection Control Program could also be implemented as part of every clinic's marketing process. It will reassure pet owners to know that their veterinarian adheres to hygiene measures that are at least as good as those used by their physician.

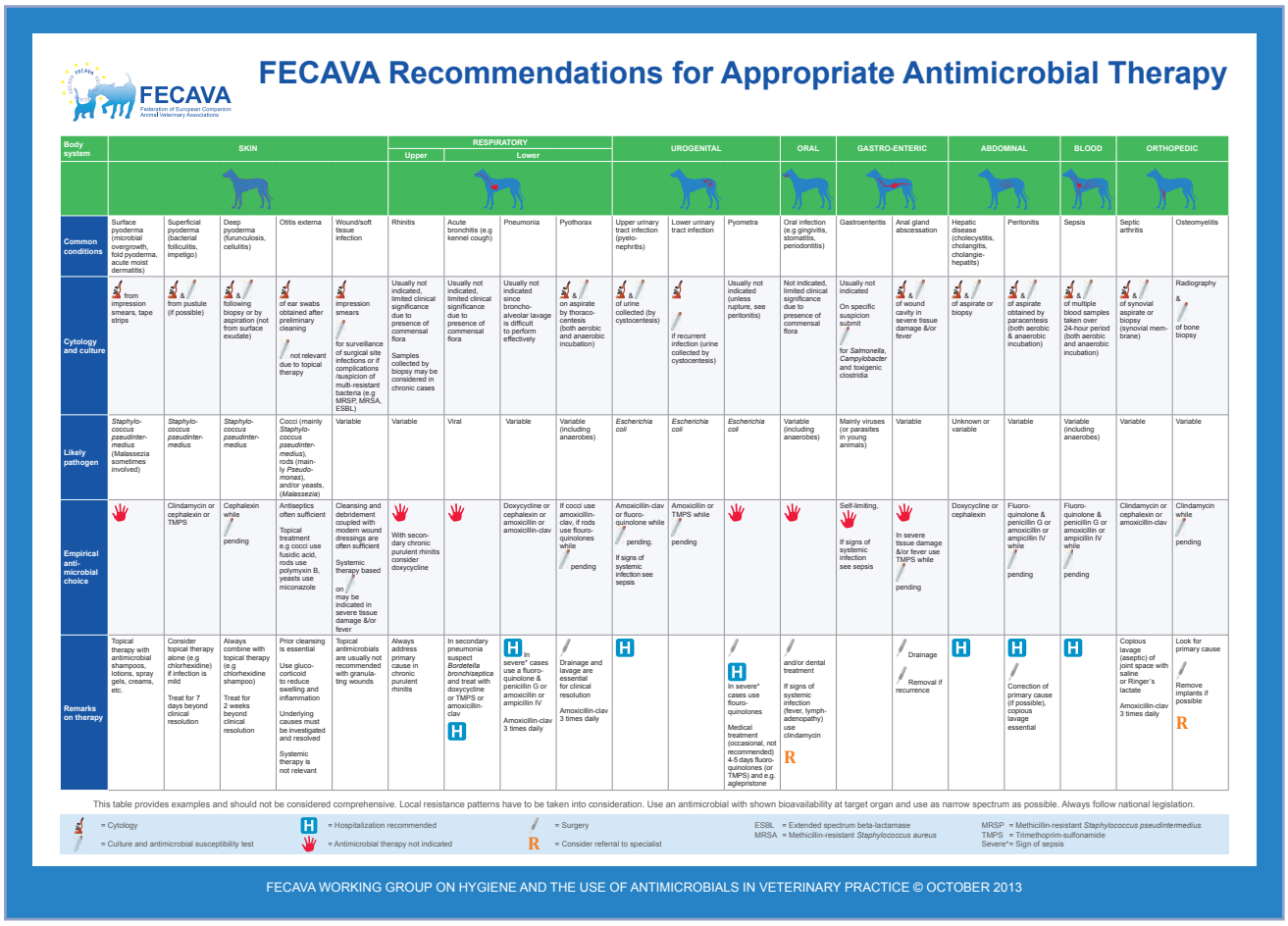


Figure 3) FECAVA Recommendations for Appropriate Antimicrobial Therapy in Companion Animals deals with the most appropriate empirical choice in different conditions.

FECAVA
Federation of European Companion Animal Veterinary Associations

FECAVA Advice to Companion Animal Owners on Responsible Use of Antibiotics and Infection Control

Inappropriate use of antibiotics (antimicrobials) could harm your pet, you and your family and is a threat to global health. Everyone needs to act responsibly including you as an animal owner.

ANTIBIOTICS ARE IMPORTANT

Many infections cannot be managed without antibiotics but resistance towards these is becoming an issue. Owners and veterinarians need to work together to solve this.

ARE ANTIBIOTICS REALLY NECESSARY?

- Not all infections are caused by bacteria, e.g. some are viral and do not respond to antibiotics. Also, not all bacterial infections require antibiotic therapy.
- Many wound and skin infections can be resolved by local wound care and antibacterial washes. Ask your veterinarian to show you how to do this.

DIAGNOSTICS ARE IMPORTANT

To investigate if a bacterial infection is the cause of your animal's illness, the veterinarian might need to collect samples to look for signs of infection or to identify the bacteria involved through bacterial culture. Supporting this will increase the chance of your animal's recovery without unnecessary risks (e.g. treatment failure).

DON'T EXPECT ANTIBIOTICS

Do not demand antibiotics if your veterinarian does not prescribe them; in most cases it is not appropriate to use antibiotics in a precautionary manner. Unless your animal is seriously ill and is admitted to an animal hospital for care, always ask your veterinarian if the prescribed antibiotics are really necessary, or if something else could be tried first.

ALWAYS FOLLOW YOUR VETERINARIAN'S ADVICE

- Give the antibiotics as instructed. Contact your veterinarian if the treatment is not effective within the recommended period.
- Do not change dosage or stop therapy in advance and keep your follow up appointments.
- Do not share antibiotics with other animals or animal owners.
- Never use left over medicines.

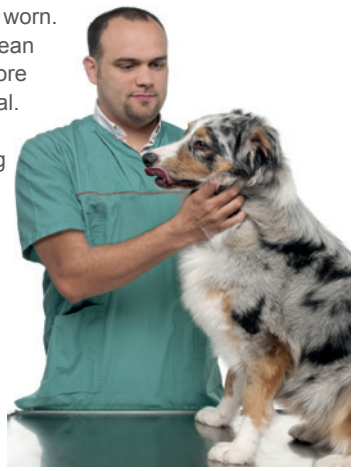
HANDLE YOUR ANIMAL IN A CLEAN WAY

Always use gloves and disinfect your hands before and after attending to wounds or cleaning ears.

KNOW WHAT TO EXPECT

If your veterinarian is aware of the correct protocols for hygiene and infection control, he/she will wear a short-sleeved shirt or coat to enable proper disinfection of hands between patients.

- No rings, wristwatches or jewellery should be worn.
- Hands should be clean and disinfected before handling your animal.
- Gloves should be worn when handling infected tissue or wounds.



This poster has been made by the Federation of European Companion Animal Veterinary Associations (FECAVA) in collaboration with the Bella Moss Foundation.

The Bella Moss Foundation

FECAVA WORKING GROUP ON HYGIENE AND THE USE OF ANTIMICROBIALS IN VETERINARY PRACTICE © OCTOBER 2013

Figure 4) FECAVA Advice to Companion Animal Owners on Responsible Use of Antibiotics and Infection Control. It is designed to be placed in the waiting room as information to the pet owners to be more aware of the problem of antimicrobial resistance.

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The Working Group on Hygiene and the Use of Antimicrobials in Veterinary Practice has during 2007-2013 consisted of FECAVA directors and external experts. This group would not have been successful without support from all contributors. The FECAVA directors that have been members of the group are Peter Murphy (Ireland), Katerina Loukaki (Greece), Alexandre Bongartz (Belgium), Jean Francois Rousselot (France), Didier Carlotti (France), Danny Holmes (Ireland) and the undersigned (Sweden). Our external experts are Professor David Lloyd (Royal Veterinary College, UK) Dr.Ana Mateus (Royal Veterinary College, UK), Dr.Ulrika Grönlund-Andersson (SVA-Swedish National Institute). The contributions of following have also been invaluable; Professor Luca Guardabassi (University of Copenhagen), Professor Scott Weese (University of Ontario, Canada), Professor Mark Papich (North Carolina State University USA), Dr.Barbro Nordquist (Dipl. ACVS, SE), Jill Moss (Bella Moss Foundation, UK), and Ashley Brooks, (Max4health, UK).

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THE FECAVA SYMPOSIUM 2013*
The proper use of antimicrobials in companion animal practice

Development of guidelines for antimicrobial use and their implementation

D. H. Lloyd[1]

SUMMARY

The FECAVA symposium at the Geneva WSAVA Congress in June 2010 presented evidence for the need for better stewardship of antimicrobials and called for guidelines suited to small animal practice. Since then the FECAVA Working Group on Hygiene and Use of Antimicrobials in Veterinary Practice has produced such recommendations as posters. However, there is a continuing need for development of detailed guidelines for small animal diseases. Development of effective guidelines requires a sophisticated and well supported approach which includes scrutiny of scientific evidence and independent evaluation, together with plans for dissemination and implementation. Even in human medicine it is clear that implementation is problematic and further research needs to be done to identify better ways of ensuring that veterinary guidelines for antimicrobial use are adopted and routinely used. There will be a continuing need for funding to support such research and to ensure that existing guidelines are maintained and improved.

Key words: Guidelines, implementation, antimicrobials, therapy, resistance.

Introduction

The symposium, of which this paper forms a part, follows up proposals for developing improved stewardship of veterinary antimicrobial use and more rigorous practice hygiene which were presented at the Federation of European Companion Animal Veterinary Associations (FECAVA) symposium on Hygiene and Antimicrobial Resistance during the 16th FECAVA Eurocongress at the World Small Animal Veterinary Association (WSAVA) Congress in Geneva in June 2010. At that meeting the FECAVA Working Group on Hygiene and Use of Antimicrobials in Veterinary Practice presented a poster on Key Recommendations for Hygiene and Infection Control in Veterinary Practice [Vilen 2011]. Dr. Ana Mateus spoke on "Stewardship of antimicrobials and hygiene protocols in practice. Are we there yet?" and quoted concerns from the UK medical profession about veterinary use of antimicrobial drugs and recommendations for banning the use of fluoroquinolones and cephalosporins in animals [Mateus 2011; Donaldson 2008]. She quoted a recent FECAVA online survey of British Small Animal Veterinary Association (BSAVA) members on knowledge and usefulness of guidelines for antimicrobial use by small animal veterinarians in the UK which showed that 40% of 295 respondents were unaware of such guidelines; amongst those who were aware (n= 173), only 38% considered guidelines to be useful or very useful whilst 16% considered them to be of little or no use. WSAVA Geneva was also marked by the establishment of the WSAVA

1 Department of Clinical Science and Services, Royal Veterinary College, Hawkshead Campus, North Mymms,Hertfordshire, GB- AL10 0EJ. Email: dlloyd@rvc.ac.uk.

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One Health Committee with a commitment amongst other things towards better veterinary stewardship of antimicrobials.

These events demonstrated international recognition of increasing antimicrobial resistance and the need to take urgent measures to reverse this trend [Lloyd et al 2009]. They also indicated the need for a better approach to the development and dissemination of effective guidelines to veterinary practitioners. The presentation at this symposium of an updated FECAVA hygiene poster and three further posters on prudent antimicrobial use is a demonstration of the effort which FECAVA has put into meeting this need.

Observance and Efficacy of Guidelines

It is commonly assumed that guidelines for antimicrobial use in both human and veterinary medicine are necessary and beneficial, and should be accepted and observed by practitioners except in extraordinary circumstances. Such assumptions are probably more widely held by those developing guidelines than by those who are expected to observe them. The problem of non-observance and its causes was reviewed by Brown in 2002 in a leading article prompted by a report on observance of national guidelines for empirical therapy of patients with bacterial meningitis in The Netherlands [van de Beek 2002]. The Dutch guidelines had been consensus-based and developed by a multidisciplinary expert group; they had been disseminated in booklet form a year before the study began. Analysis subsequently showed that only one third of patients had been treated in accordance with the guidelines. For the study, patients had been divided into four groups according to risk factor status. The largest group had been composed of patients with no risk factors and 39% of these had been treated with third-generation cephalosporin whilst the guidelines recommended penicillin as empirical therapy, reflecting the very low incidence of local resistance amongst likely pathogens.

Brown [2002] reviewed limitations and problems which can affect observance and efficacy of guidelines and these are summarised in table 1. An additional issue is the lack of recognition by clinicians that there is an antimicrobial resistance problem. In a Swedish study examining the awareness of antibiotic resistance amongst primary care clinicians and its relationship with prescribing in urinary tract infections, participants could be divided into three groups: members of group 1 said they had never seen resistance, group 2 said the problem was bigger somewhere else and group 3 recognised that resistance was serious. Only group 3 followed prescribing guidelines completely [Björkman et al 2013]. Acknowledgement of infection or resistance depends, in turn, on how this is observed and recorded, which can lead to complacency if recording is not effective. van Ramshorst et al [2013] compared independent recording of surgical site infections using a U.S. Centres for Disease Control and Prevention (CDC) definition with two systems routinely used by a surgery department in an academic teaching hospital. Compared with the CDC-based record, more than 60% of surgical site infections were unreported by either of the two regular departmental tracking systems.

Table 1. Examples of Reasons for Non-observance of Antimicrobial Use Guidelines.

Perceived problem	Possible reasons for non-compliance
Mistrust	Guidelines based on consensus. Lack of supporting scientific evidence or failure of guidelines to indicate that there is a reliable basis for the recommendations. Perceived by clinicians as a threat to clinical freedom
Too narrow	Failure to address concurrent disease and co-therapy. No consideration of patient preferences
International or regional guidelines	Preference for locally developed guidelines
Method of dissemination	Provision of documentation without ensuring delivery or incentives for study
Implementation	Lack of incentives promoting implementation. Cost of implementation. Failure to perceive likely benefit

Pressure of work and high activity levels may also be associated with failure to observe guidelines. This has been shown to be important in compliance with hygiene in hospital care. In a systematic review of 96 studies of hand hygiene guideline compliance, Erasmus et al [2010] found that there was an overall median compliance rate of only 40%. Compliance was lower in the busy intensive care units, amongst physicians compared with nurses, and lower before rather than after patient contact. Ignaz Semmelweis, the famous Austrian physician, who discovered in 1847 the value of washing and disinfection

in the control of puerperal fever and had to fight to persuade busy surgeons to observe hand hygiene, would have recognised this problem [Best and Neuhauser 2004]. It is clear that the concept that busyness is an excuse for cutting corners has a long history and that measures designed to deal with this issue need to be constantly reinforced.

It is well recognised in human medicine that pressure from patients can also promote inappropriate antimicrobial prescription [e.g. Kumar et al 2003]. In the veterinary field such pressure comes from clients rather than patients and recent data shows that this can be a problem in large animal practice. In a questionnaire study of veterinarians involved in bovine practice in Ireland, non-clinical issues including those related to professional stress, influenced the therapeutic decisions of the majority of respondents [Gibbons et al 2013]. These pressures included the farmer's desire or expectation of receiving antimicrobials, concern from the veterinarian that he/she might be blamed for not prescribing antimicrobials if they later proved necessary, and concern that if the animal did not improve the veterinarian would be called out again. Lack of confidence in diagnosis was also more likely to lead to antimicrobial prescription.

Development of Guidelines

It is clear that there are many issues affecting the effectiveness of antimicrobial use guidelines. However, when carefully designed and well implemented they can be effective. In a recent Spanish study at a human tertiary care centre, when local guidelines were supported by regular feedback together with annual objectives linked to economic incentives, inappropriate prescriptions declined from 53% to 26% over a period of a year. Antimicrobial consumption also decreased from 1150 to 852 defined daily doses per thousand bed days, an impressive change over a relatively short period of time [Cisneros et al 2013]. The earlier presentation in this symposium by Dr Greco on "Reduction of sales of antimicrobials for dogs – Swedish experiences" [Greco 2013] illustrates what can be achieved in a country where an intensive effort has been invested in promoting veterinary antimicrobial stewardship.

Thus, guidelines for antimicrobial use are needed and can have important effects in dealing with inappropriate prescription and excessive drug use. Benefits resulting from proper implementation of well-designed guidelines include direct reduced pressure on development of antimicrobial resistance and likely reduction in resistance, reduction in clinical costs, lower morbidity/mortality and improved patient well-being, and elevated levels of clinical confidence and professional satisfaction amongst clinicians. The key to success is the development of carefully designed guidelines and their dissemination and implementation in ways which will be accepted and appreciated by clinicians.

Initial development of guidelines should take advantage of established concepts and these have been developed over a number of years, particularly in the human field. Essential elements are listed in table 2; these are derived substantially from the recommendations of Brown [2002] and Kish [2001].

Table 2. Critical Elements in the Development of Antimicrobial Resistance Guidelines (after Brown 2002 and Miller and Petri 2000)

Element	Requirements
Development Group composition	Multidisciplinary, with expertise covering relevant topic areas, previous experience of guideline preparation and ability to conduct systematic literature reviews.
Existence of previous guidelines	If previous evidence-based guidelines exist they should be reviewed and, if appropriate, adapted to suit local circumstances.
Basis for guidelines	Guidelines should be based on systematic reviews of existing scientific evidence based on defined inclusion criteria. These criteria should be quoted.
Scientific evidence	Where robust evidence is not available, other supporting evidence should be validated by an objective assessment and grading system
Use of expert opinion	Expert opinion will normally be required to supplement absence of scientific evidence. This should be graded according to the strength of supporting evidence.
Readability	Guidelines should be designed to be readable by the target audience; they should not be too long e.g. not >25 pages (Kish 2001)
Validity	They should be reviewed by independent and respected experts in the field of knowledge.
Revision	The validity of the guidelines should be reviewed and updated at specified intervals, e.g. every two years. Changes should be assessed and validated with the same rigour as the original text.

It is important to ensure that those developing the guidelines have sufficiently broad and deep knowledge of the topic area. However, the development group should also include members with the ability to review the available evidence and grade it in a systematic way. Expert opinion, which will usually be necessary for some components of the guidelines, also needs to be assessed and graded against a background of scientific evidence. Finally, the text of the guidelines should be independently reviewed by respected authorities both for their validity in the context of clinical practice and also for readability by busy clinicians and relevance to clinical practice.

Implementation of Guidelines

Even the best developed guidelines will be ineffective unless they are appropriately implemented. This requires dissemination to the appropriate target group of clinicians and the adoption of measures designed to promote use of the guidelines with a high degree of compliance. Effective dissemination can be very difficult to achieve as demonstrated by the survey of BSAVA members by Mateus [2011] where 40% of respondents were unaware of the existence of guidelines despite the fact that they were available on the BSAVA website [BSAVA 2009] and had been promoted by documentation delivered to members in the post. Thus, availability cannot be equated with dissemination and incentives need to be provided to the target population to ensure that its members take advantage of their availability. Recognition that the guidelines are likely to be beneficial and can meet clinicians' requirements for particular types of disease manifestation is important [Yawn et al 2012]. Presentation of guidelines in a visually attractive educational format and delivery in concise and readily absorbed units can also promote uptake.

Persuading clinicians to observe guidelines, even if they have the appropriate documentation and are aware of the recommendations can still be a problem. In Denmark, Sørensen et al [2013] report on compliance with clinical guidelines in sampling for gonorrhoea by medical practitioners over the period 2000-2010 in the face of a fivefold increase in the incidence of the disease. Despite the clear importance of the disease threat only 13% of patients had swab sampling performed according to guidelines from the Danish National Board of Health. Much less information is available on the use of guidelines and on compliance in the veterinary field and there is a need to develop a wider range of guidelines based on more rigorous development methods and more sophisticated ways of disseminating and ensuring their implementation.

Veterinary Antimicrobial Guidelines

The scale of the need for better recognition and implementation of veterinary antimicrobial guidelines is illustrated by a cross-sectional study of antimicrobial prescribing patterns in UK small animal veterinary practice involving a total of 900 clinicians published by Hughes et al in 2012. Only 3.5% of clinicians reported that the practice had an antimicrobial use policy. When respondents were asked how they would prescribe antimicrobials in for clinical scenarios, 25% of prescriptions differed from the recommended dosages and 2.3% of prescriptions were for agents not licensed for use in dogs and cats in the UK. Teale and Moulin (2012) reviewed existing English language veterinary guidelines for prudent use of antimicrobials and showed that a variety of different codes and regulations developed by different organisations are aimed at achieving this. Thus, in Europe the European Platform for the Responsible Use of Medicines in Animals (EPRUMA) aims to promote responsible use of medicines in animals in the European Union and involves veterinarians, farmers, feed manufacturers, pharmaceutical companies and pharmacists; it has developed framework documents which are available on the EPRUMA website (http://www.epruma.eu/publications/all-publications.html). EPRUMA is working in collaboration with FECAVA and the Federation of Veterinarians of Europe (FVE) and also publishes documents from its collaborators. Such collaboration is valuable especially when it facilitates the production of specific guidelines e.g. aimed at small animal practice, which are useful at the individual practice level [Guardabassi and Kruse 2008].

At the level of individual species- or discipline-based organisations, valuable guidelines are also being produced. For example the International Society for Companion Animal Infectious Disease (ISCAID) has begun to publish guidelines for a range of diseases. The first of these, dealing with urinary tract infections, was published in 2011 [Weese et al 2011] and others are in the pipeline. Development and implementation of comprehensive and effective guidelines, as described above, is very time-consuming and labour-intensive, and involves considerable costs. Even when supported by large veterinary organisations success is not guaranteed. Indeed,

experience from the human field has shown that some of the best results have been obtained when guidelines are delivered to relatively small institutions within an educational context, and this is a further challenge. Whilst there is a clear need for more guidelines for small animal infections, there is also an urgent need for investment into the development of practical methods of ensuring that existing guidelines are properly implemented, improved and kept up-to-date.

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THE FECAVA SYMPOSIUM 2013*
The proper use of antimicrobials in companion animal practice

Antimicrobial choice: critical steps in decision-making

Luca Guardabassi[1]

SUMMARY

Veterinarians influence the microbiology diagnostic process by taking several critical decisions when visiting patients with suspected bacterial infection. In sequential order they i) decide whether bacterial culture is needed; ii) select the most appropriate clinical specimen for submission to the laboratory; iii) evaluate the need for empirical antimicrobial therapy; and iv) interpret the antimicrobial susceptibility report to initiate therapy or correct empirical therapy if necessary. The objective of this manuscript is to provide practical guidance for rational antimicrobial choice in small animal veterinary practice with focus on these critical decisions.

Keywords: antimicrobial resistance, rational antimicrobial use, clinical microbiology, antibiogram.

Introduction

In recent years, various types of multidrug-resistant bacteria have emerged in small animals worldwide. Methicillin-resistant staphylococci (MRS) and *Escherichia coli* producing extended-spectrum beta-lactamase (ESBL) are a major cause for concern because they are typically resistant to conventional antimicrobial agents licensed for veterinary use. Infections caused by these bacteria pose serious risks to animal welfare and greatly increase the complication of antimicrobial choice by veterinarians. In addition, the global spread of MRS and ESBL-producing *E. coli* in small animals raises important issues regarding nosocomial infections and zoonotic risks [1]. Thus, it is urgent to limit further spread of these multidrug-resistant bacteria through rational antimicrobial use.

The definition of rational antimicrobial use is somewhat arbitrary. Here it is defined as the use of antimicrobial agents aimed at maximizing therapeutic efficacy and minimizing risks associated with development of resistance in the strain causing infection as well as in the patient's commensal flora. Antimicrobial choice is an essential step in rational antimicrobial use as both therapeutic efficacy and risk of resistance development are strongly influenced by the type of antimicrobial prescribed. The objective of this manuscript is to provide practical guidance for rational antimicrobial choice in small animal veterinary practice with particular regard to critical decisions related to the microbiology diagnostic process (Fig. 1). In the first instance, veterinarians decide whether bacterial culture is indicated, select the most appropriate specimen for submission to the laboratory, and evaluate the need for empirical therapy. Subsequently, if samples have been submitted to the laboratory, they interpret antimicrobial susceptibility data to initiate therapy or correct empirical therapy if necessary.

1 Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, University of Copenhagen, Stigbøjlen 4, DK-1870 Frederiksberg
E-mail: lg@sund.ku.dk

* Held during the 19th FECAVA /VICAS/BSAVA Eurocongress, Dublin October 2013

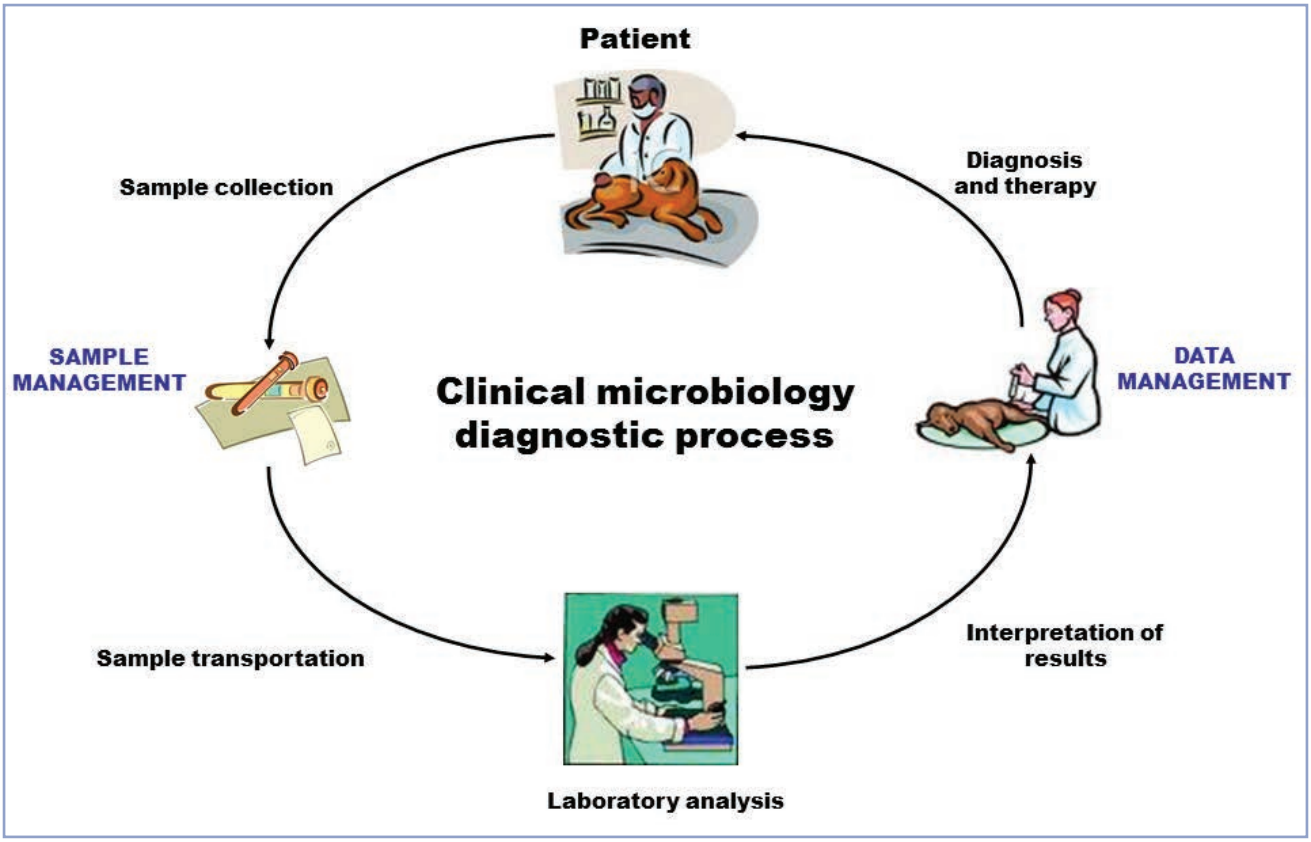

Figure 1. Schematic representation of the microbiology diagnostic process. Veterinarians influence the outcome of the process by management of samples and data.

When bacterial culture should be requested

Bacterial culture is never contraindicated. It provides definitive evidence of bacterial infection and useful information about the susceptibility profile of the strain involved. Beside its diagnostic value, bacterial culture allows collection of baseline data on antimicrobial susceptibility that can be analysed periodically together with data on therapeutic response as an aid to update local antimicrobial policies. For this purpose, bacterial culture should be performed routinely, including in uncomplicated cases, since collection of data originating from complicated cases only has the effect of overestimation of the prevalence of resistance. If it is not performed routinely, bacterial culture is strongly recommended in the following situations:
i) if there is suspicion of a complicated infection; ii) if the patient has not responded to therapy; iii) if the patient has a history of relapse or re-infection; iv) if the patient is immunocompromised; v) if the infection is life-threatening; and vi) if there is any reason to suspect infection with multidrug-resistant bacteria.

Aerobic culture alone is recommended in the vast majority of clinical cases. Anaerobic culture may be indicated in soft tissue infections where the presence of anaerobic bacteria is suspected on the basis of clinical observations (e.g. foul odour and presence of gas) or in suspected cases of abdominal sepsis. However, the clinical relevance of anaerobic culture is questionable since antimicrobial resistance is not a pronounced problem in anaerobic bacteria of veterinary interest, which are generally susceptible to anti-anaerobe drugs such as penicillins, and clindamycin. Furthermore, disk diffusion tests are not recommended for anaerobes [2] and veterinary diagnostic laboratories are often not adequately organized to perform antimicrobial susceptibility testing of anaerobic bacteria by dilution methods.

What type of sample should be submitted to the laboratory

It is important to select the most appropriate clinical specimen for each type of infection and collect it by a proper technique. Specimens should be collected from a location where the infection is active, avoiding

contamination with commensal bacteria. Particular precautions should be taken when collecting sterile body fluids (urine, blood, CSF, etc.). Culture of non-sterile biological samples such as faeces, vomitus and nasal, periodontal or perianal swabs is not recommended due to presence of commensal flora, unless these samples are submitted to detect specific pathogens that can be cultured by selective procedures. Infection-specific recommendations on how samples should be collected are provided elsewhere [3].

Common bacterial pathogens in small animals are non-fastidious organisms, generally not sensitive to the conditions of sample transport. The use of tubes containing transport medium is recommended for swabs sent via regular mail or otherwise not processed within 24 hours after collection. Transport of urine deserves a separate discussion since bacterial concentrations in urine are determined to diagnose urinary tract infections (UTIs). In general, it is recommended to refrigerate urine samples immediately after collection and submit them as quickly as possible to avoid potential changes in bacterial concentration. Recent international guidelines recommend caution in the interpretation of results and retesting if transportation of refrigerated urine samples exceeds 24 hours without urine preservatives [4]. However, this recommendation may limit the use of urine culture in clinical practice because transportation of refrigerated samples is expensive. The problem may be at least in part overcome if urine is collected by cystocentesis since specimens properly collected by this technique are normally either sterile or heavily contaminated with bacterial concentrations well above the cut off value for definition of infection (>103 CFU/ml). As an alternative to urine transportation, commercial "urinary paddles" or "dip slides" can be inoculated and submitted to the laboratory either before or after incubation. The latter approach can be particularly convenient as it saves the cost of laboratory analysis of sterile samples.

When therapy should be initiated empirically

In the clinic, antimicrobial choice is often empirical, i.e. the choice is not based on results of culture and susceptibility testing. Systemic antimicrobial therapy should only be initiated if bacterial infection is suspected on the basis of well-grounded clinical data and after excluding infections caused by pathogens other than bacteria. Empirical therapy is recommended for life-threatening infections, whereas in less severe clinical conditions it would be more appropriate to start systemic antimicrobial therapy only after bacterial infection has been confirmed by culture.

Empirical choice is determined by various factors including drug penetration and efficacy at the infection site, antimicrobial susceptibility of the suspected target pathogen, route and frequency of administration, toxicity and cost. As the last but not least important factor, the risk of increasing the likelihood of multidrug-resistant bacteria of clinical relevance should also be considered. Accordingly, if different antimicrobial agents are likely to be clinically effective, the choice should fall on the drug that has narrower spectrum, since broad spectrum antimicrobials, in particular fluoroquinolones and extended-spectrum β-lactams such as cephalosporins and amoxicillin clavulanate, have a considerable impact on the commensal flora and promote selection of multidrug-resistant bacteria. For certain types of infections (e.g. otitis and UTIs), cytology should be performed routinely to confirm bacterial involvement as well as to guide antimicrobial choice based on the bacterial cell morphology (i.e. Gram-positive cocci versus Gram-negative rods).

Acquaintance of the spectra of activity of the antimicrobial agents used in small animals and knowledge of the bacterial species associated with common clinical conditions and of their general patterns of susceptibility are essential requisites to enable rational antimicrobial choice. Some bacteria such as *Pseudomonas aeruginosa* and enterococci are intrinsically resistant to various antimicrobial classes, and can only be cured by specific drugs. Antimicrobial susceptibility is predictable in *Streptococcus canis* and other streptococci of veterinary interest, which are consistently susceptible to penicillins. Similarly, *Anaplasma phagocytophilum, Ehrlichia canis*, *Bartonella henselae*, and *Borrelia burgdorferi* are generally susceptible to doxycycline, which is the drug of choice for treatment of infections caused by obligate intracellular organisms. Resistance is less predictable in other bacterial pathogens such as staphylococci, *Escherichia coli* and other Enterobacteriaceae. When infection with these pathogens is suspected, empirical choice should be based on local patterns of antimicrobial resistance and the use of diagnostic microbiology is strongly recommended. Infection-specific recommendations on antimicrobial

choice for empirical therapy are provided by numerous national and international guidelines.

How susceptibility reports should be interpreted

Strains tested are classified as "Susceptible" (S), "Intermediate" (I) or "Resistant" (R) based on clinical breakpoints, which should be specific to each type of antimicrobial agent, bacterial species and host. "Susceptible" means that the strain is inhibited by drug concentrations achieved in plasma following administration at the standard dose. The "Intermediate" category includes strains that can be inhibited when the drug concentrates at the infection site (e.g. β-lactams, trimethoprim/sulphonamides and fluoroquinolones in urine) or can be administered at doses higher than standard. This category is also a buffer zone to minimize the risk of false positive and false negative results. Finally, the "Resistant" category indicates that the strain is not inhibited by drug concentrations achieved in plasma after standard dosage. Notably, the predictive value of antimicrobial susceptibility tests is extremely low for dermatological conditions that are treated topically (e.g. otitis externa or certain forms of localized superficial pyoderma). In fact, drug concentrations achieved locally by topical therapy largely exceed those obtained in plasma following systemic therapy, and in many instances infection can be cured even if the causative strain is reported as resistant.

Interpretation of susceptibility reports is not as simple as it may appear on the surface. One of the most common problems encountered in the interpretation of susceptibility reports is the presence of antimicrobial agents that are not used in clinical practice. Some agents are used as indicators for testing susceptibility to clinically-relevant drugs belonging to the same class or subclass. Others are used to detect specific resistance phenotypes of clinical relevance. For example, oxacillin and cefoxitin are used for detection of MRS. Table 1 provides relevant information concerning antimicrobial drugs commonly used for susceptibility testing of bacteria isolated from small animals.

As for the choice of the most appropriate drug a clear distinction should be made between empirical choice and choice based on susceptibility testing results. This important distinction is largely overlooked in most veterinary guidelines for antimicrobial use, which usually only provide recommendations on antimicrobial choice for empirical treatment. When choosing an antimicrobial based on susceptibility data, the choice should fall on the drug that has the least possible impact on selection of multidrug-resistant bacteria, provided that the drug is clinically effective and non-toxic. Off-label use of products registered for human use should only be considered if the test strain is resistant to all antimicrobial agents licensed for veterinary use.

Fig. 2 illustrates a priority system proposed in the Danish guidelines for antimicrobial use in small animals [3]. Antimicrobial classes are ranked into five categories. The lowest category includes drugs with narrow spectrum and limited risk for selection of multidrug-resistant bacteria found in small animals (e.g. penicillins, macrolides and streptomycin) or drugs that are not used for systemic therapy in human medicine (e.g. chloramphenicol). Drugs in the upper levels have an increasing importance in human medicine and higher potential for selection of clinically relevant resistance phenotypes. The fifth and upper category contains critically important antimicrobials (CIAs) in human medicine that are not licensed for veterinary use, namely carbapenems, vancomycin and linezolid. Use of CIAs in small animals is only justified in rare cases of life-threatening multi-drug resistant infections that cannot be managed otherwise. Specific requirements for the use of CIAs have been defined in the Danish guidelines [3].

Some infections often result in culture of multiple bacteria. This is often the case for wound infections, otitis externa and to a lesser extent UTIs. In these situations, the clinical relevance of each organism should be considered based on its pathogenicity. For example, *Corynebacterium auriscanis* is unlikely to be a primary pathogen as it is never isolated alone [5]. Anecdotal evidence suggests that otitis externa associated with this organism resolves if the primary pathogen is targeted by antimicrobial therapy. Targeting therapy towards the organism perceived as the primary pathogen is a reasonable approach since in some instances an antimicrobial effective against all bacterial species isolated may not be available. Furthermore, selection of drugs targeting all strains reported by the laboratory inevitably results in overuse of broad spectrum antimicrobials. Thus, a good diagnostic laboratory should not indiscriminately report everything that grows and

Table 1. Drug-specific indications for interpreting antimicrobial susceptibility reports. Modified from the Danish guidelines for antimicrobial use in small animals [3].

Antimicrobial drug	Indications
Ampicillin	It predicts susceptibility to amoxicillin and limited to Gram-positive cocci to penicillin
Amoxicillin clavulanate	It is used for detection of ESBLs, which are inhibited by clavulanic acid in the absence of other β-lactamases
Cefazolin	It predicts susceptibility to first generation cephalosporins used in clinical practice (e.g. cephalexin and cefadroxil)
Cephalotin	It predicts susceptibility to first generation cephalosporins used in clinical practice (e.g. cephalexin, cefadroxil and cefazolin)
Cefoxitin	It is used for phenotypic detection of MRSA/MRSP and ESBL. Staphylococcal strains that are resistant should be regarded as resistant to all β-lactams. ESBL-producing strains are susceptible unless they contain another β-lactamase
Cefotaxime	Resistance is indicative of ESBL production in Gram-negative bacteria. Not licensed for veterinary use
Cefovecin	No approved breakpoints are available for this veterinary cephalosporin (results of susceptibility tests are not reliable)
Cefpodoxime	Resistance is indicative of ESBL production in Gram-negative bacteria. Not licensed for veterinary use in Europe
Ceftazidime	Resistance is indicative of ESBL production in Gram-negative bacteria. Not licensed for veterinary use
Clindamycin	It predicts susceptibility to lincomycin in Gram-positive bacteria (generally not active against Gram-negative)
Chloramphenicol	Rarely used in small animals, it has been rediscovered for treatment of infections caused by multidrug-resistant strains
Difloxacin	It predicts to some extent susceptibility to other fluoroquinolones, although drug-specific breakpoints are available for enrofloxacin and marbofloxacin
Doxycycline	Results should be interpreted using doxycycline breakpoints (i.e. not tetracycline breakpoints)
Enrofloxacin	It predicts to some extent susceptibility to other fluoroquinolones, although drug-specific breakpoints are available for marbofloxacin and difloxacin
Erythromycin	It predicts inducible resistance to lincosamides (i.e. lincosamides should not be chosen if the strain is resistant)
Fusidic acid	The human breakpoint is based on systemic therapy. The clinical significance of this breakpoint is questionable in small animals where fusidic acid is used topically
Gentamicin	The human breakpoint is based on systemic therapy. The clinical significance of this breakpoint is questionable in small animals where gentamicin is mainly used topically
Lincomycin	It predicts susceptibility to clindamycin in Gram-positive bacteria (generally not active against Gram-negative)
Marbofloxacin	It predicts to some extent susceptibility to other fluoroquinolones, although drug-specific breakpoints are available for enrofloxacin and difloxacin
Nitrofurantoin	It can only be used for treatment of urinary tract infections. Not licensed for veterinary use
Oxacillin	It is used for phenotypic detection of MRSA/MRSP (only relevant for staphylococci). Resistant strains should be regarded as resistant to all β-lactams
Rifampicin	It should only be used in combination with another drug because resistance easily develops during therapy by mutations
Tetracycline	It does not predict susceptibility to doxycycline
Trimethoprim-sulfamethoxazole	It predicts susceptibility to all sulfonamides potentiated with trimethoprim

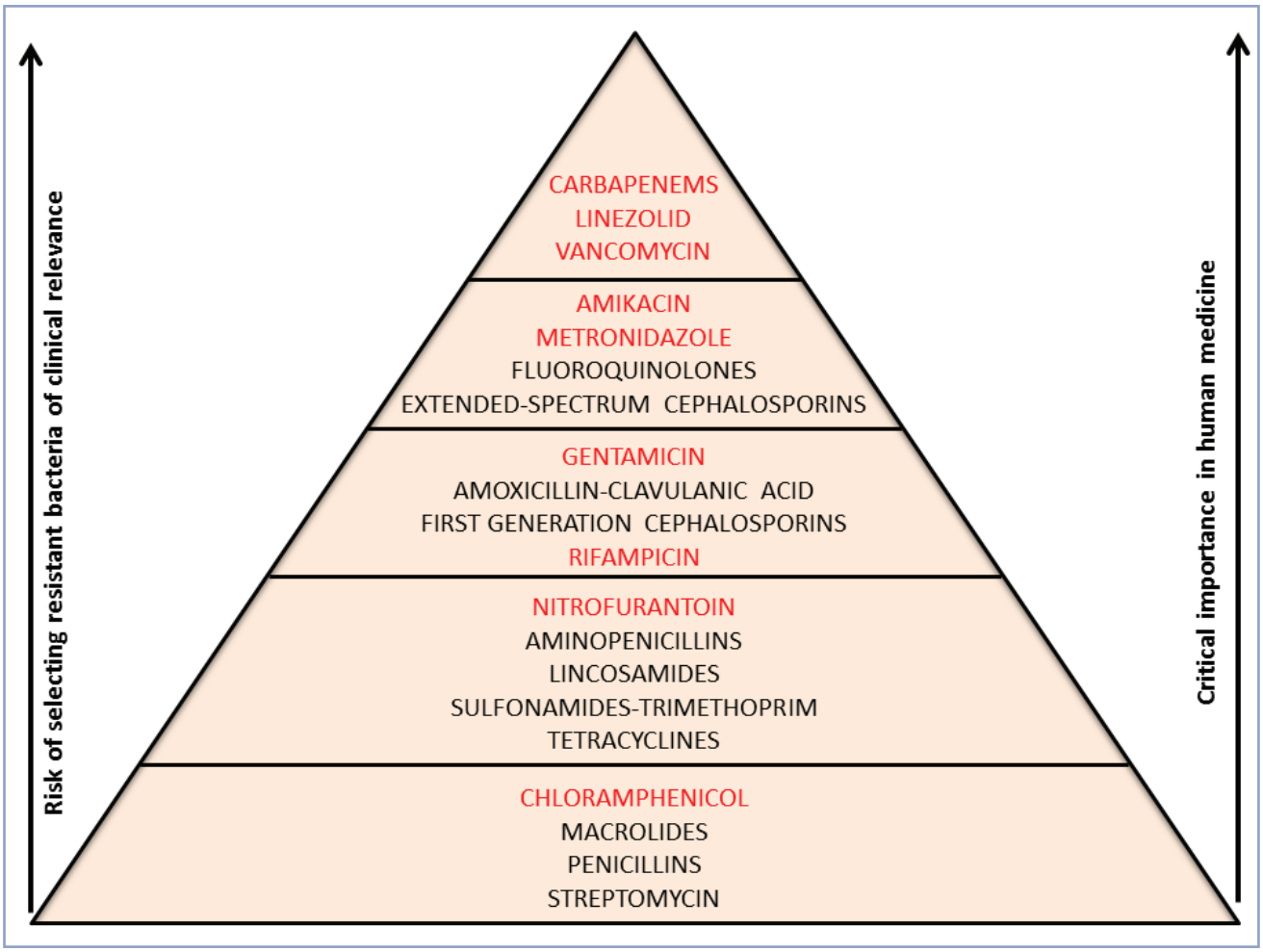

Figure 2. Classification of antimicrobial classes to facilitate antimicrobial choice based on susceptibility reports [3]. Antimicrobial drugs are classified into five groups. The risk of selecting resistant strains of clinical relevance and the drug's critical importance in human medicine increase from the lower to the upper levels. As such, drugs from lower layers should be preferred to drugs from upper layers, provided that a veterinary product is available and has been shown to be clinically effective for the relevant clinical condition. Antimicrobial agents that are not registered for veterinary use are highlighted in red.

must indicate results that may be clinically insignificant. Reporting accurate but insignificant results can be as counterproductive as reporting inaccurate results as it can result in serious consequences to patient care.

Another critical decision has to be taken when the susceptibility report indicates that the causative strain is resistant to the drug prescribed for empirical therapy. In theory, the initial therapy should be interrupted and a new drug should be chosen among those to which the strain is susceptible. However, this is not necessarily a wise decision. Various studies have shown that the therapeutic outcome is not always predicted by *in vitro* susceptibility testing and infection can be eradicated even if the causative agent is reported as resistant [6]. This apparently bizarre observation is mainly due to the fact that *in vitro* susceptibility testing does not take into consideration either the virulence of the strain causing infection or the host factors that mitigate for or against disease progression, regardless of antimicrobial effect. The predictive value of in vitro susceptibility tests is particularly low for UTIs, polymicrobial infections, outpatient infections treated with oral antimicrobials, or infections treated with multiple antimicrobial drugs [6]. It should be noted that the predictive value of veterinary breakpoints that are used to define test organisms as being resistant or susceptible is likely to be even lower compared to human breakpoints since they are often based on pharmacokinetic data originating from humans. Thus, as a general rule, patient's conditions and treatment outcome should always be checked before changing antimicrobial therapy.

Conclusions

Despite its limitations, antimicrobial susceptibility testing is a useful diagnostic tool to rationalize antimicrobial choice if performed and interpreted correctly. Rational antimicrobial choice is intrinsically tied to appropriate use of bacterial culture and correct interpretation of antimicrobial susceptibility testing. This chapter emphasizes the active role played by veterinarians in the microbiology diagnostic process, which should not be regarded as a practice of sole responsibility of the laboratory. Indeed, quality of the diagnostic process is influenced by several decisions taken by veterinarians. Awareness of this role is a first but important step to identify specific knowledge gaps and continuing education activities that can be used to fill such gaps. Moreover, interactive communication between the veterinarian and the diagnostic laboratory is an essential requirement to ensure rational antimicrobial choice.

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THE FECAVA SYMPOSIUM 2013*
The proper use of antimicrobials in companion animal practice

Antimicrobial resistance and the work of the Bella Moss foundation

Mark Dosher MSc[1], Jill Moss[1 #]

INTRODUCTION

The Bella Moss Foundation was established as a charity to inform and support owners of domestic pets that either developed, or were at risk of developing, antimicrobial-resistant infections. Key elements in achieving this have been the development of a close working relationship with the veterinary profession particularly with regard to creating accurate and verifiable information for pet owners, support for improvements in day-to-day veterinary practice, continuing professional development for vets, and the promotion of collaborative understanding between vets and pet owners.

Development

The Bella Moss Foundation (BMF) was initially conceived as a an information website for pet owners following the death in 2004, from the effects of MRSA and Pseudomonas contracted following cruciate ligament surgery , of a ten-year-old Samoyed, Bella. The goals of The Foundation have remained broadly unchanged since its inception in 2005 and fall into two areas; firstly, providing information and support to pet owners whose pets contract, or are at risk of contracting, resistant infections, and secondly, to provide information and access to professional support to the veterinary profession.

These aims were not adopted at the same time. Initially, The Bella Moss Foundation (BMF) was created only to provide the information to pet owners on resistant infections that, in 2005 at least, was virtually non-existent in the public domain. Additionally, even though centres such as The Royal Veterinary College had conducted research on resistant infections in dogs, there was little attention paid to this by a significant proportion of front-line vets. In seeking collaboration with leading researchers and academics to develop an accurate and accessible source of information for pet owners it was realised that raising the issue with vets through the same mechanism would have greater benefits than limiting the focus to pet owners alone, but this took time to develop; at the outset the main target audience was pet owners.

Jill with Bella

1 The Bella Moss Foundation (charity headquarters),135 Edgwareburry Lane Edgware,Middlesex, GB-HA8 8ND

Corresponding author, President Bella Moss Foundation. E-mail: jillmoss@btconnect.com

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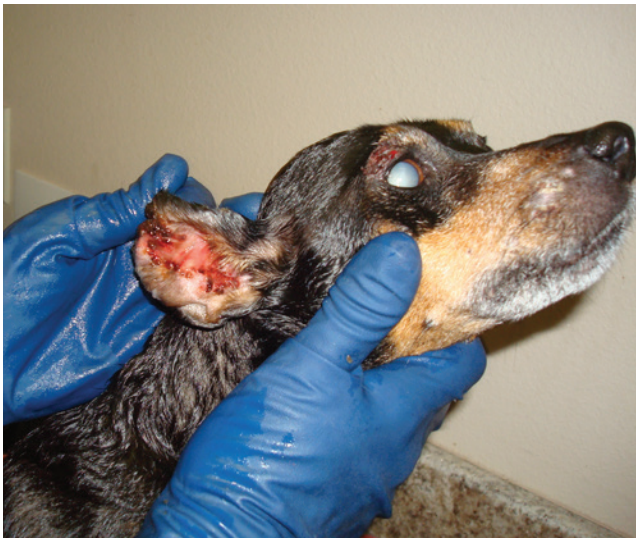
In developing the material for pet owners, which was The Foundation's first task, the priorities were to ensure that the information was presented in an understandable way with an emphasis on the need to comply with antimicrobial administration, understand potential risks of transmission of pathogens from pet to owner and vice versa and carriage of multi-resistant microorganisms without overstating the risks or consequences of resistant infection. In the general public, certainly in 2004/5 there was great fear and dread of contracting MRSA, although it is also fair to say that few lay people properly understood the important details relevant to the risks of such infections. Therefore The Foundation sought to emphasise proper caution without descending into irrational catastrophism.

Certainly at the beginning the focus of The Foundation was less on overcoming antimicrobial resistance and more on reducing exposure and minimising the consequences to pets. Owners were guided towards a more rigorous process in selecting their vet with particular emphasis on finding out if a practice had infection-control protocols in place and was using antimicrobials, particularly the broad-spectrum antibiotics, appropriately. Information also sought to put risks in their proper context with an emphasis on the resilience of healthy animals and the vulnerability of those not in good health, as well as the importance of moderating owners' expectations of having antibiotics routinely prescribed. The aim was, and remains, to develop a greater sense of awareness and responsibility among pet owners as a means of reducing the risks.

All of the health-related information published on The Foundation's first full website, including what to look for in a veterinary practice, issues of vulnerability and good health-awareness, was either written or approved by the veterinary professionals who had agreed to help, and this ensured that should vets or other health professional come across the website, they would find nothing objectionable in the clinical content.

Among the veterinary professionals assisting The Foundation at this time there was also an acknowledgement that vets and vet nurses needed the opportunity to discover where research into resistant pathogens in animals was going, and so in 2006 The Foundation, in association with the University of Liverpool, presented the 1st International Conference on MRSA in Animals. Supported by Defra and with significant sponsorship, the event attracted delegates from across Europe and the United States, and presented the most recent research and opinion on the issue.

Importantly for The Foundation, this event led to the establishment of an informal advisory group of expert clinicians. This had now become a pressing issue because, since its launch in 2005, The Foundation had received regular requests from pet owners for help in dealing with the practical, and sometimes veterinary, aspects of coping with a resistant infection in their pet. Frequently this



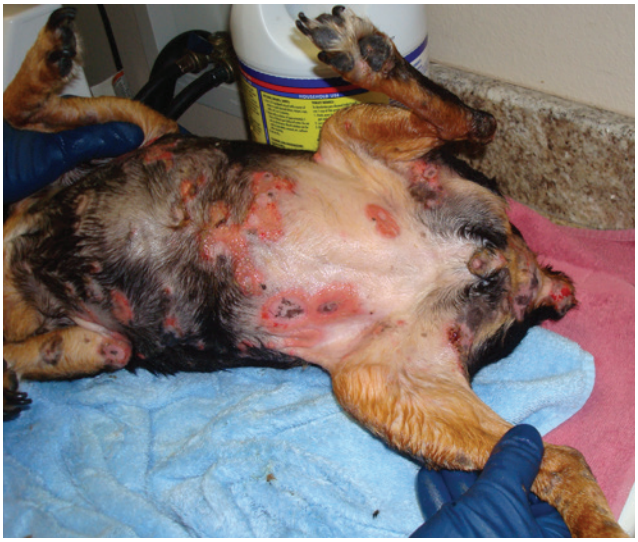
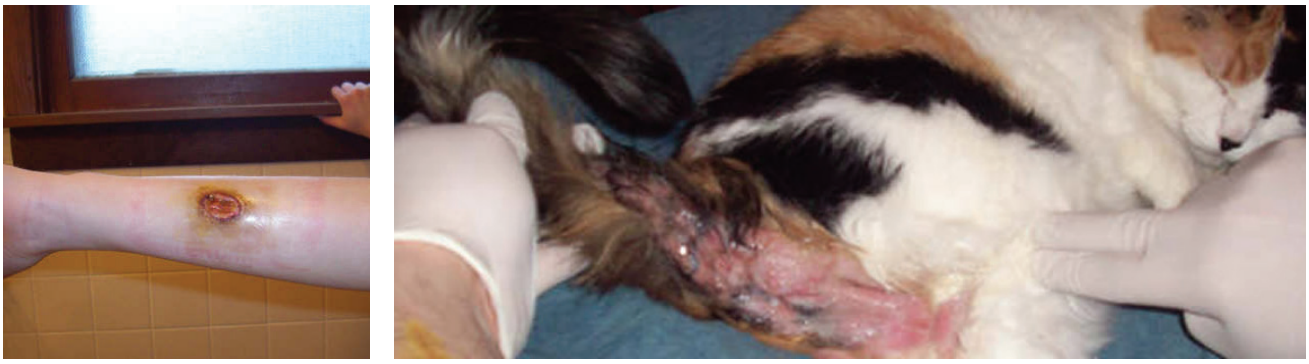


Photo 2a) and b)
Princess.
Princess had seen three different veterinary surgeons and each had failed to achieve any improvement with treatment and gradually Princess's condition worsened. After a gradual decline and only after several weeks of lack of response to treatment were samples sent for examination. MRSA was identified and a very poor prognosis was given. From a sense of desperation, her owner searched the internet and came across the BMF website.
Dr Scott Weese *(our Canadian clinical advisor) was asked to help and talked to the vet treating Princess. A new clinical regime was put into place which effectively saved her life.*



Photos 3a and b illustrate the case of Cassandra and her cat, Chloe. Cassandra had been diagnosed with MRSA infection of he arm and contacted BMF. She was advised her to take her cat to see her vet, who sent off a sample for bacterial culture. The results confirmed that the cat also had MRSA. How transmission occurred was never clear, but here is what Cassandra said in press statements:
"I was terrified and both my cat and I suffered for many months with a resistant infection. I am so grateful to the Bella Moss Foundation for support and information that we desperately needed."

amounted to concerns about the risk to the rest of the household, but often it related to questions of clinical judgement or outcomes of courses of treatment. With a group of veterinary experts The Foundation would be able to offer expert guidance to vets if they wanted it.
The key issue for The Foundation though, was that these contacts almost always occurred after a vet had come across MRSA. Typically, these concerned long-term or non-responding skin infections or infections following surgery or use of catheters. Consequently, input from The Foundation's advisors focussed on dealing with clinical problems rather than preventing their occurrence in the first place. This situation led to the decision to begin developing information specifically for practising vets and which would include recommendations for good practice that would reduce the potential for exposure to resistant organisms.

In discussions with the leading veterinary researchers and academics it was determined that front-line vets would best be helped by information that focussed on the need to ensure that animals were only treated with antimicrobials when appropriate, that when necessary the right antimicrobials were used, and to use isolate analysis where feasible to inform those two decisions. In addition it was felt important to emphasise the need for awareness of how proper hygiene protocols would contribute to the clinical outcomes within the practice.
The most significant step in achieving this at the time was the development of The Foundation's travelling Seminars. These day-long events were presented by leading researchers and academics and combined the facts about resistant bacteria with the appropriate clinical practices and approaches to treat and prevent them. They took place across the UK and Ireland in two series between 2007 and 2009, and represented the first proper attempt to take the facts on the issue out to the localities where vets practised.

Realising that veterinary nurses would also benefit from dedicated information, The Foundation collaborated with the College of Animal Welfare on a website, Veterinary Nurse Training Online (VNTO), to provide the sort of information that would emphasise good clinical practice and give nurses the opportunity to test their knowledge and obtain a Certificate of Achievement.

In parallel to these developments in UK-based events, The Foundation's website began to reflect a changing profile in visitors.

In the beginning, the aspiration of the founders had been to provide information for UK-based pet owners only, but without any promotion other than its presence on the Web, contact was being made by pet owners and some vets in the United States who were struggling with the same lack

'The Foundation's website began to reflect a changing profile in visitors.'

of information that The Foundation had been created to correct.

Fortunately, the contacts that The Foundation had made at its conference included experts based in North America more than willing to offer guidance and advice to vets working there, and now The Foundation's profile became international.

Just as the target audience was broadened, the initial limited focus on MRSA was also expanded over time to include details of *E. coli, Pseudomonas aeruginosa,* and *Enterococcus spp*. which are known to develop resistance to antimicrobials and also have the potential to pass elements of that resistance on to other pathogens.

These two strands of work - the development of information and support for veterinary professionals and pet owners and specifically dedicated to each with updates and refinements to reflect progress in the real world - would now become The Foundation's main activity.

Refining and improving this would be a constant process, and in 2012 the website underwent a complete redesign to include dedicated sections for pet owners and vets, and including newly developed video clips answering specific clinical and care issues. Again, collaboration was the key and contributions were made by many experienced clinicians and academics, and the content underwent an exhaustive review.

Structure of the Bella Moss Foundation

Like many small organisations that arise from the personal experience of an individual, The B M F started small with limited ambition and no clear idea of how to proceed. Formulated as a Charitable Company with two Directors, it achieved charitable status in 2007 managed by two Trustees. Although it was initially planned to fund activities through public donations, the bulk of The Foundation's income came from commercial sponsorship for specific projects such as conferences, the travelling seminars and VNTO.

With funding limited The Foundation relied on the generosity of supporters both within and without to provide the skills and abilities that the Trustees lacked.

Two important decisions were made at the outset; 1) to keep access to the website content free to all visitors and, 2) to decline requests from commercial companies to endorse particular products or sell such products in return for cash considerations and to apply the same prohibition to paid advertising.

For the first of these the main consideration was the predicted disincentive that would result in requiring visitors, pet owners particularly, to pay for access; but more than that, The Foundation held the view that the information of the website should be accessible to everyone regardless of their ability or willingness to pay.

For the second, it was felt that The Foundation needed to remain unaligned to everything except the need to improve the care and treatment of pets. Therefore, the only commercial presence on The Foundation's website remains the logos of companies that have sponsored projects or events and have expressed support for The Foundation's aims and objectives.

While this has severely limited the Foundation's income and freedom to spend, it has allowed it to remain truly independent of outside influence. This independence has, in part, been the reason why The Foundation has been able to engage with so many different professional and governmental organisations.

The issue of funding was also behind the decision not to attempt the move into clinical research either as a primary researcher or as funder of others' research projects. While the profile of the charity would doubtless have been enhanced, it was clear that The Foundation was completely unequipped to undertake such a role.

The Foundation had worked since 2005 with just two main activists. By 2013 the need to broaden the skill base had become acute and so three additional Trustees were appointed to bring specialised and general clinical expertise and business experience into the heart of the organisation. The new Board of Trustees began to operate in September 2013.

Future Developments

The Foundation constantly seeks to convey its message by promoting and producing events, leaflets and online resources. Three major initiatives are in development:

1) A conference to bring human and animal health professionals together in 2014 supported in the UK by the Department for Environment, Food and Rural Affairs (Defra), by Defra, the Department of Health and all of the major veterinary organisations of Europe under the banner of the One Health concept. Simply put, the approach sees human and animal health as inextricably linked, that each is affected by the other, and that approaches to issues in one can benefit from an understanding of the other. This conference has drawn widespread support from all

areas of health, both animal and human, and will aim to present work of value to both.

2) A video series under development with the Peoples Dispensary for Sick Animals (PDSA) aimed at improving the quality and scope of the information available to pet owners. This will offer accessible information on a range of topics of value to pet owners
3) Collaboration with the Royal College of Veterinary Surgeons on a series of clinical protocols to go in tandem with its own Practice Standards Scheme.

Refinement of the content of the website will continue in order to reflect developments in clinical knowledge and changes to the structure of The Foundation and its Governance will undoubtedly evolve.

What Has Been Achieved?

When The Foundation was created there was virtually no information available to the public on resistant infections in animals. After the website 'thebellamossfoundation.com' had been running for a year it was still the most common result from a web search. Now, however, a similar search will produce many pages of results from a wide range of source. This is, in part, due to the greater awareness among veterinary organisations and owners groups, particularly in the UK, that has come, in part, from the work of The Foundation.

In the UK, too, pet owners are better informed than they were a decade ago and demand more of their vets. Fortunately, this has been matched by a rapid improvement in both awareness and practice within the UK veterinary profession. The emphasis has changed in the profession towards preventing exposure to resistant microbials and The Bella Moss Foundation can take some of the credit for that.

The Foundation's most important achievement has been, as a small charity run by people outside of the veterinary profession, to raise the profile of antimicrobial resistance and provide a forum where accurate information can be freely accessed. The BMF is well recognised within the UK veterinary profession, and is seen as an ally of good veterinary practice. Achieving this would have been impossible if the urge to become a strident, campaigning voice intent only on confrontation with the veterinary profession had been followed. That it was resisted has reaped benefits for vets and pet owners alike.

Further relevant Information

BMF infection control website for vets and nurses
www.veterinarynursetrainingonline.org
One Health Conference www.onehealthbmf.com

THE FECAVA SYMPOSIUM 2013*
The proper use of antimicrobials in companion animal practice

Reduction of sales of antimicrobials for dogs – Swedish experiences

Christina Greko[1]

SUMMARY

Prudent use of antimicrobials is a cornerstone in any strategy against antimicrobial resistance. In Sweden, guidelines for the use of antimicrobials in companion animal medicine were published in 2002. The total number of prescriptions of antimicrobials for oral use in dogs increased by 36% from 1996 to 2005, indicating poor adherence but from 2006 to 2012, the total sales of antimicrobials decreased substantially. Among factors that probably triggered this change in prescribers' behaviour were the appearance of the first cases of methicillin resistant staphylococci in 2006 and the availability of statistics on antibiotic use. Both these areas received considerable attention; both amongst veterinarians and in the media. The intense debate increased prescribers' awareness of the problems with antimicrobial resistance. With the early involvement of respected peers who took action and shared their experiences, and with the data that was made available on antibiotic use, it was clear that there was room for improvement. This in turn generated a 'need to know more' and national experts were able to allocate resources to support the process. Finally, local discussions that often led to the production of local consensus guidelines was probably important. The challenge for the future is to keep this discussion going with the aim of further improving the quality of use of antimicrobials and reducing the risk of transfer of resistant bacteria between patients.

Key words: antimicrobial resistance, antimicrobial use, guidelines on antimicrobial use, dogs

Introduction

Antimicrobials are probably the most valuable addition to the therapeutic arsenal in human and veterinary medicine. But use of any antimicrobial exerts a selective pressure for the emergence and spread of bacteria resistant to these important medicines. With the escalating crisis of antimicrobial resistance among bacteria causing infections in humans, the use of antimicrobials for animals and its potential impact on public health is increasingly scrutinised. Resistance can spread between animals and people, as shown in numerous studies documenting the spread of, e.g. *Salmonella, Campylobacter*, or methicillin resistant *Staphylococcus aureus* (MRSA).

[1] Department of Animal Health and Antimicrobial Strategies, STRAMA National Veterinary Institute (SVA) SE-751 89 Uppsala, Sweden

E-mail: christina.greko@sva.se

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The discussions and controversies mainly relate to food producing animals, but dogs and cats share the environment of their owners and the opportunities of direct or indirect transfer of resistant bacteria or transferrable resistance genes between companion animals and people are numerous. This area has received little attention, but the spread of MRSA between dogs and people is well documented [1]. There are also indications of the spread of multi-resistant Gram-negative bacteria or resistance determinants such as extended sprectrum beta-lactamases[2].

The potential consequences of resistance to antimicrobials in bacteria causing disease in animals are less frequently discussed; with increasing prevalence of resistance, the number of potentially effective treatment alternatives decrease. Most programmes for monitoring antimicrobial resistance in veterinary medicine focus on bacteria from food producing animals, and mostly on potentially food borne bacteria. In companion animal medicine, there is a shortage of good quality data on the prevalence of resistance in major pathogens. This makes assessment of trends difficult, but judging by the increasing number of reports of multi-resistant infections in dogs the problem is increasing. The most salient example is the emergence and spread of multi-resistant methicillin resistant *Staphylococcus pseudintermedius* (MRSP)[3]. An apparent clonal spread of MRSP has been documented, and the dominant clones are resistant to all antimicrobials currently authorised for use in dogs in most European countries[4]. Enterobacteriaceae such as *Escherichia coli* or *Klebsiella* spp. resistant to higher generations of cephalosporins by production of extended spectrum betalactamases or plasmid mediated AmpC-enzymes are another cause for concern, as are multidrug resistant *Pseudomonas* spp. and *Acinetobacter* spp.[2,5-8]

This situation is a challenge to veterinary medicine, and also gives rise to ethical questions such as if and when drugs that are “last-resort” treatment in human medicine can be used for treatment of pets. Strategies to contain antimicrobial resistance in companion animal medicine are urgently needed. National and international organisations all agree that prudent use of antimicrobials is a cornerstone in any strategy against antimicrobial resistance[9-10]. Guidance on use of antimicrobials in veterinary medicine have been published in many countries, but adequate systems for follow up of adherence are mostly lacking.

In Sweden, antimicrobials are only dispensed by pharmacies and it is possible to extract data on sales of prescriptions for dogs. The total number of prescriptions of antimicrobials for oral use in dogs increased by 36% from 1996 to 2005[11-12]. Guidelines for use of antimicrobials in companion animal medicine were first published in 2002 and the prescription data indicate poor adherence to this guidance. However, from 2006 to 2012, the total sales of antimicrobials decreased substantially while the number of dogs increased, indicating a true change. Below, the statistics on sales will be examined more closely and possible reasons for the observed changes discussed.

The context

Sweden has a population of about 9.5 million people and the number of dogs was estimated to 784 thousand in 2012. More than 75% of the dogs are insured which is comparatively high.

In both human and veterinary medicine, there is a long tradition of working to contain antimicrobial resistance. The overall use of antimicrobials for animals has decreased substantially since the mid 80ies and is today among the lowest in the EU[13-14]. General guidance on prudent use of antimicrobials was adopted by the Swedish Veterinary Association in 1998[15]. In 2002, guidelines specific for companion animals were published followed by a revised version in 2009[16]. Guidance for the use of antimicrobials in cattle and pigs were adopted in 2011 and for horses in 2013.

All antimicrobials for animals are used on prescription only basis and as noted above, only pharmacies may dispense antimicrobials. All pharmacies are obliged to submit sales data to an infrastructure company, Apotekens Service. The animal species must be noted on the prescription. Data on sales of antimicrobials for oral use where “dog” was noted on the prescription (both veterinary medicines and products authorised for human use) was extracted from the database for years 2006 and 2012. This corresponds to what is called ‘out-patient use’ in human medicine. Results will be presented as the number of prescriptions or number of packages per 1000 dogs. It has previously been shown that the number of packages has a good correlation with the number of prescriptions[11].

Sales of antimicrobials for dogs

In 2006 the sales of antimicrobials for systemic use in dogs from Swedish pharmacies was 563 packages per 1000 dogs, or measured as number of prescriptions for dogs was 402 prescriptions per 1000 dogs. In the same year, the out-patient sales of antimicrobials for people was of the same magnitude; 436 prescriptions per 1000 individuals. It has recently been estimated that if guidelines were fully adhered to, the use of antimicrobials in human medicine in Swedish out-patients could be reduced by at least 40% without negative consequences for public health. It is therefore probable that in Swedish companion animal medicine, the use of antimicrobials could also be reduced substantially.

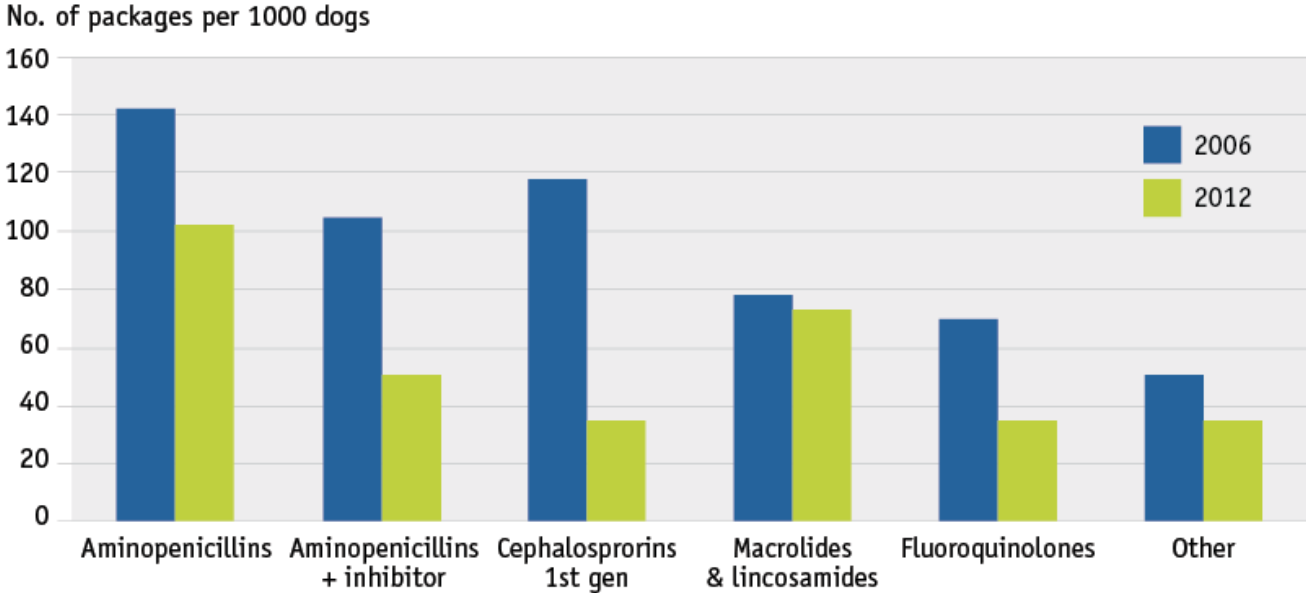
In 2012, the sales of antimicrobials for dogs were 330 packages per 1000 dogs, a decrease by 42% compared to 2006. The proportion of the total sales that were drugs authorised for use in human medicine was around 6%. The most prominent decrease was noted for the cephalosporins (-70%), but reductions were also recorded for the fluoroquinolones (-51%) and clavulanic acid potentiated aminopenicillins (-52%) (Fig.1). A drop in sales of aminopenicillins was also noted. The only class for which the observed decrease was minimal were the 'macrolides and lincosamides'.

From paper to practice – triggers for change

As noted above, guidance on sales of antimicrobials for dogs was published in 2002, and yet sales apparently continued to increase. Also, the proportion of the total use that was broad spectrum antimicrobials, including fluoroquinolones, was high. Thus, the mere publication of guidelines is not likely to be connected to the subsequently observed decrease. Instead, a sequence of events has probably triggered a change in prescribers' behaviour, leading to increased adherence to the guidelines.

In the autumn of 2006, the first clinical cases of methicillin resistant MRSA and of MRSP were confirmed by the National Veterinary Institute, SVA[13]. In human medicine in Sweden, MRSA is notifiable and source tracing compulsory. The findings of MRSA in dogs therefore led to a significant interaction with the County medical officers in the animal hospitals where the cases were found. Regarding MRSP, it soon became evident that one multi-resistant clone was spreading within and between animal clinics and hospitals[17]. During 2007, statistics on the use of antimicrobials for dogs were also published[18]. These findings were communicated to Swedish veterinarians in various ways, and were also given considerable attention in the media, including the radio, TV and as front page news in major daily newspapers. The increased attention triggered a number of activities.

Figure 1. Sales of antimicrobials for oral use in dogs in Sweden in 2006 and 2012.



The first cases of MRSP were mainly from larger referral hospitals. Thereby, opinion leaders and respected peers became aware of the need to take action to curb a further development at an early stage. They called for expert assistance and arranged local seminars on use of antimicrobials and on infection control. Work on local policies for infection control and prescription of antimicrobials was initiated. They also raised the alarm and shared their experiences by communicating with others. This led to a generally increased demand for training and communication on issues relating to antimicrobial resistance. During 2007, experts from SVA gave speeches on more than 50 occasions at seminars and workshops on antimicrobial resistance, the prudent use of antimicrobials, and on infection control. The venues spanned from the Swedish Veterinary Congress to local workshops at animal hospitals and veterinary clinics around the country. Many hospitals and clinics other than those first affected by MRSP and MRSA initiated work on local guidelines on the use of antimicrobials and correct hygiene.

Independently to the revision of the overall guidance, the Swedish Veterinary Dermatology Study Group issued new guidelines on use of antimicrobials for skin conditions in 2007. The importance of a good diagnostic workup was reiterated, and for some conditions, non-use of systemic antimicrobials was advised. Lincosamides were recommended as the drug of choice for first-time pyoderma, and cephalosporins for recurrent pyoderma only after bacteriological sampling. The sharp decrease in use of cephalosporins and the modest change in use of macrolides and lincosamides shown in Fig. 1 are in line with these recommendations.

From 2008 and onwards, the issue of antimicrobial resistance in companion animal medicine has continued to be assessed. In 2008, confirmed cases of MRSA and MRSP in animals were made notifiable as is the case in human medicine. Antimicrobial resistance and prudent antibiotic use was on the agenda of the Swedish veterinary congress each year between 2008 and 2011. The guidelines for use of antimicrobials in dogs and cats were revised, printed and sent out to all veterinarians subscribing to the Swedish veterinary journal in 2009. Further guidance on the management of MRSA in dogs, cats and horses was developed by a multidisciplinary group hosted by the Board of health and welfare in 2011. Guidance on infection control in companion animal practice was adopted by the Swedish veterinary association in 2012. The demand for training and discussions supported by experts continued, and between 2008 and 2012 experts from SVA annually participated in more than 60 lectures, seminars or workshops (to include all animal species).

Taken together, the factors discussed above interacted and led to a generally increased awareness of the problem of antimicrobial resistance. Matters relating to antimicrobial policy and hospital hygiene in small animal medicine were intensively discussed both locally and nationally. National and local initiatives, supported by data from monitoring of antimicrobial use and resistance, by education, and by expert advice, probably led to changes in prescribers' behaviour which in turn explains the downward trends recorded for sales of antimicrobials for dogs.

Occurrence of MRSA and MRSP

Occurrence of resistance in animal pathogens in Sweden is monitored by the Swedish veterinary antimicrobial resistance monitoring programme (SVARM) and the results are published annually jointly with results from human medicine. Including the fist cases in 2006, only 18 cases of MRSA in dogs have been reported. The types of MRSA found are those that are the most prevalent in humans, and the low figure is probably a reflection of a comparatively low prevalence of MRSA in humans in Sweden[13]. Regarding MRSP, a total of 122 cases, mostly in dogs, were notified in 2009 to the Swedish Board of Agriculture. Thereafter, the number of cases has decreased to 54 in 2012[13]. Whether this reflects a true reduction in the number of cases or a gradual increase in under-reporting is uncertain. Nevertheless, it is possible that the intensive activities relating to the prudent use of antimicrobials and better infection control has curbed a further increase in prevalence.

Conclusions and perspectives

The Swedish experience in this area may to some extent be context specific, but some aspects are likely to be of a more general nature. Some of these factors have been reported as important in the improvement of the quality of antimicrobial prescribing in human medicine: awareness of the problem, educational strategies, feed-

back of prescribing habits, locally developed guidelines and local champions[19-20]. In the case of companion animal medicine in Sweden, the intense communication increased prescribers' awareness of the problems with antimicrobial resistance with regard to their own practice and more generally. The early involvement of respected peers who took action and shared their experiences was probably also of importance. It was clear from the data on use of antimicrobials in dogs that there was room for improvement, and this in turn generated a 'need to know more'. At that time, it was possible for national experts to allocate resources to support the process. Finally, local discussions that often led to local consensus guidelines were probably important. Interestingly, in a recent survey of factors influencing the veterinarian's prescribing of antimicrobials, Swedish veterinarians ranked guidelines highest among sources of information in contrast to the answers aggregated for all respondents which only ranked this source in the eighth place[21]

Multiresistant MRSP, multiresistant Gram-negative bacteria and zoonotic infections such as MRSA have emerged among dogs and cats in Europe. Nosocomial spread has been documented, and is probably under-reported. In some cases, the options for treatment are few. The situation is a challenge to all veterinarians involved in companion animal medicine. There are many gaps in knowledge and further research is needed, but meanwhile action must also be taken. Stringent implementation of the principles of the prudent use of antimicrobials and of the protocols for infection control are key elements for an effective strategy to contain antimicrobial resistance. The Swedish experience illustrates that it is possible to improve prescribing habits rapidly. The challenge for the future is to keep this discussion going with the aim of further improving the quality of use of antimicrobials and reducing the risk of transfer of resistant bacteria between patients.

Conflicts of interest

None to declare

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