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Vol 06 | Issue 01 | March 2019

Get Your Fix on Fracture Repair

Diagnosis and Management: Cutaneous Drug Reactions in Dogs and Cats

CPD Accredited Article
Histology and Immunophenotyping

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Editor's Note

Hello to all for 2019, and I hope the year treats us all well.

Thanks to Prof Andrew Leisewitz for agreeing to assist me this year with writing, curating and editing articles for a dermatology section in the next 5 editions. Lets face it - dermatology makes up a big proportion of our practices and these cases are really frustrating for the patients, owners and vets, so I am excited that we will get some good quality practical advice from him in these next 5 editions.

Sarah Clift has also written a nice summary of what is new in the world of lymphoma diagnosis. Basically it's more than just B or T cell - and all this sub-classification provides much better patient specific information regarding prognosis and treatment. Naturally we are just getting acquainted with all the new tests and many are not yet available in SA, but there are laboratories overseas which can do these tests if you so wish.

Our surgical article expands upon the new philosophy in bone fracture repair of leaving as much of the supportive structure intact. From exact carpentry to organic gardening – where you allow the body maximum chance to heal itself without disrupting the tissue . Having said that - as a gardener - I would still not even think of trying any orthopaedic surgery - carpentry is still the basic skill I think - just less rigid and more holistic.
I hope you enjoy this edition

Regards

Liesel

Index:

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SAVA South African Veterinary Association Suid-Afrikaanse Veterinêre Vereniging

PREVIOUS EDITION: November 2018

- Aspiration Pneumonia
- [CPD] Feline CKD and Proteinuria
- The ABCs of Veterinary Dentistry: 'P' is for Periodontal Pockets

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We welcome any comments, contributions, topic suggestions and letters for publication. Send them to:
The Editor, PO Box 232, GROENKLOOF, 0027
Tel: (012) 346 1590, 082 575 6479. Fax: 086 671 9907
Email: lieselvdmvet@gmail.com
(Dr Liesel van der Merwe)

Madaleen Schultheiss

Get Your Fix on Fracture Repair

We all know orthopedic surgery and fracture repair is sexy, but does that mean you should be performing it?

Sarah J. Wooten, DVM

For the average general practitioner, performing complex fracture repairs lives in the realm of referrals. Whether you repair or refer, there are important rules and new techniques that David Dycus, DVM, MS, CCRP, DACVS (small animal), wants you to know.

Fracture repair is NOT typically an emergency surgery

Many patients that present for fracture repair are victims of vehicular trauma. It's imperative to check and stabilise vitals on these patients before working up any lameness, Dr. Dycus says. HBC patients can suffer from pulmonary contusions and arrhythmias secondary to traumatic myocarditis. Letting them recover for a couple of days before attempting surgery usually resolves these life-threatening issues.

Dr. Dycus recommends thoracic and abdominal radiographs, with or without AFAST, and bloodwork. And don't forget proper analgesia as soon as possible with a pure mu agonist, such as morphine, hydromorphone, oxymorphone, methadone or fentanyl. Butorphanol is not adequate, Dr. Dycus says.

Why exactly is that patient not walking?

While a fracture may be evident on radiographs, it may not be the only reason your patient isn't walking. Perform thorough orthopaedic and neurological examinations, and advise your client about the risk of temporary or permanent nerve damage. Dr. Dycus says neuropraxia can cause temporary deficits, distal humeral fractures can cause radial nerve damage, and ilial fractures can damage the sciatic nerve, even to the point of shearing right through the nerve.

Open fracture? Cover that up ASAP!

No matter how dirty, infected or nasty that open fracture is or how clean you think your hospital is, the bacteria that rode in on that wound will be no match for the super bugs that are lurking in your clinic. Dr. Dycus advises covering open fracture wounds with a sterile dressing as soon as possible to prevent implant infection, osteomyelitis and potential sequestrum formation.

Dr. Dycus recommends flushing open fracture wounds with copious amounts of sterile saline solution, to the tune of 2 to 4 liters. He advises against using dilute povidone-iodine or chlorhexidine to avoid potential cytotoxicity—the success of your fracture repair will depend on healthy tissue. He also recommends the use of external skeletal fixators for open fractures in order to access the wounds daily for cleaning and inspection.

See both sides of the issue

If there is one thing you need to remember, it is to take orthogonal radiographs. This includes at least two views—a lateral and a craniocaudal—of any fracture. Fracture classification depends on six factors:

anatomic location, severity, configuration, whether or not a growth plate is involved, contamination and displacement. You can NOT determine displacement without orthogonal views. For example, in Figure 1 and Figure 2, if you took just a lateral radiograph, the fracture may be missed. By taking orthogonal views, you can see there is a right Salter-Harris IV distal lateral humeral condylar fracture.

External coaptation or internal fixation? Now THAT is the question.

Now that you know you have a fracture, the question is how do you fix it? Surgical repair will lead to earlier return to function and may be better to maintain joint motion, but when is it clearly indicated?

Correct application of external coaptation requires immobilization of the joint proximal and distal to the fracture, and it should only be used in fractures distal to the elbow and stifle. Internal fixation is indicated for fractures that are subjected to compression, shearing, or tensile forces, that are comminuted or long oblique, or that cannot be reduced appropriately.

Use the 50/50 rule to determine whether or not reduction is appropriate. The 50/50 rule states that fracture ends should have at least 50% contact to expect fracture healing, and 50% reduction (contact) is the absolute minimum for bone healing to be possible, not probable. If the fracture cannot be reduced at least 50%, then internal fixation is indicated.

Ethical questions

Even if you know you can repair a fracture, Dr. Dycus advises to ask yourself if you really should.

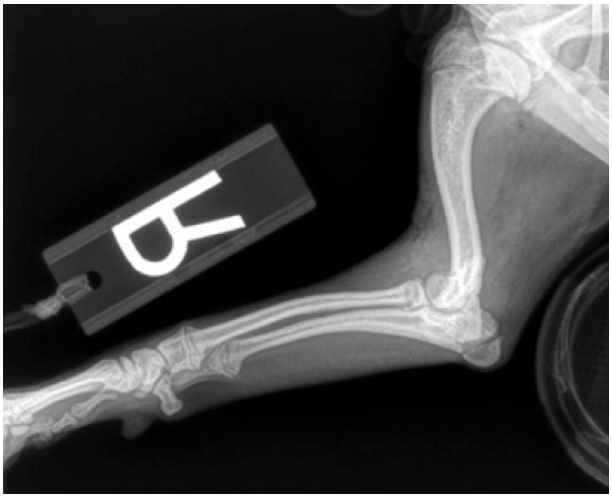


Figure 1. A lateral radiograph. All looks good! (Photos courtesy of Dr. David Dycus)

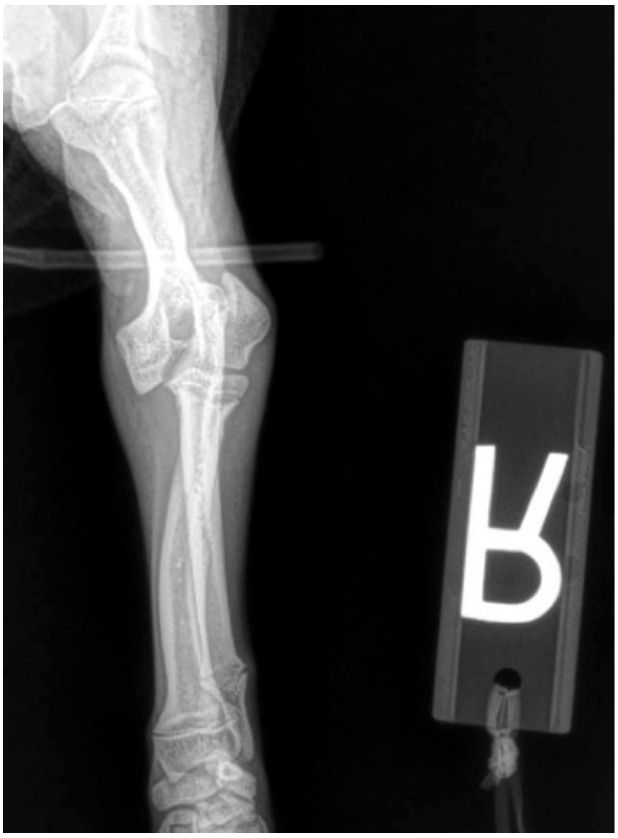


Figure 2. In a craniocaudal radiograph of the same limb as in Figure 1, a fracture is evident.

Fracture repair is highly individualised based on fracture classification; configuration of the fracture (transverse, oblique, spiral); the patient's age, activity level, and body condition; any comorbidities; and client finances and postoperative compliance.

Additional factors include the availability of fixation techniques and your own experience and skill set. If you are going to repair fractures, then he stresses the need to have multiple types of implants available. The downside is implant sets are expensive. If you only have intramedullary pins and cerclage wires, then ethically, you are limited as to what type of fractures you should repair.

It doesn't have to be pretty

The first stage of secondary bone healing after trauma is haematoma formation. You may be tempted to remove the haematoma to get better visualisation. Don't! This haematoma is a massive source of growth factors and cytokines that establish the blood supply needed for healing. Leave it there. Furthermore, leave bony fragments that have soft tissue attachments. The body will reabsorb fragments or incorporate them into the bony callus.

The historical technique of fracture repair was complete anatomic construction, very neat and clean with everything put back in its place, similar to the work of a carpenter. The downside to this technique is haematoma and blood flow disruption, which delays healing. Carpenter-type fracture repair is now only indicated for fractures that involve the articular surface.

The new thought process is less like a carpenter and more like an organic gardener. The idea is to be minimally invasive, be friendly to tissues, and use indirect fracture reduction to preserve blood flow. Blood supply comes from the surrounding soft tissues, so be kind. Overall, joint alignment and function is the goal of fracture repair. Neatness doesn't count.

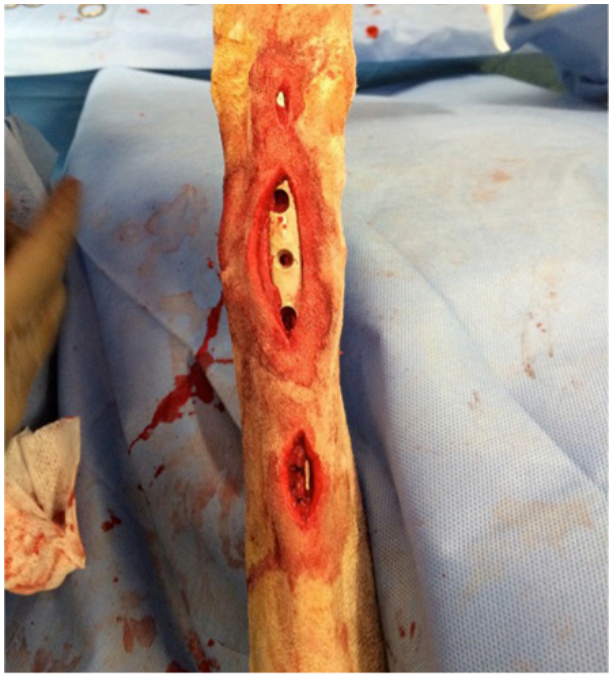
What is MIPO and why should you care?

Do you know what MIPO is? It stands for **minimally invasive plate osteosynthesis**. This technique involves using fluoroscopy to reduce the fracture and then sliding a long plate in via stab incisions (Figure 3 & 4). MIPO is rapidly becoming popular and could have benefits for your patients with various fractures—yet another good reason (I think) to refer.

Keep calm and mind the gap

One final note: If you are rechecking your fractures at four weeks following external coaptation or after surgery and notice that the fracture line seems to have widened slightly, don't panic! Part of the healing process involves the fracture maintaining an interfragmentary strain of < 2%. The interfragmentary strain is the deformation occurring at the fracture site relative to the size of the gap. By keeping the interfragmentary strain < 2% the body is able to allow bone to be laid down in the fracture gap.

This process can cause apparent widening of the fracture line seen on radiographs and can give you the wrong impression that that fracture is getting worse! Understanding this phenomenon will help you interpret your radiographs and, more important, help you sleep at night.



Figures 3 and 4: Intraoperative photos of minimally invasive plate osteosynthesis

5 Ways to Achieve Immediate and Maximal Profitability from Your Practice

Alan Robinson B.V.Sc. MRCVS DMS

Most vets work far too hard for far too many hours for too little return. The principle cause of this is vets' failure to charge profitably for their professional time. Often they don't know what their professional time is worth except in terms of the consultation or surgical fee and these are often determined by what other practices charge rather than based on the needs of the practice finances and profitability.

Then vets often 'give away' (the free consult), discount (the repeat consult) or miss real opportunities to sell their professional time through fear of 'selling' resulting in failure to offer full compliance veterinary services to the client and fulfilling the clients and patients needs. These activities have serious financial, clinical, and customer service implications on the practice and the staff.

This article will show how practices can budget accurately, cut costs, determine a realistic veterinary professional fee based on their financial needs and then demonstrate the consequences of giving away or discounting their professional time and missed opportunities for practicing good veterinary medicine for the benefit of the client, the patient and the practice.

As a comprehensive assessment of your practice we will show you how to analyse your practice finances from five perspectives;

- Profit analysis and Cost Control
- Debt Control
- Pricing
- Implementation and consistency of charging
- Missed opportunities for professional services

1. Profit analysis and cost control

Cost and profit analysis to allow you to:

- Analysis of the separate Strategic Business Units – Equine, Small and Farm practice, 1st opinion and referral practice, hospital and branch practice.
- Analyse cost and cash flow to produce accurate monthly management accounts.
- Set accurate budget projections for the year.
- Set quarterly planning and review meetings with practice owners.
- Focus on key cost areas (stock control) for analysis and budget setting.

2. Debt control

In veterinary practice more time, effort, energy, and heartache is spent on debt collection and getting the money in than any other activity. Debt control is about clear systems and protocols, Credit and Debt Management policies - that prevent outstanding debt occurring in the first place improving cashflow, profitability and client compliance.

3. Strategic pricing of preventative care, clinical care and drugs

In practice some products and services such as vaccines and visit fees are more competitive and are often discounted. Drug sales may come under threat from regulation and internet providers. Professional veterinary fees make up a relatively small percentage of practice income. With the investment in vets, staff and equipment professional fees need to be priced profitably to cover costs and make a profit for the business to thrive.

4. Correct invoicing

Correct invoicing is about setting and sharing Standards of Care based on the best medicine for the patient and clear information to the client. These processes will be discussed and implemented to enhance the use of insurance and clinical work rather than drugs and preventative fees.

5. Proactive medicine

Proactive medicine is based on the Standards of Care that the practice chooses to adopt. It will generate more income (profit) from each client transaction through taking up missed opportunities for professional services and encourage vets to visit

each client more frequently (more transactions).

If practices took up all the opportunities for professional services that were offered to them, they invoiced the work they did do properly and collected the money they invoiced they would improve their cashflow, income and profits overnight by 50% -100%

How to achieve maximal profitability from existing business

Veterinary practice is a reactive business. Practices tend to wait and see what happens to them (e.g. cascade, internet, competition, etc.) then react positively or negatively to the consequences. As a result life in practice can be chaotic, reactive and stressful – many vets working far too hard for too many hours for too little return.

There are opportunities for managers to adopt a more pro-active role in the provision of veterinary services thereby taking control of the practice (and their life), improving profitability and quality of life. Specifically we will look at:

1. Strategic Pricing - Profitably price all services & drugs
2. Vet Sales Performance criteria

Correct Pricing + Correct Invoicing will generate more money from each sale – Increase the Average Transaction Value (ATV). This has the potential of adding an immediate

30% - 40% in pure profits to the bottom line. Every member of staff needs to know about the need for profit and the link between revenue and salaries & investment. Income growth depends on delivering better medicine and better service.

Every practice needs good Invoicing Rules

- Set the fees and charges,
- make sure that they are implemented,
- no freebies,
- no (unofficial) discounts,
- charge for everything.

This is a management issue not a democratic process!

If you are selling on Value and Quality there will always be some people complaining about price. If not, you're too cheap. Get your vets to accept 10% rejection. Relative high prices DO NOT scare clients away. This does:

- Poor service
- Poor quality
- Poor price information

If fees increased, you can afford to lose a percentage of transactions (clients) without losing any profit, e.g. if profit margin is 20% & you increase fees by 10%, you can reduce number of transactions (clients) by 33% without losing existing profit.

If fees decreased, you have to increase the number of transactions (clients) to maintain your profit, e.g. if profit margin is 20% & you decrease fees by 10%, to maintain profit at same level, you must increase transactions (clients) by 100 %

In senior animal (>7 years old) 70% - 80% of drugs and services are **repeatable** medication

- Vaccines /Wormers / Flea control
- Diets - Prescription and non-prescription
- NSAIDS / Arthritics
- Dental products
- Cardiac / Thyroid / Skin / Ear preps
- Clinical & Laboratory monitoring

Once an animal has been prescribed these 'chronic medications they should provide a revenue stream for the ` rest of the animals life. Unfortunately the average compliance of these products is less than 3 months in many cases because of cost, poor case management and inconvenience to the client. A far better strategy is to provide full case management with lower cost drugs over a longer period of time – make less on the drugs initially but more on the additional services over a longer time.

Have a pricing strategy for:

1. Clinical pricing (non-competitive)
   - Low Volume - Vet & Nurse TIME / Value – based pricing
2. Preventative Health Care (competitive)
   - High Volume - Nurse & Reception Bundled PRODUCT+ SERVICE price-based
3. Drugs (by usage – NOT Category)
   - Acute short-term & service driven – high mark-up
   - Chronic long-term product driven – low mark-up + service

Measuring and monitoring vets performance is the quickest and most efficient way of increasing average transaction value. Key Performance indicators are:

- Repeat visits C1:C2 > 100%
- Diagnostics – lab, x-ray & U/S
- Dentals charges
- Hospitalisation & treatment charges
- Preventative HealthCare - vaccines, flea, worm, etc.

Missed and failed opportunities to provide services by the veterinary surgeon in the consulting room.

As we have said before this strategy is driven not primarily by profit but by the desire to practice as

good veterinary medicine as we can – keeping our standards of care as high as possible. With that said we now need to make sure we do three things to achieve a profit:

1. Price our products and services profitably and agree that they are fair
2. Invoice correctly – just charge for what we actually do
3. Do the work that is put before us – practice to the standards that we have agreed.

Compliance studies from the AAHA show that the largest drop off in compliance from vets recommendation for products and services is the vets failure to recommend in the first place based on the feeling that the procedure is too expensive or the client will not want what is being offered. From the clients perspective the reasons for the same non compliance comes down to:

- Lack of effective recommendation by the vet
- Didn't know about it (it wasn't recommended)
- Too much information in a short time (confusion)
- Need or benefit not explained (no prognosis)
- Lack of reinforcement by veterinary team (no follow up

The following 5 consultation tips are offered to increase compliance:

1. Be willing to charge a fair price for your professional time
2. Aim to be respected first and liked second!
3. Learn to live with 10% rejection!
4. Clients want a PROGNOSIS - not a DIAGNOSIS
5. Don't assume clients can diagnose & prognose - Refer cases back for YOU to examine

The process of regularly looking at invoices and discussing the best protocols for treatment between vets can massively improve standards of care, consistency of treatment and increase revenues immediately.

DAY 01

09:00	Welcome & drinks
09:30	Welcome and Sponsor Introduction
10:00	The Challenges of Veterinary Practice
11:15	Break
11:45	The 5 waves of change in the Vet profession
13:00	Buffet Lunch
13:45	Navigating the 5 Stages of Practice Growth
15:00	Break
15:15	The Veterinary Business Spectrum - where are you?
16:00	Close
16:30	Relax and network drinks in the bar

DAY 02

09:00	Welcome / Sponsor Session
09:30	Measure it to Manage it - Practice Data
11:00	Break
11:30	Vets - Motivation & Performance
12:45	Lunch
13:30	3 simple ways to add an extra R850 000 per vet, per year
15:00	Break
15:15	Q&A, Case Studies and Action Plans
16:00	IVPD Wrap up
16:15	Close

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Exclusive Report

New Study Reveals Insights into Pet Owners' Purchasing Decisions

Pet Owner Paths research pinpoints differences in how younger pet owners choose pet care

Kristi Reimer Fender, News Channel Director

A new study of pet owner behavior has found important differences in the ways millennial pet owners make decisions about their pets' care compared with older pet owners—and how and when both groups decide to involve a veterinarian.

The Pet Owner Paths research, sponsored by Merck, Unfenced (an animal health creative agency) and Kynetec (a market research firm), looks at the specific steps pet owners take when making decisions about their pets' health. The research was released exclusively to dvm360.

In addition to looking at younger versus older pet owners, researchers examined decision making by product category (including dental, dermatology and pain), differences between dog and cat owners, differences when a pet is sick versus when it's healthy, and more.

Here are some key topline findings from the research.

Millennials are the future—and the future is now

According to the American Pet Products Association, millennials are now the largest segment of pet owners. They are conscientious and poised to be excellent veterinary clients, a report on the research states. Specifically, according to the report, millennials are:

- Investing more time in their pets, evaluating their needs more thoroughly and spending more money.
- More likely to use veterinary products preventively rather than just as a treatment.
- More likely to use products continuously versus intermittently.
- More likely to get dental cleanings and use dental rinses.
- More likely to see veterinarians as integral to their journey as pet owners.

Millennials are invested in the 'learning journey'

For younger pet owners, decision making is "a long, complex and often iterative journey," the Pet Owner Paths report states. This journey takes them substantially longer than it does older pet owners, and it does not always end with a purchase. "Even after researching and evaluating options, millennials are less likely to purchase a product and stop the process; they often want to keep looking," the report says. Millennials tend to cast a wide net when they're looking for information to support a decision—they "actively gather, curate and assess information from many, many sources."

Veterinarians are integral to the millennial's journey

According to the Pet Owner Paths research, millennials are more likely to involve their veterinarian in their journey than older pet owners (57 percent versus 42 percent). They're also more likely to report that they ultimately follow the veterinarian's recommendations (50 percent versus 31 percent).

On the other hand, millennials are more likely to get their information from multiple sources in the veterinary clinic (veterinarians, technicians and front office employees); traditional pet owners rely almost entirely on the veterinarian.

Millennials demand instant access and communication

When millennials were asked what they most valued as a veterinary service offering, they chose 24/7 chat or texting availability as one of their top options—it was

No. 1 for dog owners and No. 2 for cat owners. These pet owners are also more likely than older clients to reach out to the veterinarian using alternative methods (social media, email), and they are also heavy users of on-demand information sources.

Cat owners are not small dog owners

The Pet Owner Paths researchers discovered that cat owners as a whole spend more time on the decision-making journey than dog owners, regardless of generation. They're more likely to use online sources to gather information, jumping on the web immediately to find answers to their questions. Cat owners are also more inclined to read product packaging than dog owners, and more millennial cat owners than millennial dog owners recall receiving a specific recommendation from their veterinarian. Millennial cat owners are the most likely of any segment to use alternative communication methods (email, social media posts) to reach out to their veterinarian.

Veterinarians and pet owners see the world differently

The research also highlighted important differences between how veterinarians and pet owners view various aspects of pet care:

- **Preventive health.** Veterinarians see preventive care as spaying and neutering, providing vaccines and establishing a parasite control program. They believe they are responsible for defining preventive care appropriately and providing it for the pet. Pet owners on the other hand believe preventive care involves emotional well-being, exercise, nutrition, play and veterinary care. They think they are the ones responsible for providing these things.

- **The veterinarian-client-patient relationship (VCPR).** In the veterinarian's mind, the doctor assumes responsibility for making medical judgments regarding patient health and the client agrees to follow those instructions. For the pet owner, the VCPR is a trusting bond with a significant care provider who knows and cares about the pet and participates with the pet owner to provide the best care.

- **The purpose of a veterinary visit**. For veterinarians, it's to evaluate and determine the best course of action. For the pet owner, it's to get expert advice to include in the decision-making process.

- **Dr. Google.** For veterinarians, the web is a "dangerous, misinformed competitor to the veterinarian's authority and client relationships," according to the report. For pet owners, it's an on-demand source of copious information that they can curate to be more informed as they make decisions.

Additional insights

Here are some other interesting trends identified in the research:

- Millennial dog owners are moving away from small dog ownership and toward medium-sized dogs (in one segment of the study, 50 percent of millennials owned a medium-sized dog compared with 34 percent of older owners of dogs).

- Pet ownership is becoming more balanced between men and women. More millennial dog owners are male (39 percent) compared with older dog owners (29 percent), and more millennial cat owners are male (46 percent) compared with older cat owners (31 percent).

Implications

While the Pet Owner Paths study contains much more information (look for further coverage in dvm360 magazine, Vetted and Firstline as well as on dvm360.com), veterinarians can take immediate action by engaging with millennials differently, researchers report: They can embrace alternative methods of communication, stop trying to compete with Dr. Google and instead embrace it, and have patience with the long and involved decision-making journey millennials need to travel for their pets' health.

Histology and Immunophenotyping

on Lymph Node and Spleen Samples

Dr Sarah Clift BVSc, MSc (Path)
Senior Lecturer
Section of Anatomic Pathology, Department of Paraclinical Sciences,
Faculty of Veterinary Science, University of Pretoria
sarah.clift@up.ac.za

The advent of immunophenotyping (determination of B- or T-cell lineage) and its development as prognostic marker, especially in canine lymphomas throughout the 1990's led to complete revision of the historical classification systems, with the most updated and accurate system to date being the World Health Organization (WHO) system.

Malignant lymphoma is one of the most commonly diagnosed tumours in dogs and cats and it's the neoplasm most frequently treated by veterinary medical oncologists. Most cases of lymphoma in dogs and cats can be successfully managed with chemotherapy but appropriate chemotherapy protocols can only be applied if lymphomas are properly staged by veterinary practitioners and graded by experienced veterinary pathologists.

The goal of the WHO system was to correlate each lymphoma category with behaviour and degree of malignancy. This system, which is widely used by veterinary pathologists worldwide to classify lymphoma in dogs (and to a lesser extent cats), is based on the WHO classification system for non-Hodgkin's lymphoma in humans. It is the only classification system to combine histomorphology (including tumour growth pattern, nuclear morphology and mitotic count) as well as immunophenotype on as many as 300 canine lymphoma cases. Seventeen well-qualified (non haematopathology specialist) veterinary pathologists evaluated and classified each case and intra- and inter-observer variability was thoroughly assessed. The overall accuracy of the 17 pathologists looking at all 300 lymphoma cases was 83%, and when only the six most common diagnoses were considered (these corresponded with 80% of the 300 cases), the accuracy rose to 87%.

1. Canine lymphoma

Of all the domestic species, lymphoma has been most extensively studied in dogs. It is the most common haematopoietic malignancy in dogs with an estimated incidence rate of 20 to 100 cases per 100 000 dogs per year. As for humans, the incidence of lymphoma in dogs has increased over the past few decades, possibly due to environmental risk factors, although genetic susceptibility has been strongly indicated for certain dog breeds e.g. Rottweilers, Scottish terriers and bullmastiffs. Environmental toxins and pollutants, viruses, bacteria, electo?magnetic fields and a dysfunctional immune system have all been implicated in the aetiology of lymphoma in dogs and other animals. Middle-aged to older dogs and middle-sized to large breed dogs are most susceptible to lymphoma, but there is no apparent sex predilection.

1.1 Staging canine lymphoma

Lymphomas may occur in any organ in the body, but they usually arise in lymph nodes and spread to other organs such as the liver, spleen and bone marrow. Clinically, approximately 75% of dogs present with multicentric lymphoma, in which the neoplasm first becomes apparent in lymph nodes. As such, multicentric lymphoma is classified into 5 stages by the WHO In summary,

- Stage I refers to lymphoma in a single lymph node or lymphoid tissue in a single organ
- stage II refers to the regional involvement of multiple lymph nodes on the same side of the diaphragm
- stage III refers to the generalized, painless involvement of lymph nodes on both sides of the diaphragm
- stage IV refers to stage III with secondary involvement of the spleen and/or liver
- Stage V refers to the generalized involvement of lymph nodes on both sides of the diaphragm with bone marrow and/or blood involvement as well as involvement of the central nervous system (CNS) and/or other organs.

Sub-staging (indicated by the suffix A or B) further indicates absence (A) or presence (B) of systemic signs of illness (including weight loss, pyrexia or hypercalcaemia), which are associated with decreased survival.

Apart from multicentric lymphoma, alimentary, mediastinal and a variety of extranodal forms of lymphoma (including cutaneous lymphoma) have been described. Presenting clinical signs obviously depend on the anatomic location of the lymphoma.

In multicentric lymphoma, lymph nodes are moderately to severely enlarged, firm or rubbery and non-painful. The lymph nodes generally bulge on cut surface and foci of haemorrhage and necrosis may be observed. Importantly, nodes are quite commonly attached to the surrounding tissues due to capsular invasion of neoplastic cells into the peri-nodal tissues. Other gross lesions of lymphoma may include diffuse organomegaly, multiple cream-coloured to pink nodules within viscera and/or thickening of the walls of tubular organs e.g. in alimentary (gastrointestinal/GIT) lymphoma.

Canine lymphoma mimics human non-Hodgkin's lymphoma in terms of clinical presentation, histomorphology, molecular biology and response to treatment. Non-Hodgkin's lymphoma refers to a large group of different histoypes of lymphoma of T- and B-lymphocyte lineage and of variable malignancy. This group includes a variety of so-called chronic, indolent (slow-growing) lymphomas as well as various more aggressive (fast-growing), potentially life-threatening subtypes. Hodgkin's lymphoma on the other hand, refers to a type of lymphoma with far fewer histological subtypes, all of which have been well-described in humans, where they are commonly (but not always) associated with Epstein-Barr virus (EBV) and HIV/AIDS infection. Reports on Hodgkin's-like lymphoma in animals are extremely rare.

1.1.1 The 5 most common lymphoma histotypes

According to the most recent literature on canine lymphoma, there are five lymphoma histotypes that occur most frequently and at least, for these subtypes, accurate (usable) data is present regarding their response to treatment.

The five histological subtypes from most to least common include:

1. Diffuse large B-cell lymphoma/DLBCL (54% prevalence)
2. peripheral T-cell lymphoma, not otherwise specified/PTCL-NOS (16% prevalence)
3. nodal T-zone lymphoma/TZL (14% prevalence)
4. T-cell lymphoblastic lymphoma/T-LBL (5% prevalence),
5. indolent marginal zone B-cell lymphoma/MZL (4% prevalence)

(prevalence data from the USA, SA unknown)

1.1.2 Requirements for accurate lymphoma histotyping in nodal biopsies

Classification of canine lymphoma into these and other histological subtypes requires thorough assessment of tumour growth pattern (which involves analysis of nodal architecture), as well as lymphocyte nuclear size, shape, chromatin pattern and prominence and location of nucleoli, calculation of the mitotic count and assessment of the presence/absence of tingible body macrophages*

Evaluation of nodal architecture requires that the nodal biopsy submitted for evaluation be at least an incisional wedge biopsy (preferably half the node), but ideally 1-2 whole nodes should be excised for histopathology. This is so that the lymph node capsule, peri-nodal tissues, subcapsular, cortical and medullary sinuses and medullary cords can be properly evaluated for the purpose of accurate classification.

For example, it is important that nodal diffuse large B-cell lymphomas/DLBCLs (immunoblastic sub-type) be differentiated from nodal indolent marginal zone (MZ) B-cell lymphomas, because more aggressive DLBCL's respond well to CHOP therapy (C: cyclophosphamide; H: hydroxy doxorubicin; O: vincristine and P: prednisone) but nodal MZL's do not require CHOP therapy (they respond well to a combination of prednisolone and chlorambucil). Both are B-cell lymphomas, both may invade the capsule (but DLBCL is generally more invasive), and both consist of neoplastic lymphocytes with

*tingible body macrophages are those phagocytosing apoptotic lymphocytes - if numerous, this is often indicative of a higher mitotic count

prominent single central nucleoli. However, MZL cells are medium-sized (nuclei 1,5 erythrocyte diameters, on average) with more cytoplasm, while DLBCL cells possess larger nuclei (1,5 to greater than 2 erythrocyte diameters) and cells are often crowded together, with overlapping nuclei, due to minimal cytoplasm.

Marginal zone lymphomas are usually (at least in the early stages) nodular in pattern, centred on fading germinal centres that have been replaced by irregular clusters of small mantle cells. MZL's are indolent, with no to very few mitoses in 10 non-overlapping high power (400X) fields, while DLBCL's have a variable mitotic count, but it's not usually as low as in MZL's. Tingible body macrophages are far more common in DLBCL's, but can also be seen in late-stage MZL's, when mitoses may also become more frequent.

There are of course, a number of cases where it is difficult to classify the lymphoma accurately. Usually however, these are cases where the biopsies were Tru-cut biopsies that were simply too small with no discernable capsule or sinuses. Also, poor fixation (including delay to fixation) can lead to autolysis or significant cell dehydration with contraction artefact, making it nearly impossible to further classify the lymphoma. Immediate formalin fixation is preferable, but a delay of less than 30 minutes is acceptable. *(ed: so do not wait until you are clearing up post-op to pop the biopsy into the formalin)*

1.1.3 Reactive lymphoid hyperplasia, atypical follicular hyperplasia and fading follicular hyperplasia – some important definitions

Reactive lymphoid hyperplasia refers to the normal response of lymphoid tissue (B- and/or T-lymphocytes) to persistent antigenic stimulation during infection or inflammation. In these cases, follicular germinal centres and/or paracortical areas are often greatly expanded, sometimes with invasion of the peri-nodal tissues, but the essential nodal architecture is not disrupted.

The nodal atypical and fading follicular hyperplasias represent a grey area between reactive follicular hyperplasia and certain types of lymphoma. Atypical follicular hyperplasia, which is most often observed in cats with FeLV/FIV infection, consists of a range of irregularly-enlarged and -shaped germinal centres, often with irregularly attenuated mantle cell cuffs that may distort nodal architecture, and such cases may even exhibit peri-nodal invasion of lymphocytes. However, there is still cellular heterogeneity within the variably expanded germinal centres, and the peripheral sinus is visible and not compressed by the lymphoid expansion.

Occasionally, clonal expansions of lymphocytes may be caused by certain infectious diseases rather than lymphoid neoplasia, and a common example of such an infectious disease that is particularly common in sub-Saharan Africa is ehrlichiosis, caused by Erlichia canis.

Fading follicular hyperplasia refers to the presence of involuting germinal centres that may appear "faded" due to the collapse of small mantle cell B-lymphocytes into the germinal centres. Almost all cases of marginal zone lymphoma/MZL occur against a background of fading follicular hyperplasia. In summary, the atypical hyperplasias require histology for a definitive diagnosis and for their differentiation from indolent lymphomas in particular.

1.2 Prerequisite lymph node sampling for histopathology and immunophenotyping

Importantly, all samples should be collected before commencing therapy (including treatment with glucocorticoids) in order to limit excessive lymphocytolysis which impacts negatively on histological grading and immunophenotyping. In the case of a single enlarged node, ideally, the entire node should be carefully dissected out (excisional biopsy) or, at the very least, a decent-sized incisional wedge biopsy (preferably half the node) should be submitted for histopathology and immunophenotyping via immunohistochemistry (IHC). Tru-cut needle biopsies can be useful, but in the author's experience, they are often too small and crushed with little discernable architecture. Simply put, the larger the biopsy the greater the likelihood of accurate lymphoma diagnosis (with grading). In the case of more than 1 enlarged node, at least 2 nodes from different anatomical regions should be submitted for histopathology.

It is preferable that, if there's a choice that the submandibular node/s NOT be submitted, since they drain the mouth and often show a degree of hyperplasia and inflammation. As a result these can be difficult to interpret and may not even be representative of the more widespread lymphadenomegaly. Therefore, the popliteal and prescapular lymph nodes are preferred if also enlarged.

Care should be taken to handle lymph nodes carefully since they are easily crushed when fresh. A sharp scalpel blade should be used to incise the node longitudinally so that formalin is able to permeate the node/s properly. If not incised, often only the tissues immediately beneath the capsule fix and the inner cortex and medulla do not and the cells in these areas are therefore poorly fixed and may be autolysed or dehydrated and contracted. If multiple nodes are sampled they should be placed in separately labelled containers and at least 1-2 nodes should also be kept in the freezer in case the lymphadenomegaly is due to an infectious process, in which case fresh node is available for PCR or bacterial culture, as necessary.

1.3 Current trends in lymphoma diagnosis

Typically, in the mind of the South African small animal practitioner, a diagnosis of lymphoma depends on cytology and/or histopathology of the node/s or organ in question with the observation of a uniform population of medium to large, "blastic" lymphocytes with coarse chromatin, one or more prominent nucleoli and numerous mitoses. Thereafter, basic immunophenotyping (B or T cell ontogeny) may be requested due to the association between T-cell lymphoma and a worse prognosis compared with the more common B-cell lymphoma in dogs. However, research on canine lymphoma in particular has burgeoned in the last decade.

Many studies have investigated histomorphology, immunophenotype (using immunohistochemistry/IHC, immunocytology/IC, flow cytometry/FCM or PCR for Antigen Receptor Rearrangement/PARR) as well as clonality (also via PARR) of canine lymphoma and compared the data with human lymphoma data.

As a result, there are currently more than 30 described histotypes of canine lymphoma, all based on the degree of cellular maturation and B- or T-cell lineage.

Many of these lymphoma subtypes have at least some prognostic data that has largely relied upon the maturation level of the neoplastic lymphocytes and their lineage. Within the last 5 years in particular, canine lymphoma studies have focused on the response of the most common canine lymphoma subtypes to various chemotherapy protocols.

Therefore, it is no longer adequate to simply assess nodal cytology and request basic immunocytology, unless a case is cost-constrained and the owners have been made aware of the diagnostic limitations of these methods. The diagnosis of lymphoma in human medical oncology relies on histomorphology and immunohistochemistry at the core, with the addition of newer modalities such as FCM, PARR and in situ hybridization (ISH) for specific genetic mutations. Selection of appropriate treatment protocols in humans and animals depends on establishing a definitive diagnosis, which, in the case of veterinary medicine, requires detailed histological classification and grading with IHC at the very least.

1.3.1 Lymph node cytology, immunocytology, flow cytometry and PARR

Lymphoma can be diagnosed and immunophenotyped in cytological smears or aspirates by means of immunocytology, flow cytometry (FCM) or PCR for antigen receptor rearrangements (PARR). PARR can also be performed on archived formalin-fixed, paraffin-embedded tissues.

1.3.1.1 Immunocytology

Immunocytology (IC) requires a minimum of 4 adequately cellular, air-dried, unstained glass slides, prepared as for standard cytological evaluation. A common problem is the poor cellularity of some smears and we are limited by the number of slides submitted, especially when one considers that a Diff-Quik-stained smear is prerequisite for the evaluation of cytomorphology which is necessary for the accurate interpretation of the IHC immunophenotyping results. One advantage of IC over immunohistochemistry is the preservation of more cell antigens in fresh versus fixed tissues. However, cell morphology is often inferior in cytological preparations and cells also wash off easily during staining.

1.3.1.2 PARR

Apart from its immunophenotyping capacity, PARR is used especially when histomorphology and immunohistochemistry results are inconclusive (e.g. when lymphoid hyperplasia cannot easily be distinguished from one of the early indolent lymphomas due to a lack of significant nodal architectural effacement). The PARR technique involves the amplification of variable regions of immunoglobulin genes or T-cell receptor genes in order to detect the presence of clonal (versus polyclonal) lymphocyte populations. The presence of a clonal population of lymphocytes is generally strongly indicative of malignancy, versus a polyclonal lymphocyte population, which is generally more indicative of a reactive hyperplastic lymphoid population.

However, as was mentioned above, E. canis is an example of an infectious agent that can cause a clonal proliferation of (T-) lymphocytes in nodes. There have also been reports of T-cell lymphomas producing aberrant immunoglobulins, leading to erroneous immunophenotyping via PARR. Interestingly, some recent studies that have evaluated immunophenotyping modalities for canine lymphoma have shown that FCM is more sensitive than PARR for establishing immunophenotype, the limitation being that FCM requires fresh tissues.

1.3.1.3 Flow cytometry

Flow cytometry is a laser-based technology based on the use of antibodies that target specific cell surface markers expressed by lymphoid (and other) cells, which help to identify and characterize cell populations of interest in a sample. Differentiation between various cell populations is not only based on phenotype, but also on pattern of expression of cell surface markers as well as differences in cell size and granularity. In this way, FCM rapidly analyses

and identifies large numbers of cells individually within a sample – dividing the sample into various sub-populations of cells. These are then compared with cell sub-populations in similar samples from normal animals. FCM has become extremely useful compared to immunocytochemistry and immunohistochemistry, due to the increased availability and variety of antibodies against haematologic antigens in dogs. Importantly however, FCM requires viable (living) cells, so in cases of lymphoma where there is widespread lymphocytolysis (e.g. in animals that were on prednisolone treatment prior to sampling), the results yielded by FCM might be inaccurate.

In summary, none of the abovementioned modalities is completely reliable when used on its own for the diagnosis of specific lymphoma subtypes. Flow cytometry and PARR have the advantage that they can be performed on cell aspirates from lymph nodes, compared to histopathology and immunohistochemistry, which require biopsies to be submitted for evaluation (far more invasive and expensive diagnostic modalities). However, FCM and PARR results should always be interpreted in conjunction with cytomorphology and/or histomorphology.

1.3.1.4 What is currently available in South Africa?

Unfortunately in South Africa, neither flow cytometry or PARR) is available for immunophenotyping/lineage assignment of animal lymphomas, although there are plans to investigate the feasibility of offering these modalities in the country.

1.3.1.5 Feasible alternative to immunocytology and immunohistochemistry in difficult cases

For interested veterinary clinicians, formalin-fixed, paraffin-embedded (FFPE) tissue blocks or stained/unstained cytology slides or fresh material including bone marrow aspirates and blood (in EDTA tubes) as well as effusions or fine needle aspirates in PBS buffer can be submitted for PARR (and, in the case of fresh material, also for FCM) – to the Clinical Pathology Laboratory at the University of Veterinary Medicine in Vienna, Austria. The cost is approximately R3 000.00 per analysis depending on the sample(s) submitted.

2. Feline lymphoma

Lymphoma is one of the most common feline malignancies, accounting for approximately one third of all neoplasms in cats with an estimated incidence rate of approximately 200 cases per 100 000 cats per year. Based on recent research, it seems that T-cell lymphomas predominate in cats (as opposed to B-cell lymphomas in dogs), but the number of feline lymphomas that have been phenotyped is low overall, meaning that lymphoma phenotype in cats still requires further investigation.

2.1 Anatomic forms of lymphoma

The most common anatomic forms of lymphoma are also recognized in cats and include alimentary (gastrointestinal), mediastinal, multicentric and extra-nodal forms, with the alimentary and mediastinal forms being the most common. Peripheral and/or visceral nodal involvement of lymphoma in cats is relatively uncommon, with multicentric lymphoma more commonly involving multiple organs (e.g. spleen and liver), without necessarily involving peripheral and/or visceral nodes. The most common extra-nodal forms occur in the nose, kidneys and CNS. Other extra-nodal forms of lymphoma include laryngeal, pharyngeal, tracheal, pulmonary, ocular, retrobulbar and cutaneous forms.

2.1.1 Alimentary lymphoma

Alimentary lymphoma, the most common form of feline lymphoma in practice, accounts for approximately 50% of all feline lymphomas. They may occur as single nodules or as a diffuse thickening of the gastrointestinal wall. The oral cavity, oesophagus, stomach, small and large intestine, mesenteric nodes, pancreas and liver may be affected. Feline alimentary lymphomas have been classified on the basis of cell type (large or small), grade (low or high mitotic count) and pattern of infiltration (epitheliotropic and confined largely to the mucosa or non-epitheliotropic and transmural with extensive infiltration into the submucosa and muscular tunic).

Generally, the epitheliotropic, mucosal lymphoma consists of small cells and tends to be low grade, responding well to chemotherapy, while the transmural lymphoma consists of large cells, tends to be high grade and responds poorly to chemotherapy. Large granular lymphocyte (LGL) neoplasia (of T-cell immunophenotype) has also been reported in the feline GIT, with evidence of epitheliotropism in more than 50% of cases, as well as infiltration into mesenteric nodes, liver, spleen, kidneys and/or bone marrow in most cases. These LGL lymphomas tend to respond poorly to chemotherapy. The neoplastic cells are thought to derive from intra-epithelial lymphocytes since the neoplastic LGLs share phenotypic characteristics with feline intra-epithelial lymphocytes (IELs).

While endoscopic superficial grab biopsies are useful for the diagnosis of stomach lymphoma, they are not sufficient to differentiate between inflammatory bowel disease (IBD) and lymphoma

in the small intestine. Full-thickness biopsies are pre-requisite for the diagnosis of lymphoma (versus IBD) in intestinal samples.

2.1.2 Mediastinal lymphoma

The other common form of lymphoma, namely mediastinal lymphoma, can involve the thymus (predominantly T-cell lineage), mediastinal and/or sternal lymph nodes. These lymphomas occur most commonly in young FeLV-positive cats, and tend to be high grade T-cell lymphomas requiring aggressive CHOP-based chemotherapy protocols. Young FeLV-negative Siamese cats with mediastinal lymphoma tend to respond well to chemotherapy and often attain complete, durable remission, resulting in cessation of treatment.

2.1.3 Nasal lymphoma

Nasal lymphoma has been reported in cats and from the few cats that have been investigated, these lymphomas tend to be diffuse large B-cell lymphomas (DLBCLs), often of the immunoblastic subtype (with prominent, single, centrally situated nucleoli). It may well be that the DLBCL histotype has been overrepresented in feline nasal lymphomas, since not many feline nasal lymphoma cases have been thoroughly investigated, including submission for lineage determination. It therefore follows that the prognostic effect of the B-cell phenotype in feline nasal lymphomas is as yet unexamined. If localized, the nasal form of lymphoma in cats responds well to radiation therapy alone, but if systemic involvement is suspected, chemotherapy should be used in conjunction with radiation therapy.

2.1.4 Renal lymphoma

Cats with renal lymphoma usually have bilaterally affected kidneys, they tend to be FeLV-negative (although they may be FIV-positive), cats are often older and there is usually involvement of other organs as well (especially the CNS). Renal lymphomas tend to be high grade and of B-cell phenotype.

Very broadly speaking, mediastinal, multicentric and B-cell lymphomas in cats seem to have a longer duration of response to chemotherapy (increased survival time), compared with the alimentary and renal forms. It seems that in cats, the initial response to chemotherapy (over the first 4-6 weeks) is the best prognostic indicator (to date). Complete remission after initiation of chemotherapy is associated with far longer survival times than is the case in cats with partial remission or no response to therapy.

In feline lymphoma, most of the focus has been on anatomic site and stage of lymphoma which have been associated with treatment protocols and data on remission and survival times. There is no doubt that veterinary practitioners in South Africa and elsewhere in the world have been reluctant to submit feline lymphomas for immunophneotyping. This is probably due to the results from a study performed in the late 1990's where the authors indicated that CD3 immunohistochemistry did not correlate with survival in cats.

2.2. Lymphoma and FELV

One form of nodal lymphoma that has been reported sporadically from the late 1990's onwards, in feline leukemia virus/FeLV-negative cats and that seems to be restricted to single lymph nodes of the head and neck (e.g. single submandibular or cervical nodes) is the T-cell-rich B-cell lymphoma or Hodgkin's-like lymphoma. This lymphoma histotype seems to follow an indolent course, although more intensive investigation in a greater number of cats is required.

In young cats (5 months to 2 years of age) with generalized peripheral lymph node enlargement one should rather consider non-specific antigen stimulation and test for FeLV, which can cause atypical paracortical lymphohistiocytic and plasmacytic hyperplasia. In most of these cases the cats test positive for FeLV, but the lymph node enlargement is usually self-limiting/transient.

The age at which cats present with lymphoma is bimodal with two peaks occurring at 2 years and 10 years of age, respectively. Young cats with lymphoma are far more likely to be FeLV-positive, although effective vaccination programmes over the last 20 years, especially in developed countries, have seen a decline in FeLV-associated lymphoma (most commonly mediastinal T-cell lymphoma), and an increase in non-FeLV-associated alimentary lymphoma in older cats (10 years of age on average). The risk of lymphoma development increases in cats infected with FeLV and FIV and survival times tend to be shorter in cats with concurrent retroviral infections, probably due to the development of additional diseases (over and above the lymphoma). The Siamese breed is overrepresented in the FeLV-negative young cat population that presents with lymphoma, and also in the FeLV-negative older cat population that presents with alimentary lymphoma. This apparent breed predilection for certain anatomical forms of lymphoma also requires further investigation.

2.3 Staging feline lymphoma

As for dogs, the main aim of staging lymphoma in cats is to ascertain all areas of involvement, which requires, if possible (finances permitting), a thorough diagnostic investigation of the whole patient.

- Stage I refers to lymphoma in a single lymph node or organ, including primary intrathoracic neoplasms
- Sstage II refers to 1-2 extranodal tumours with or

without regional lymph node involvement on the same side of the diaphragm or 2 or more nodal tumours on the same side of the diaphragm, as well as any resectable primary alimentary tumour, with or without associated mesenteric node involvement
- Stage III refers to two single extranodal tumours on either side of the diaphragm, or 2 or more nodal tumours on both sides of the diaphragm as well as extensive unresectable intra-abdominal masses and all epidural or paraspinal masses, regardless of other sites of tumour development. Stage IV refers to stages I to III with secondary involvement of the spleen and/or liver.
- Stage V refers to stages I to IV with central nervous system and/or bone marrow involvement.

As for dogs, sub-staging (A or B) indicates absence (A) or presence (B) of clinical (systemic) signs of illness, e.g. malaise, anorexia, weight loss, etc, which are negative prognostic factors, similar to dogs with lymphoma. Stage I lymphomas, which are most commonly extranodal in cats (e.g. localized nasal lymphomas) carry the best prognosis (compared to stage IV/V lymphomas), but the anatomic site of lymphoma development currently also dictates outcome in feline patients.

It is clear that, just as for lymphomas in dogs, feline lymphomas MUST be submitted for histopathology for detailed grading as well as immunophenotyping via IHC, FCM or PARR, as was discussed under the section on canine lymphoma. The largest study ever done on feline lymphomas in 2000 by Valli et al., looked at 602 cases and graded them according to the National Cancer Institute working formulation for the classification of human lymphomas. This system was used to categorize the feline lymphomas as low, intermediate or high grade tumours based on their natural rate of progression. Immunophenotyping was not performed on any of these cases. Clearly, as many feline lymphomas as possible need to be graded according to the more recent and highly accessible WHO system, which includes immunophenotyping, and prognostic data needs to be accumulated based on this grading system, in conjunction with anatomic form and clinical staging data.

Flow cytometry and PARR have been optimized in various laboratories overseas (including the one in Vienna) for feline patients and may be extremely useful in challenging cases, where there is no staining via IHC, or the neoplastic lymphocytes stain positive for both pan B- and T-cell markers, or where there is difficulty in distinguishing between (atypical) nodal hyperplasia and especially the various subtypes of indolent lymphoma. A large database of properly staged, histologically graded and immunophenotyped lymphomas would undoubtedly inform rational treatment choices for the individual cat, especially those with extranodal lymphomas, for which prognostic factors are still very poorly defined.

3. What the veterinarian needs to know regarding Splenic pathology in dogs

If the spleen is diffusely enlarged or has one or more nodules/masses and there is enough indication to remove the organ, there are 3 basic options for submission of the entire organ to the pathology laboratory

a. Refrigerate the whole spleen overnight then double-bag it and submit it to the pathology laboratory in an adequately-sized plastic or polystyrene box with ice-packs strategically placed around the specimen. The sample should not be frozen or submitted on ice (so as to avoid freeze artefact). It should be submitted as quickly as possible to the laboratory for immersion in formalin (to prevent excessive autolysis). This is the least favourable option unless the pathology laboratory is close by.

b. The preferred option is to "bread-loaf" or cut deep (not full-thickness) parallel (transverse) incisions at 5-10mm intervals throughout the entire specimen and then pre-fix it in 10-40% neutral buffered formalin in an adequately-sized container (allowing 1 part tissue to at least 9 parts formalin) at room temperature for 2-3 days. Formalin can be changed daily if there is excessive blood conta¬mi¬nation. After 2-3 days the specimen should be fixed and can be double-bagged (minus the formalin) as has been described above, and transported on ice packs to the veterinary pathology laboratory. At least in the first 2 instances the pathologist is able to see the entire specimen with normal tissue orientation.

c. The last option is to draw or take a digital photo of the whole spleen with the lesion/s of interest. The length, breadth and thickness of the entire spleen and the lesion/s (if a nodule) should be recorded in cm on the photo/diagram. You must also demonstrate CLEARLY on the dia¬gram/image EXACTLY how the organ/specimen was sampled. Labelling on the sample bottles (A, B, C or 1, 2, 3, etc.) should correspond with the attached diagram/image for cross-referencing. The rest of the specimen can be stored in formalin (as for b above) and the pathologist should be informed that you still have the rest of the spleen in case more tissue is required.

In summary, I hope that you as small animal veterinary practitioners have a far better appreciation of the rationale behind sampling of the major lymphoid organs for the purpose of attempting to obtain a definitive diagnosis. In essence, histopathology is CENTRAL but in terms of lymphoma diagnostics and diagnostic investigation of splenic pathology, immunophenotyping is also prerequisite – and not only in dogs!

References available online: www.vetlink.co.za

Aggressive Versus Palliative Veterinary Decision Trees for Pet Cancer

By Michael O. Childress, DVM, MS, DACVIM (oncology)

These basic algorithms provide every veterinarian a framework for diagnosing cancer and deciding with pet owners on the right course of treatment for a cure, a longer life or improved quality of life. Surgery, radiation therapy and chemotherapy—the mainstays of cancer treatment in pets—can confer significant benefit to cancer patients. However, they are equally capable of producing significant morbidity if used without discretion. Your two key questions are these: "What benefits can a patient derive from cancer therapy?" and "How do you judge whether a patient is likely to experience these benefits?"

What do we hope for?

To address the first question, let's look at the three fundamental ways cancer patients benefit from therapy:

1. The pet's cancer is cured
2. The pet's life is extended in the absence of cure, while quality of life is concomitantly maintained or improved
3. The pet's quality of life is improved in the absence of cure or extension of life.

To achieve a cure in patients with advanced cancers, aggressive therapy is usually required. With aggressive therapy comes a significant risk of treatment-related complications. In contrast, treatments with more palliative intent frequently improve quality of life and may also extend life if used carefully. It should be noted that the use of the term "palliative" here is not synonymous with hospice-style care for a terminally ill patient. Radiation therapy, chemotherapy and even surgery all can be used with palliative intent. However, as opposed to the rationale for their use in the aggressive treatment setting, the focus of palliative therapy is to minimise treatment-related morbidity. This necessarily comes at some expense to the prospects of curing a cancer or extending a patient's life.

Can it happen?

Fully answering the question of how to judge whether a patient is likely to derive benefit from therapy requires some review of the typical diagnostic and staging process for cancer patients ...

The purpose of biopsy is to obtain histopathologic confirmation of the tumour type and, where applicable, tumour grade. A decision central to this

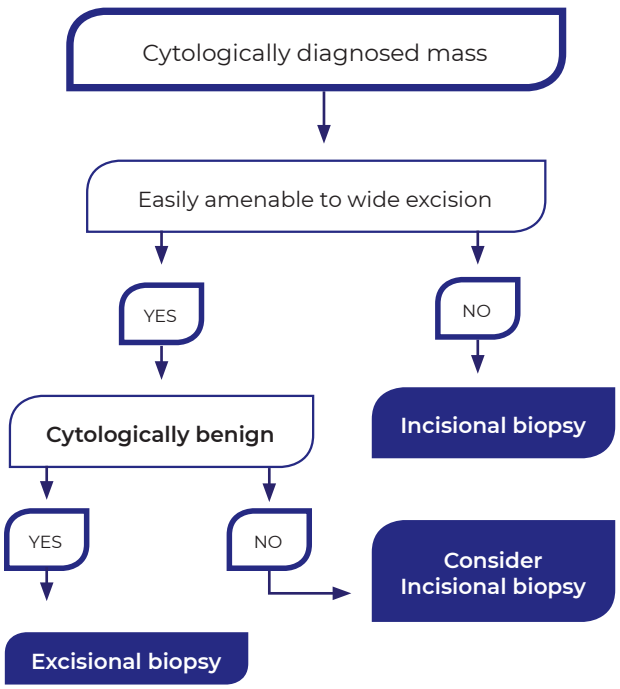

Figure 1, a decision tree on collection of biopsy specimens from tumours

process is whether incisional or excisional biopsy is the most appropriate choice for a given tumour (see Figures 2 and 3). Note that incisional biopsy is still potentially useful for tumours amenable to wide excision. Here, it may provide information about the tumour's biological aggressiveness, which may sway a pet owner's decision to comply with your recommendation for curative-intent surgery.

Figure 1 details the initial decision-making process for a patient with a newly diagnosed tumour, assuming that the tumour has been sampled by fine-needle aspirate cytology. If cytology suggests cancer, then collecting biopsy samples for histopathologic confirmation of this diagnosis is of paramount importance. Ideally, the biopsy should also define the cancer grade (how malignant the tumour's behavior is likely to be). Low-grade tumours tend to grow slowly and metastasize with reluctance, and are curable with wide surgical excision. High-grade tumours, in contrast, grow rapidly and metastasize readily, and are rarely curable even with aggressive surgical excision.

When planning a biopsy, the clinician must decide whether to remove the tumour entirely via excisional biopsy or to perform an incisional biopsy and wait for the histopathology results before planning definitive therapy. An example of a tumour suitable for excisional biopsy is presented in Figure 2, while a tumour for which incisional biopsy may be more appropriate is presented in Figure 3.

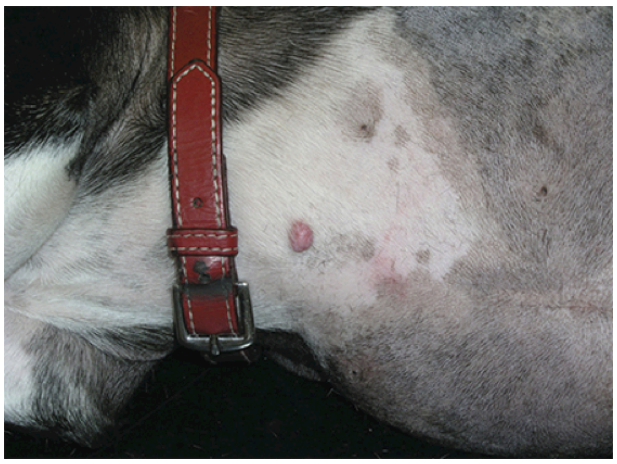

Figure 2. This low-grade cutaneous mast cell tumour makes this dog a candidate for excisional biopsy (Photo courtesy of Dr. Michael Childress)

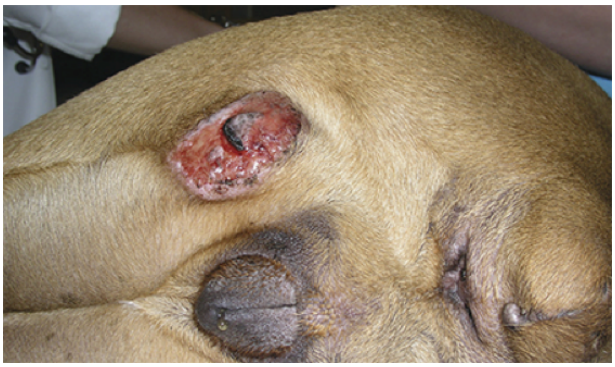

Figure 3. This high-grade cutaneous mast cell tumour makes this dog a candidate for incisional biopsy. (Photo courtesy of Dr. Michael Childress)

This tumour in figure 2, measuring approximately 1 cm in maximal diameter, is confined to the dermis and located over the lateral thorax. The dog owner noticed that it grew slowly to this size over many months. The size, depth of extension, and anatomic location make the tumour amenable to wide surgical excision. These features, along with the slow growth rate, further suggest a benign biological behavior. Collectively, these characteristics support the tumour's suitability for excisional biopsy.

This tumour in figure 3, measuring approximately 4 cm in maximal diameter, is palpably invasive to the subcutis and located over the caudal thigh, lateral to the vulva. The dog owner noticed that it grew rapidly over the past several weeks. It has an ulcerated surface, implying an aggressive biological behavior. As such, extensive surgical resection is likely necessary to provide durable local tumour control.

However, the proximity to the vulva and depth of invasion will limit the extent of surgery that can be performed. Because the tumour may be aggressive and local control may be difficult to achieve surgically, incisional biopsy is indicated prior to planning definitive therapy.

Although pet owners may baulk at the added expense of incisional biopsy, poorly planned excisional biopsies

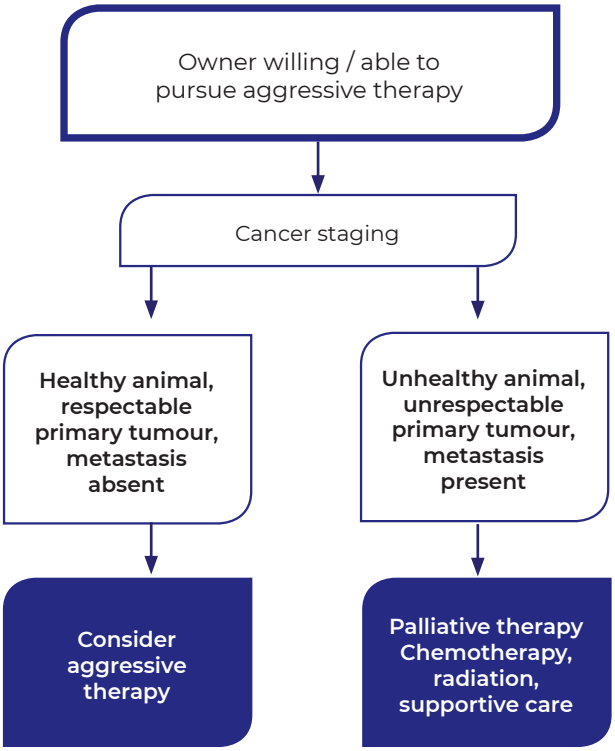

Figure 4, a decision tree for initial choices between aggressive and palliative therapy a tumour.

can lead to such serious complications as wound dehiscence and tumour recurrence. In patients in which an aggressive cancer is suspected, an incisional biopsy can provide valuable information as to what types of benefit may be derived from therapy as well as the extent of treatment necessary to achieve these outcomes. Many pet owners may, quite reasonably, forego surgical tumour removal if an incisional biopsy suggests the pet's prognosis for survival is poor.

Treatment choices are based on tumour stage and the patient's overall health. Healthy patients with low-stage cancers are the most appropriate candidates for aggressive therapy, while unhealthy patients with advanced-stage disease are candidates for palliative therapy

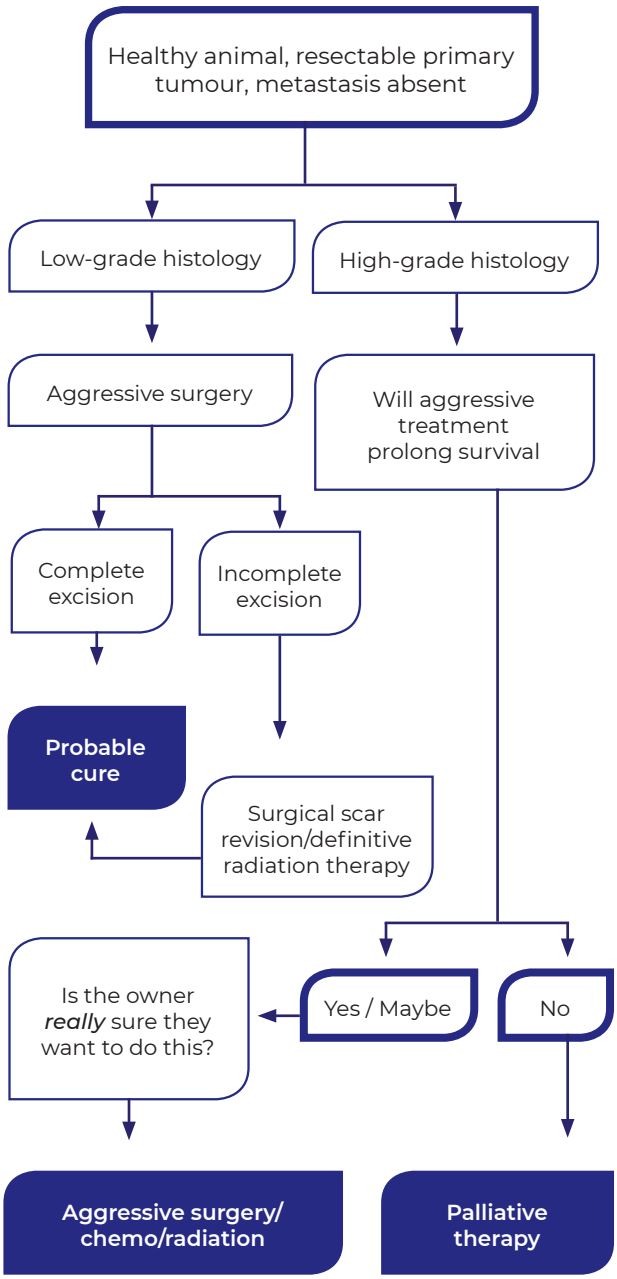

Figure 5, a decision tree on final decisions between aggressive and palliative therapy for a tumour.

When clients wish to pursue cancer treatment for a pet after a biopsy diagnosis, staging tests should be ordered to determine the extent of its cancer and its ability to tolerate therapy (Figure 4).

The staging process typically consists of a battery of diagnostic imaging studies to estimate the primary tumour's size and to screen for metastatic lesions. Laboratory tests typically are also performed to gauge the pet's overall health. Pets with no serious comorbid disease, resectable primary tumours and no evidence of metastatic disease are the best candidates for aggressive cancer therapy. Pets who don't meet these criteria should be considered more appropriate for palliative treatments.

For healthy patients with low-stage tumours, the decision to pursue aggressive therapy is further dictated by the histopathologic tumour type and grade. Indolent, low-grade tumours have the best chance to be cured by aggressive therapy. Aggressive, high-grade tumours may benefit from aggressive therapy, but are unlikely to be cured. Clear communication with pet owners on the goals of therapy is an essential prerequisite to pursuing aggressive treatment in patients with high-grade tumours. Since aggressive therapy may not extend survival and may produce serious side effects, palliative therapy may be a better option for many of these patients.

The final decision to pursue or forego aggressive cancer therapy takes information from both the tumour biopsy and the staging process into account (Fig. 5). Animals with low-grade, resectable, nonmetastatic tumours are ideal candidates for aggressive cancer surgery and are often cured of their cancers.

In contrast, animals with high-grade tumours are considerably less likely to be cured, even with aggressive, multimodal therapy. For these patients, the key question is, "Can aggressive therapy extend their lives to a greater extent than would be possible with palliative therapy?" For most high-grade cancers, aggressive therapy has yet to a show a clear survival advantage over palliative therapy. While an aggressive approach may still benefit some patients with these cancers, the decision to pursue aggressive therapy should only be made after careful discussion with your client.

With these principles in mind, usually it's possible to generate a treatment plan for pets with cancer that balances clinical benefit with treatment-related morbidity. Striking this balance is critical to affording a satisfactory outcome from treatment to both the patient and the pet owner. Moreover, it also honors that time-tested medical aphorism: Never make the treatment worse than the disease.

Michael O. Childress, DVM, MS, DACVIM (Oncology), is associate professor of comparative oncology at Purdue College of Veterinary Medicine

CPD Questions

Aggressive Versus Palliative Treatment in Pet Cancer and Histology & Immunophenotyping on Lymphnode and Spleen Samples

AC/2069/19

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01. Which one of the tumours listed below is most amenable to excisional biopsy?
a. slow growing mass
b. rapidly growing mass
c. ulcerated mass
d. mass on the distal limb
e. Client willing to go for curative therapy

02. Which one of the following is the MOST CORRECT definition of the term palliative treatment in veterinary oncology?
a. supportive symptomatic care for the terminal patient
b. the use of chemotherapy, surgery and radiation therapy with curative intent
c. Pain control in the pet with cancer
d. Lower dose chemotherapy or radiation to extend and improve quality of life
e. The use of alternative medications as a treatment option for the pet with cancer

03. Which one of the factors listed below is not a true risk factor for the development of lymphoma in dogs?
a. Breed susceptibility
b. Environmental toxins and pollutants
c. Dysfunctional immune system
d. Frequent vaccination
e. Electromagnetc fields

04. Which one of the following statements regarding canine lymphoma is INCORRECT?
a. Multicentric lymphoma occurs in about 75% of dogs
b. Middle-aged to older and medium-sized to larger dog breeds are more affected
c. Canine lymphoma mimics non-hodgkins lymphoma in humans
d. Sub-staging has little to no prognostic significance
e. WHO classifies canine lymphoma in five stages

05. The most recent literature classifies 5 most common lymphoma histiotypes. Which one of the 5 listed below is INCORRECT?
a. Indolent marginal zone B cell lymphoma
b. Peripheral T cell lymphoma
c. Lymphoblastic T cell lymphoma
d. FeLV-induced T cell lymphoma
e. Diffuse large B cell lymphoma

06. Which one of the methods listed below is most helpful in getting the best out of your lymph node biopsy?
a. The sample must be allowed to stand for at least 30 minutes before placing into formalin
b. The mandibular lymph nodes are most reactive so are the best ones to biopsy in generalised lymphadenomegaly
c. Tru cut needle biopsies are advantageous as they provide multiple areas of tissue to evaluate
d. Excise at least a third, but preferably remove the whole lymph node for histopathology
e. The lymph node sample must be cut in with a scissors to allow proper penetration of the formalin

07. Which one of the following statements regarding newer diagnostic methods for canine and feline lymphoma is CORRECT?
a. PARR is used when histopathology cannot reliably differentiate between lymphoid hyperplasia and lymphoma
b. Flow cytometry analyses different cell populations based solely on phenotype and differences in cell size and granularity
c. Immunocytology retains superior cell morphology and is therefore more reliable than immunohistochemistry
d. Immunohistochemistry will usually differentiate between a clonal and non-clonal population of lymphocytes.
e. Cytology and immunocytochemistry is sufficient to diagnose the most common histiotypes

08. Which one of the following statements regarding histological subtyping of lymphoma is INCORRECT?
a. Histological subtyping affects prognosis
b. Histological subtyping facilitates selection of the best treatment protocols
c. Histological subtyping allows for targeted research into specific tumour types
d. Histological subtyping can be made using an incisional biopsy of a lymph node
e. Histological subtyping cannot be made using cytology alone

09. Which one of the following statements regarding feline lymphoma is INCORRECT ?
a. T-cell lymphomas predominate in cats
b. Alimentary lymphoma is a common anatomic form in cats
c. Peripheral and/or visceral lymph node involvement is common in cats
d. Young cats < 2years old with generalised lymph node involvement often have lymphoid hyperplasia secondary to FeLV
e. Mediastinal lymphoma in FeLV negative Siamese cats can often be totally cured

10. Which one of the statements regarding the different histiotypes of lymphoma is INCORRECT?
a. Feline epitheliotropic small cell intestinal lymphoma is low grade and responds well to chemotherapy
b. Feline large cell transmural lymphoma is high grade and respond poorly to chemotherapy
c. Endoscopic biopsies are sufficient to differentiate IBD from intestinal lymphoma in cats
d. High grade nodal diffuse large B cell lymphomas are aggressive, requiring CHOP therapy
e. Nodal marginal zone lymphomas in dogs respond well to prednisolone and chlorambucil

Diagnosis and Management of Cutaneous Drug Reactions in Dogs and Cats

Prof Andrew Leisewitz
BVSc, MMedVet(Med), PhD
Senior Lecturer
Department of Companion Animal Clinical Studies
Faculty of Veterinary Science

Adverse drug reactions (ADR) are common in human patients. It is estimated that ADR occur in approximately 10-20% of hospitalised human patients. Approximately 300 000 people are hospitalised annually in the USA as a result of ADR and it is considered to rank as the 4th to 6th most common cause of death in hospitalised humans.

The incidence of ADR in the veterinary population is much harder to establish. Although with the increase in the number of companion animals receiving veterinary care and the increase in the number of drugs used in this population, ADR are likely to become increasingly common. Almost all are self-limiting and resolve with removal of the offending drug. In rare instances, the reaction can be very severe and even result in death. Toxic epidermal necrosis (TEN) carries a 30-40% mortality rate in humans and close a 0% survival rate in veterinary medicine.

Adverse reactions are divided into either dose dependent and those that are regarded as idiosyncratic reactions. In dose dependent reactions, the adverse response is directly associated with the dose of the drug causing the reaction and the clinical signs are known adverse reactions to the drug. The event is directly related to chemistry of the drug or its metabolites. These are relatively common, could happen to any animal and are predictable.

Idiosyncratic reactions on the other hand are independent of the drug dose and are not a direct consequence of the drugs physical or chemical properties. These are relatively uncommon and unpredictable. The pathogenesis of these reactions is poorly understood but hypersensitivity reactions (typical of what is associated with allergy) are thought to play a major role in these adverse events. This brief review will focus on adverse cutaneous events although it is worth remembering that ADR may also be associated with hepatotoxicity, blood dyscrasias and other organ pathology.

Pathogenesis

Immune mechanisms are the most important pathogeneis and they are typically classified according to the Gell and Coombs system. The antigen in this case is the drug or its metabolite or a drug metabolite – protein complex.

1. Type I hypersensitivities

These reactions are characterised by rapid development (minutes to hours). The components of a type I hypersensitivity include antigen bound IgE which then interacts with an Fc receptor on mast cells and basophils causing their degranulation and subsequent inflammation. Examples of type I hypersensitivities include angioedema, urticara and anaphylaxis. These reaction types are common.

2. Type II hypersensitivities

This is a non-immediate reaction that is IgG and IgM dependent and is sometimes referred to as cytotoxic. Antibodies are bound to an antigen present on a cell membrane surface which then results in cell damage or lysis, often involving the complement cascade. Examples include

drug induced pemphigus and immune mediated haemolytic anaemia or thrombocytopaenia.

3. Type III hypersensitivity
These are also non-immediate type reactions and are IgG mediated. Antigen – antibody complexes form which then deposit on blood vessel endothelial surfaces resulting in a vasculitis. Examples include systemic lupus erythematosus and other lupoid type reactions, vasculitis, glomerulonephritis and polyarthritis.

4. Type IV hypersensitivity
These are cell mediated reactions and are also classically delayed (up to 2 weeks). Antigen specific T cells bind cognate antigens, become reactive, release cytokines and thus mediate tissue damage recruiting macrophages, cytotoxic T cells and other cell phenotypes. Examples include erythema multiforme, TEN and contact dermatitis.

There are currently four different theories which attempt to explain drug hypersensitivity pathogenesis:

1. (Pro)-hapten hypothesis
This theory postulates that because drug molecules on their own are too small to result in an immune reaction, they bind to a tissue protein and the complex of drug-tissue protein is then the immunogenic molecule. The tissue protein is called a hapten. The hapten-drug complex is taken up by antigen presenting cells (APC's) and presented within the context of a MHC-II molecule on the APC's surface to T cells. These T cells are activated, proliferate and induce an immune response which is then injurious to host tissues. In a case series of 34 dogs that had a sulphonamide hypersensitivity reaction, 50% of these dogs were shown to have anti-sulfonamide antibodies.

2. Danger theory
A general principle in immunology states that the hosts immune system should be tolerant of self and intolerant to non-self. The danger theory emanates from the idea that it is not 'foreigness' itself that elicits an immune response (as for example, the gut is full of foreign material but the immune system is tolerant of these molecules), but rather a 'danger' signal elicits an immune response (such as cell debris, the products of oxidative injury or of inflammation). The mechanisms whereby a drug could trigger such a 'danger cascade' are not well worked out. Many drugs associated with ADR are however known to induce the formation of products from oxidative injury. It is thus quite possible that drugs or their metabolites could be associate dwith the formation of so called 'danger signals'.

3. The Pharmacological Interaction (PI) concept
This concept proposes that a drug can directly interact with the MHC II molecule or T cell receptors in a non-covalent fashion and in this manner induce a potent immune reaction. This mechanism is similar to what is seen in the response to so called 'super antigens' which have the capacity to indiscriminately activate the immune system.

4. Viral reactivation
This proposed mechanism suggests that there is a relationship between viral diseases and drug allergies. Underlying viral infections (such as Herpes) may increase an individual's susceptibility to an ADR through virus specific T cells.

Common clinical presentations

Drug hypersensitivities can look like almost any skin reaction and can affect any body surface area (Fig 1 and 2) . Specific clinical signs cannot be attributed to specific drugs as each drug may elicit any number of different clinical signs depending on the individual patient.

Biopsy is frequently not collected in less severe cases and as such diagnosis is frequently circumstantial based on acute presentation and resolution following removal of suspected drugs.

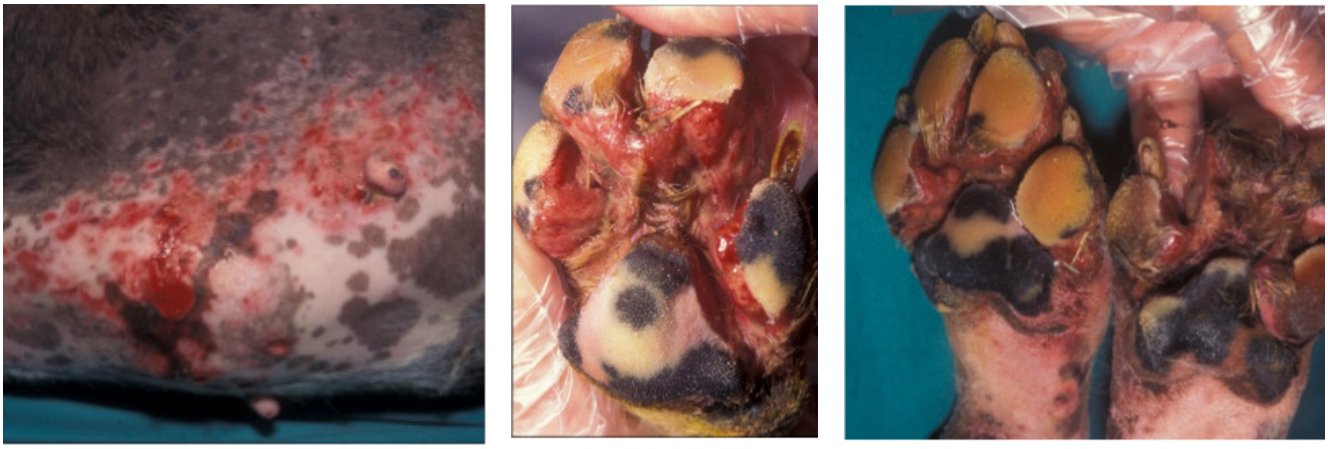

Fig 1. An adverse drug reaction to an orally administered cephalosporin. The images represent the healing phase of the disease after the drug had been withdrawn.

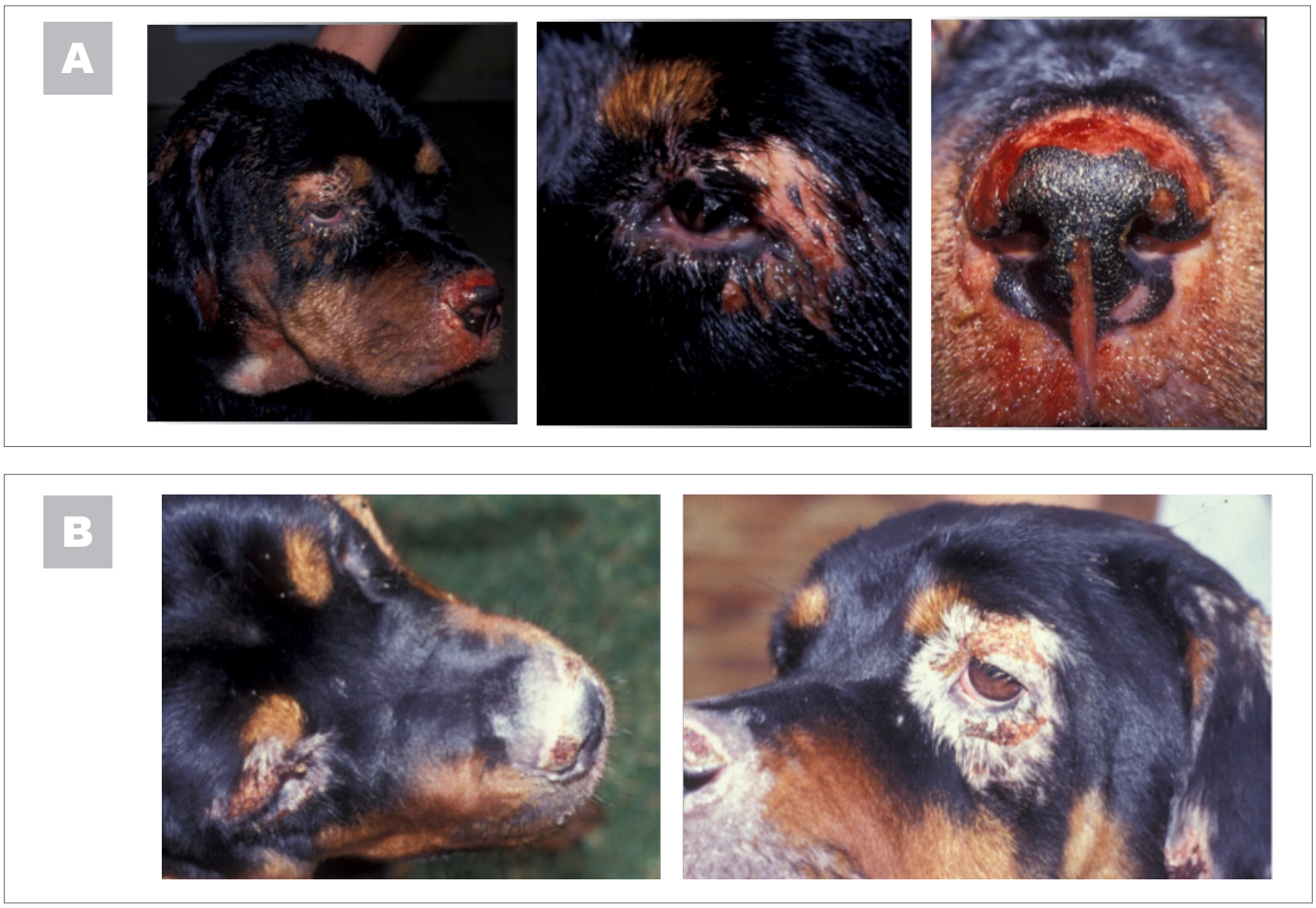

Fig 2 (A) cutaneous adverse drug reaction to a topically applied ear polypharmacy agent. A: the skin rapidly developed a moist exudadtive dermatitis around the head with alopecia. A biopsy was not performed. (B) Upon withdrawal of the drug, the skin healed over several weeks but with permanent depigmentation and scarring.

1. Urticaria and Angioedema

These lesions result from the degranulation of mast cells and basophils and are Type I reactions. The typical primary lesion is a hive or wheal (Fig 3). In the case of urticaria the lesion is restricted to the dermis (Fig 4). In angioedema the reaction involves subcutaneous tissues making this presentation much less distinct. Urticaria are most easily observed on the glabarous body surfaces and are usually present for less than 24 hours once the offending drug has been removed. Agioedema is usually observed on the face and lips. Pruritus is variable.

Drugs associated with these reactions include penicillin, ampicillin, tetracycline, vitamin K, propylthiouracil, amitraz, ivermectin, moxidectin, radio-contrast media, vaccines, antivenoms, foods and some shampoos. These reactions are very unusually seen in cats.

2. Pruritus

This is common and may be the only manifestation of an ADR. The mechanism and mediators are those of a type I hypersensitivity. The initial presentation is usually a symmetrical pruritus without lesions. In one veterinary series of 101 dogs with cutaneous ADR, 11.9% presented as primary pruritus. Methimazole has been seen to induce facial pruritus in up to 15% of cats.

3. Lupus-like (Lupoid) drug reactions

Allergic drug reactions may mimic the skin signs associated with SLE. The skin findings include erythema, depigmentation, scaling, crusting, erosion, and even ulcerations and alopecia. Mucocutaneous regions may be involved. If a vascular lesion is present then the ear tips, foot pads and prepuce may be involved. The disease may also present with other findings that typify SLE (such as thrombocytopaenia, anaemia and protein losing nephropathy). In dogs sulfonamides, primidone and vaccines have been reported to trigger SLE.

4. Pemphigoid or Pemphigus like drug reactions

This ADR mimics what is classically seen with pemphigus foliaceus. In a drug induced pemphigus, the disease resolves when the drug is withdrawn. There is a sub-group of cases (so called 'drug triggered' pemphigus) in which discontinuation of the drug does not result in resolution of the disease. The distinguishing features of drug induced pemphigus may include an unusually rapid onset of disease, unusually young animals affected and lesions not typical for pemphigus (such as oral ulcerations). Drugs with a reported association with this manifestation include sulfonamides, oxacillin and cephalexin. It should be remembered that topically applied acaricides may also induce this disease. More severe

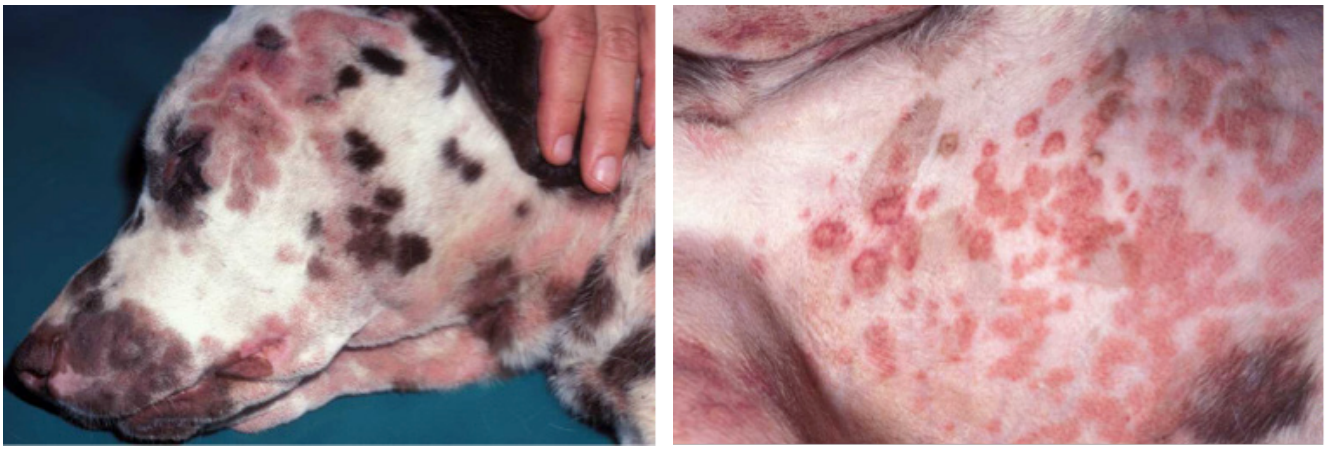

Fig 3. An urticarial reaction in the skin as a result of a dietary allergen. The disease relapsed with exposure to a particular commercial food and resolved when the dog was fed a single novel protein diet.

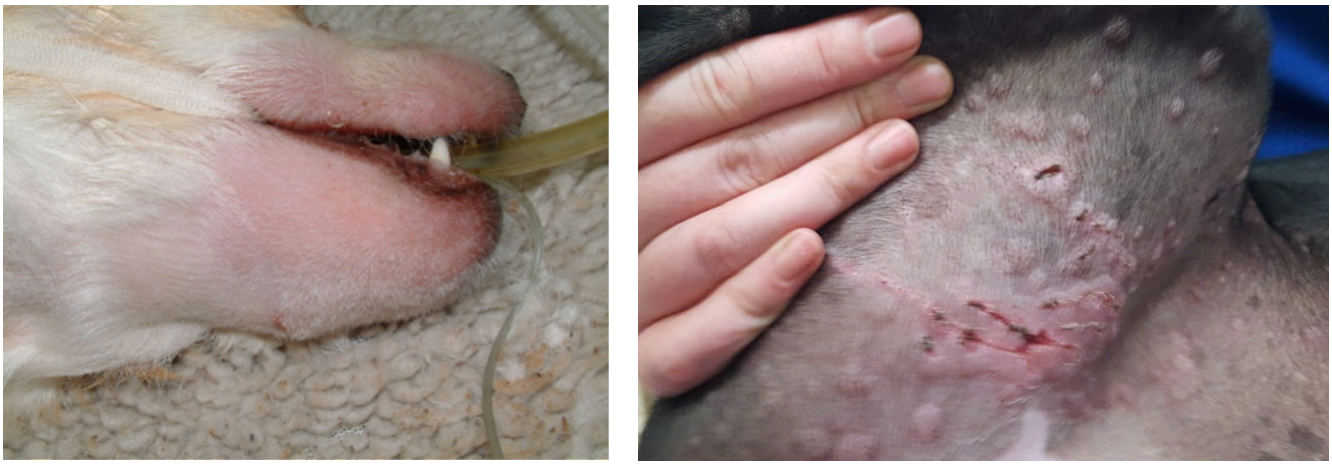

Fig 4 (A) Facial angioedema in a dog following the intravenous use of the South African polyvalent snake bite antivenom (B) Generalised urticaria immediately post injection with an IV cephalosporin.

forms of pemphigus (*pemphigus vulgaris*) have also been reported to be drug associated.

5. Vasculitis

An immune mediated, perivascular, neutrophil rich infiltrate has been associated with ADR. It is typically understood to be a type II hypersensitivity. A wide spectrum of disease has been reported from single organ involvement to multi-organ involvement with death. The skin findings include oedema, erythema, petechial bleeding, erythematous plaques, skin necrosis and ulceration (Fig 5). Areas of poor collateral circulation are more commonly involved and include the ear tips, foot pads, tail tip and over boney prominences. The more severe the lesions the more likely pain will be part of the presenting complaint.

6. Fixed drug eruption

These are well circumscribed erythematous lesions that begin as oedematous plaques and progress to bullae which may rupture leaving an ulcer. The hallmark feature of a fixed drug reaction is the repeated formation of the same lesions in the same place upon repeated drug exposure.

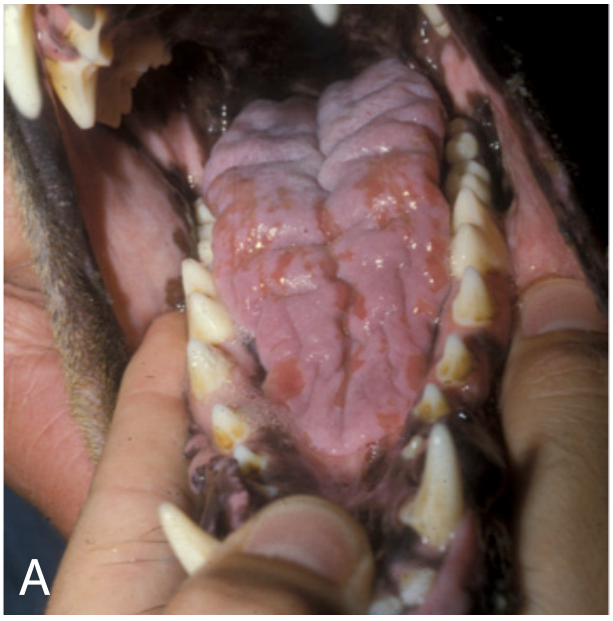

Fig 5 A-C. A case of idiopathic vasculitis that may have been precipitated by an adverse reaction to a drug. The disease resulted in a zone of well delineated er tip necrosis, ulcerative glossitis and depigmentation of the pads.

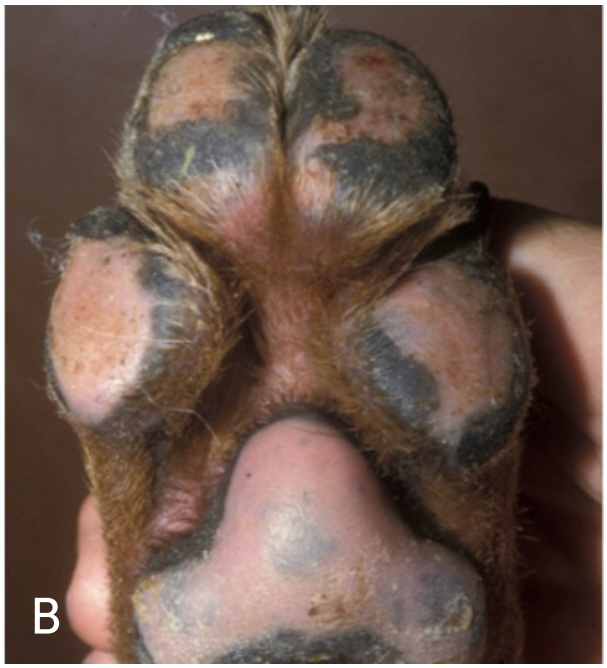

Fig 5B

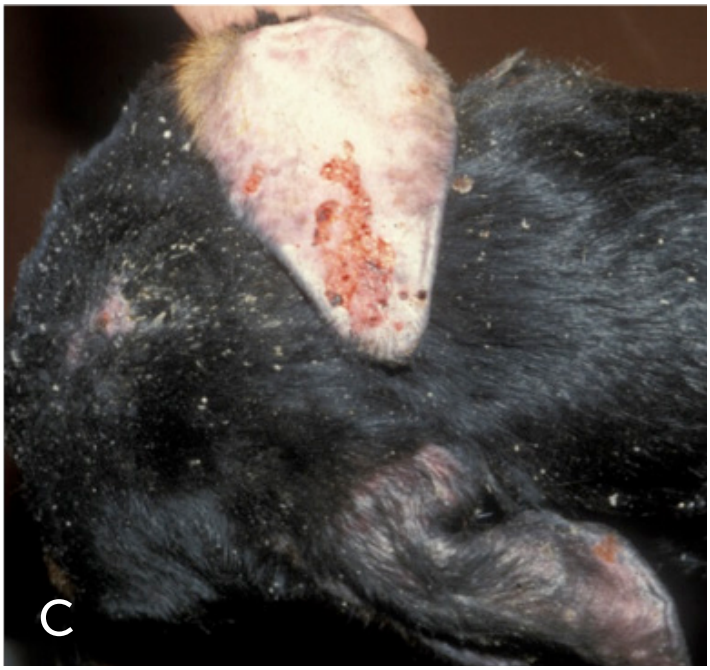

Fig 5C

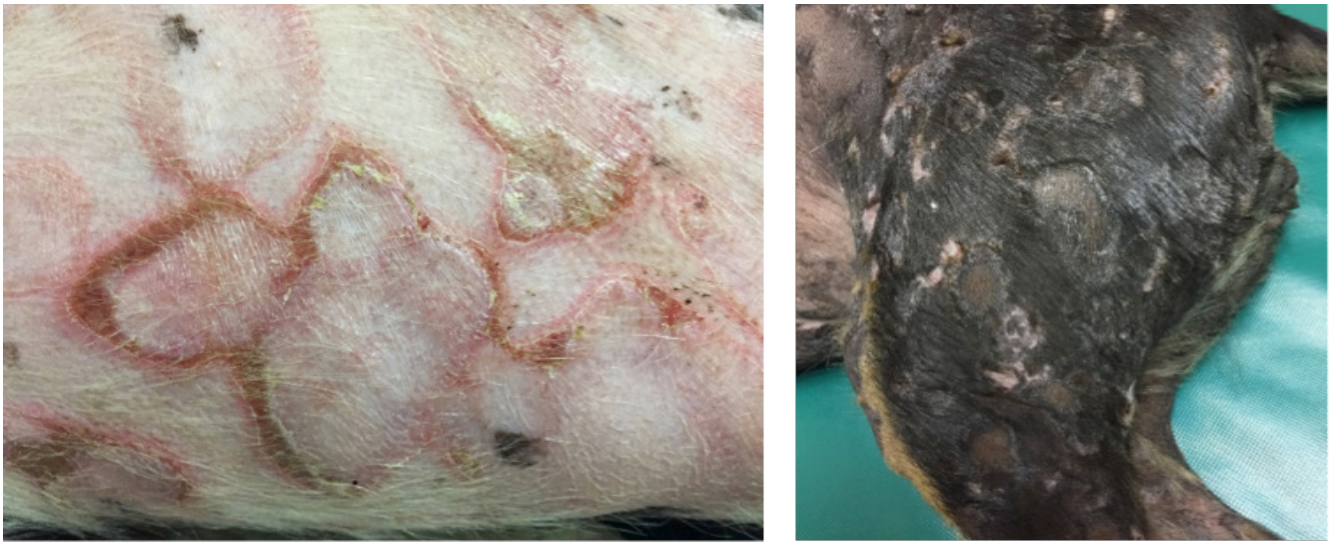

Fig 6. A case of Erythema Multiforme confirmed histologically. The dog had been on several non-essential medications, all of which were withdrawn, and he made a full recovery.

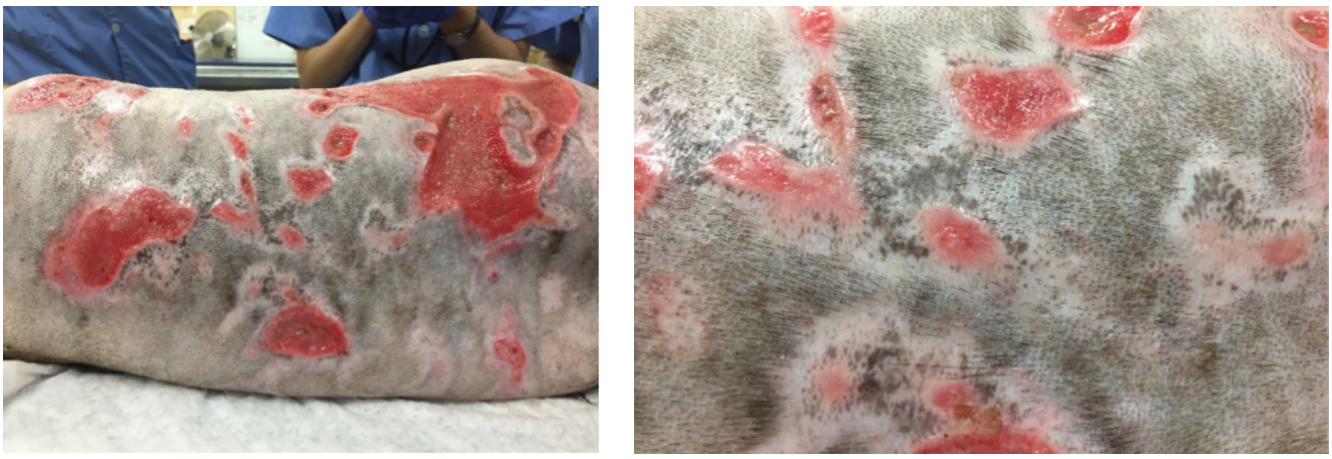

Fig 6. A case of suspected Erythema Multiforme in a dog which had received penicillin treatment post-operatively.

7. Erythema Multiforme (EM)
This is an uncommon skin disease with a very variable clinical presentation. There are many putative eatiologies – including drugs. It is believed to be a type II hypersensitivity reaction in which lymphocytes mount an immune response to keratinocytes carrying drug-protein complexes. This results in the classic single cell apoptosis observed histologically with this disease. Ulceration may be substantial and may even involve oral mucous membranes (Figures 4 5 and 6). Pain may be a feature.

Drugs associated with EM include sulfonamides, cephalexin, chloramphenicol, gentamicin, penicillin, levamisole and levo-thyroxine. Some breed may be predisposed (German Shepherds, Welsh Corgi, Old English Sheepdogs, Chows).

8. Toxic Epidermal Necrolysis (TEN) and Stevenson-Johnson Syndrome (SJS))
This disease is characterized by detachment of the epidermis from the dermis at the basement membrane over large tracts of the body surface. TEN typically involves more than 30% of the body surface, whilst SJS is less severe involving less than 10% of the body surface. Both conditions are rare and serious – in many cases becoming life threatening.

A rapid necrosis of the skin and stripping of the epidermis predisposes the patient to sepsis and fluid and protein loss. Almost all cases of TEN and SJS are drug associated. The pathogenesis is believed to be associated with cytotoxic T-cell mediate keratinocyte apoptosis of large numbers of keritinocytes with the parallel release of large amounts of pro-inflammatory cytokines (particularly TNFa).

Widespread erythema is followed by necrolysis and sloughing of the skin surface even with gentle contact (such as clipping of the hair). The skin is typically very painful. Mortality in humans approaches 50% of cases even with advanced treatment in burn wound wards. In veterinary patients death is almost certain and usually occurs within 2 days of the onset of signs.

Drugs which are associated with this disease include flea dips, sulfonamides, penicillin, cephalexin, griseofulvin, levamisole, quinolones, cephalosporins, NSAIDS, allopurinol and glucocorticoids.

9. **Miliary dermatitis** in cats me be a reaction pattern associate with an ADR. **Injection site sarcomas** are also regarded as an adverse event in cats seen with some vaccines.

The Recognition and Diagnosis of ADR

History and physical examination
History and physical examination are crucial to diagnosis and eliminating the possibility of an ADR from the differential list. The client should be carefully questioned about all previous drug use (both systemic and topical and this should include all compounds not just allopathic medications). The time interval between medication and the appearance of clinical signs is important. Because drug allergies are not all immediate, even chronically used medications should be considered possible culprits. Previous use of the same drug may also be important as, being an immune reaction, earlier sensitization may well have played a role. This is especially true in skin disease that has evolved very acutely.

Many clinicians are familiar with the role antibiotics may play in ADR and as such may inadvertently ignore non-antibiotic drugs. The physical examination should be complete but special focus on the skin is warranted. This would require a careful look at oral mucous membranes, mucocutaneous junctions ear canals and foot pads. Diagnosis is complicated by the plethora of cutaneous reaction patterns that may be caused by ADRs and the way these patterns may mimic more common diseases. This means that an ADR may well be part of the differential list for a very wide range of presentations. Ruling out other more common diseases is thus important.

Complete blood count and biochemistry
The more severe a skin disease the more important a complete blood count and serum biochemistry profile becomes. It is rare that these evaluations are very contributory to diagnosis but findings that may be associated with malignancy or systemic immune mediated disease (such immune mediated haemolytic anaemia, thrombocytopaenia, renal failure and proteinuria, hepatotoxicity) are important. Eosinophilia is a common finding in ADR that have an allergic basis. Hypoproteinaemia may be seen in cases of excessive dermal suppuration.

Histopathology
This is especially important in cases that are severe. Punch biopsies are usually sufficient but it is very important to collect a full range of lesions (from very early subtle primary lesions to advanced secondary lesions). Sometimes collection of an elliptical excisional biopsy that includes an interface between affected and non-affected skin may be helpful. Histology may on occasion be as difficult to interpret as the clinical presentation as the microscopic reaction pattern may be as non-pathognomonic as the clinical presentation.

Dechallenge and rechallenge
The most commonly performed diagnostic test is removal of the potentially offending agent (dechallenge). Most would make a presumptive diagnosis of an ADR upon resolution of the skin signs following dechallenge. This is cost effective and usually very helpful diagnostic approach. A patient on multiple drugs at the same time can be more challenging to diagnose this way. One approach to this problem is to discontinue all drugs, wait for resolution of disease

and then rechallenge one drug at a time (starting with the drug least likely to be a problem). Alternatively, the drugs most likely associated with ADR can be removed first, one at a time. This is helpful only in patients that do not have serious disease or that are on critically important medications.

The gold standard of diagnosis is rechallenge with the suspected drug culprit. This is not something that many practitioners are enthusiastic about and careful consideration should be given to the seriousness of the disease caused. It must also be remembered that a second exposure to a drug to which a patient has become sensitised to may result in a significantly more serious disease (even an anaphylaxis and death). Rechallenge should thus not be performed except in those cases where it is absolutely necessary (the patients long term outcome depends on the continued use of the suspected drug where there are no alternatives). If done, it should only be performed in a hospital environment where immediate intensive care facilities are available.

There are various other more academic methods that have been explored to diagnose ADR. These include antibody testing to determine total IgE titers which if elevated, may strengthen the suspicion of type I hypersensitivity. Anti-drug IgG titers have also been explored. Lymphocyte transformation testing has been evaluated for delayed type hypersensitivity reactions.

Management of cutaneous adverse drug reactions

Supportive care

Almost all adverse drug reactions are not life threatening and will resolve on simple dechallenge. In these cases treatment is supportive based on clinical signs. Severe disease will necessitate more robust support in the form of IV fluids, colloidal support (especially in the case of hypoproteinaemia) and antibiotic treatment to treat or prevent sepsis. Antibiotic choice should be from a class of drug unrelated to any antibiotic that may be suspicious as the catalyst for the disease. Where pain is a feature (such as with TEN or pemphigus), analgesia should be applied. Other supportive measures may be required where other organs are involved (such as in the case of blood transfusion in immune mediate haemolytic anaemia).

Anti-inflammatory and Immunosuppressive Treatment

In some cases, antihistamines may be beneficial in Type I reactions. This may assist in cases of intense pruritus due to allergic reactions. The use of glucocorticoids in ADR is controversial. Higher doses that are immunosuppressive (2 – 4 mg/kg daily) suppress both cellular and humoral immunity. In cases of drug induced pemphigus that do not resolve with dechallenge, long term glucocorticoid use will be required to control signs. Other immune mediated ADRs treated with glucocorticoids have resulted in mixed responses that are very patient specific.

Typically, both systemic and topical glucocorticoids are used. The dose, how long they are required and how quickly they can be tapered must be individualised depending on patient response, comorbidities and steroid associated side effects. Clinicians must be mindful of the increased risk of sepsis (especially in TEN and SJS) when glucocorticoids are used. Other immunosuppressive drugs used have included azathioprine and cyclosporine in more severe skin disease such as in cases of pemphigus, EM and TEN that fail to respond well to dechallenge. It should be remembered that both of these drugs have a significant lag period between administration and peak therapeutic benefit so an immediate benefit should not be expected.

Human intravenous immunoglobulins have been used in cases of TEN and EM with some success. It must be emphasized that the number of cases treated with these drugs are small (restricted to uncontrolled case reports) and as such the evidence for efficacy is weak.

Longer term Considerations

If a drug hypersensitivity is diagnosed or strongly suspected, the drug must be avoided for the rest of that animal's life. Re-exposure, even in small amounts, may well result in devastating disease as a result of an anamnestic immune response. Drugs with related chemical structures should also be avoided. For example, sensitivity to cephalosporins may well translate to a hypersensitivity to all drugs containing a beta-lactam ring (although this is unusual). Should an adverse reaction to a drug be suspected, it is important to remember that the reporting of that adverse event is important.

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CPD WEBINAR MORE INFO www.vetlink.co.za/webinar

Canine and Feline Pododermatitis

Pododermatitis is defined as inflammation of the skin of the paw(s). Affected tissues may include interdigital spaces, footpads, nail folds (paronychia), and nails. Pododermatitis is often seen in general practice and one of the more challenging manifestations of skin disease, both in terms of establishing a definitive diagnosis and providing effective care. This webinar will look at the different causes, discuss a diagnostic approach and general treatment and discuss the more common causes such as pododemodicosis, allergic pododermatitis, infectious pododermatitis, interdigital follicular cysts (also known as sterile pyogranulomatous pododermatitis), hepatocutaneous syndrome and feline plasma cell pododermatitis in more detail.

Dr Heidi Schroeder
Small Animal Specialist Physician BVSc MMedVet(Med)

Dr Heidi Schroeder obtained her BVSc degree in 1988 and her MMedVet(Med) degree in 1994, both from the Faculty of Veterinary Science, Onderstepoort. She was a senior lecturer in the Small Animal Medicine Department, while completing her specialist degree. She left the University in 1996 to start a Small Animal Medicine referral practice in Pretoria. She has a special interest in Dermatology and attends to many dermatological referral cases. She has been lecturing to veterinarians all over South Africa on a variety of dermatological topics and has written several CPD articles on various dermatology topics. She is a co-founder of the South African Veterinary Dermatology Interest group which aims to promote dermatology in South Africa.

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The ABCs of Veterinary Dentistry

'Q' is for Quality, not Quantity

Has the flurry of dental appointments that accompanies Pet Dental Health Month compromised the careful dental care of our patients? Let's take a look at the true meaning of Q in veterinary dentistry.

Jan Bellows, DVM, DAVDC, DABVP, FAVD

In 1993, the president of the American Veterinary Dental Society, Ken Capron, DVM, FAVD, DAVDC, wanted to draw attention to the dental needs of dogs and cats. To raise awareness, Dr. Capron created Pet Dental Health Month, which takes place every February. Two years later, Hill's Pet Nutrition added much-needed national marketing, which continued for 25 years. With the help of Hill's, Robert Wiggs, DVM, DAVDC, spoke on national television in over 22 cities in the United States about National Pet Dental Health Month.

What initially began as a campaign for dental awareness, Pet Dental Health Month in some practices has morphed into discounted dentistry to bring clients and their pets into veterinary offices in the prime of winter. Some hospital administrators gauge the health of their practices based on how many "dentals" are performed in February. This is far from the original intention of Drs. Capron and Wiggs.

All of this to say—squeezing in numerous discounted dental cases where veterinary assistants remove plaque and calculus from the crowns of teeth without conducting a tooth-by-tooth evaluation, including probing and intraoral radiographs and treatment of all periodontal pockets, is the practice of quantity, not quality medicine.

Achieve quality with COPAT

The challenge is incorporating quality dentistry into everyday practice. How do you focus on quality over quantity of dental cases without harming the hospital's bottom line by doing fewer cases? Answer: By adopting COPAT—comprehensive oral prevention, assessment and treatment.

Prevention involves measures taken to prevent the development or progression of oral disease by means of routine oral examinations, professional dental cleanings, home oral hygiene, etc. The COPAT visit is not complete until you discuss with the client how to keep their pet's mouth clean and how to minimise recurrence of disease.

Assessment is the collection and analysis of data to identify the patient's needs and includes obtaining a patient history from the owner and performing a physical examination of the conscious patient, laboratory and other tests to determine patient health and anesthetic risks, and a tooth-by-tooth intraoral examination including diagnostic imaging while the patient is anaesthetised.

Treatment is the oral care recommended and performed by a professional based on the findings from the anaesthetised tooth-by-tooth and oral cavity examination. The client's input is important in order to tailor individual treatment plans based on the exam findings and the client's financial ability and willingness to provide home care for further prevention.

Executing the perfect setup

The COPAT appointment is made based on the veterinarian's recommendation during a general examination or when a client calls concerned with oral malodour. The receptionist booking the appointment should discuss the process—patient examination,

preanaesthetic testing, general anaesthesia, tooth-by-tooth examination including probing and intraoral radiographs, dental scaling, polishing, treatment of pathology, sealant application, and prevention recommendations.

Generally, drop-off appointments are not recommended for the initial conscious examination. It helps for the client to be present while the veterinarian initially examines the mouth. The receptionist should also explain that further care recommendations will be discussed with the pet owner after the veterinarian examines the teeth and oral cavity while the dog or cat is anaesthetised. If time is not available to treat discovered pathology, or if the client wishes to consider treatment options longer, the cat or dog should be recovered from anaesthesia and a future appointment made to complete treatment.

Fees for the visit should be discussed by the receptionist when booking the appointment. Keep in mind, the receptionist cannot tell the pet owner what the final charges will be to care for the patient without the anaesthetised diagnostic doctor examination. Expenses for what is known, such as preanaesthetic examination, preanaesthetic tests, anaesthesia, monitoring, dental scaling, polishing, sealant application, and dental radiographs, can be quoted. The pet owner should be advised there will be additional fees to care for any potential pathology found, which would be discussed before additional therapy is provided.

Before the patient goes under ...

Unless a recent examination has been conducted, the veterinarian usually performs a general physical examination with the client present. This exam typically includes as much of an oral assessment as the patient will allow. It's important that the examination be conducted in a fear- and pain-free manner.

The extent of an examination on a nonsedated animal depends on patient cooperation and expertise of the examiner and assistant. Most dogs and cats will allow an initial evaluation of their teeth and oral cavity when approached in a slow, gentle manner. Some are too fractious to inspect without chemical restraint, which can be accomplished in the exam room setting or during general anaesthesia. Periodontal probing should never be done in an awake patient.

The gingival margin lies next to the tooth coronal to the attached gingiva. Healthy gingiva appears light-pink. Gingival inflammation clinically presents as erythema and is often accompanied by rounding of the originally knife-edged gingival margins. As periodontal disease progresses, tooth roots may be exposed secondary to gingival recession.

Exam findings and the plan for the day are shared with the client together with a printed list of estimated fees for the assessment (preoperative blood/urine/heart/radiographic tests based on age and condition; dental probing; and intraoral radiographs), teeth cleaning, polishing and irrigation with sealant application. The client is given a time to return to the office to learn what additional care is needed or a callback time to discuss findings and the treatment plan after the tooth-by-tooth examination (Figure 1).

The patient is anaesthetised and monitors attached. Teeth are scaled, crowns are polished, and the gingival sulcus is irrigated to remove plaque and calculus. Full-mouth radiographs are taken and prepared for the veterinarian to examine. The veterinarian or technician performs a tooth-by-tooth exam, noting missing, fractured or mobile teeth and periodontal pockets. All abnormal findings are charted, providing a graphic report of the pet's teeth and mouth in order to develop an accurate and comprehensive treatment plan

While the patient is under ...

The patient is anaesthetised and monitors attached. (Figure 2)Teeth are scaled, crowns are polished, and the gingival sulcus is irrigated to remove plaque and calculus. Full-mouth radiographs are taken and prepared for the veterinarian to examine. (Figure 3) The veterinarian or technician performs a tooth-by-tooth exam, noting missing, fractured or mobile teeth and periodontal pockets. All abnormal findings are charted, providing a graphic report of the pet's teeth and mouth in order to develop an accurate and comprehensive treatment plan.

Don't forget this while the patient is out

Once the tooth-by-tooth therapy plan is generated, contact the client to discuss and gain approval. In cases where time doesn't permit treatment after dental scaling and diagnostics, appointments are made for future care (Figure 4).

Figure 1: An assessment of a patient's teeth.

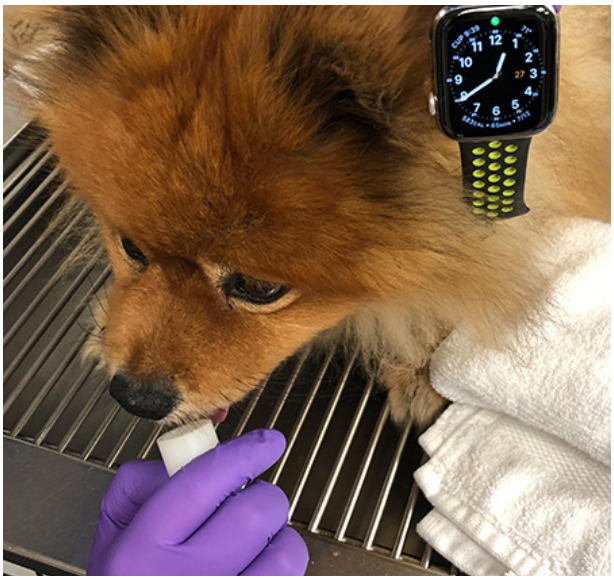

Figure 2. A patient being preoxygenated before anesthesia.

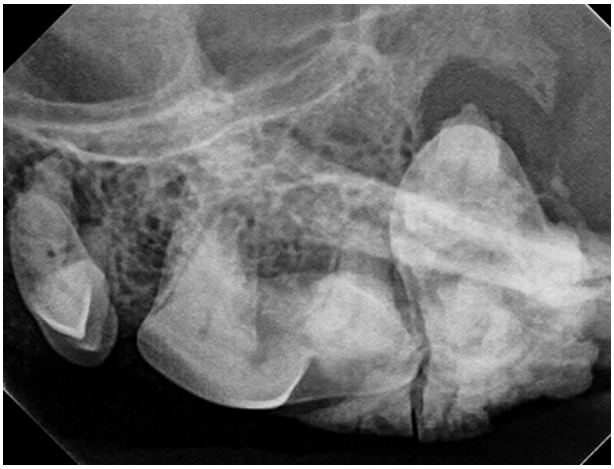

Figure 3. Left maxillary cheek teeth radiographs revealing advanced periodontal disease affecting the third premolar and first molar teeth.

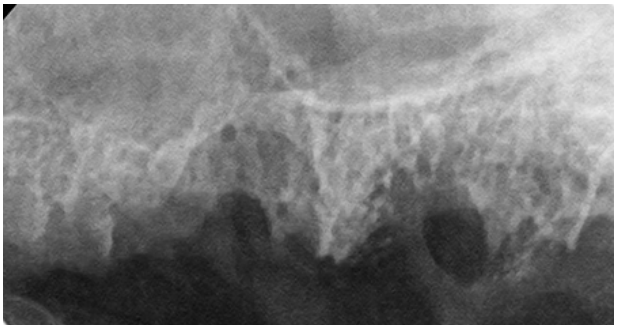

Figure 4. Postoperative intraoral radiographs of the left caudal cheek teeth confirming complete removal of all hard dental tissue.

Before you go ... thoughts after surgery

At the completion of surgery, postoperative intraoral radiographs are taken and examined for remaining dental hard tissue (Figure 4). The patient is recovered with continuous monitoring. (Note: Most adverse anaesthesia events occur during the postoperative period). After the patient fully recovers, the dental chart is completed and a report is generated to review with the client (Figures 5-6).

Dental home care highlights for clients

One of the challenges in veterinary dentistry is diminishing the accumulation of plaque and calculus after the COPAT visit.

Before periodontal treatment is initiated, talk with pet owners about their commitment and ability to provide aftercare. There is little reason to perform intermediate or advanced periodontal surgical procedures if the pet owner will not, or cannot, actively participate in ongoing plaque control. If there is little to no commitment to home care and follow-up examinations, it's better for the veterinarian to extract teeth affected with stage 3 or 4 periodontal disease.

After the professional oral hygiene visit, schedule weekly progress examinations until the owner is comfortable with the home care process. Thereafter, recheck advanced periodontal surgical cases every two to three weeks and, eventually, less frequently.

Pets that have been treated for stage 1 or stage 2 periodontal disease and whose teeth are brushed or wiped once or twice daily can be reexamined every three months. The automatic reminder interval for recalls can be linked by the practice's software to the degree of periodontal disease (i.e. if the patient is treated for stage 3 periodontal disease, a monthly progress reminder can be automatically generated).

The sweet spot: Quality and quantity

Quality dentistry takes more time to deliver than quantity dentistry. But with at least 80 percent of adult dogs and 70 percent of cats nationwide suffering from periodontal disease, there is a lot of quality dentistry that needs to be delivered. Invest the time and resources to find the cause of your patient's halitosis. As a result, the proper therapy will generally be approved and charged accordingly. Charge what you need to keep the patient and hospital healthy.

The Dental Top 10

Options for basic and advanced dental care

1. Future follow-up within six to 12 months after dental scaling in cases where pathology is found in a pain-free, functional mouth.

2. Dental scaling, irrigation, polishing and application of professional plaque barrier gel or sealant in cases of stage 1 gingivitis (inflamed gingiva without evidence of support loss) and stage 2 nonpocket periodontal disease (< 25 percent support loss) as evidenced by gingival recession.

3. Local antimicrobial administration: Clindoral (Trilogic Pharma) and Doxirobe (Zoetis) may be helpful in periodontal disease stage 1 bleeding on probing areas, stage 2 and stage 3 (25 to 50 percent support loss) where there are periodontal pockets from which plaque and calculus have been removed and where the pet owners can provide home care to control periodontal disease progression. Locally applied antimicrobials are not indicated in deep infrabony pockets and should not be administered without first taking and examining intraoral radiographs.

4. Periodontal surgery to save teeth if the tooth and patient are appropriate. Operculectomy (removal of the gingiva over an unerupted tooth crown) is indicated in a young dog or cat (less than 8 months old) where the tooth is expected to fully erupt in normal alignment once the obstructing gingiva is excised. Open-flap surgery for cleaning and débridement is used to expose a tooth root in selective cases where the periodontal pocket extends greater than 5 mm and the client is committed to providing home care to save the pet's teeth despite a guarded prognosis. Gingivectomy can be performed to remove pseudopockets in cases of focal or generalized gingival enlargement.

5. Vital pulp therapy is performed to treat a recent (less than 48 hours) crown traumatic fracture that has penetrated dentin exposing the pulp. Vital pulp therapy and crown restoration can also be performed after reduction of crown height for the treatment of tooth malposition causing gingival trauma.

6. Root canal therapy is often the treatment of choice for end-stage pulp disease secondary to fracture, chronic pulpitis or caries. Therapy planning must consider the age of the animal, duration of pulp exposure, importance and condition of the tooth and periapical structures.

7. Crown reduction with gingival closure can be used to treat type 2 root resorption. Crown reduction and restoration can also be used to alleviate a traumatic occlusion.

8. Orthodontic care can reposition teeth into functional occlusion. An inclined plane fabricated from acrylic composite or metal can move linguoverted mandibular canines, and orthodontic buttons can be cemented on teeth affixed with elastics to move malpositioned teeth into functional nonpainful positions.

9. Oral surgery is usually the treatment of choice to care for oral masses, both benign and malignant. When considering oral surgery, generally a 1-cm margin is indicated for benign masses and 2-cm or greater margins for malignant tumours.

10. Extraction is the chosen therapy to treat moderate and advanced periodontal disease, fractured teeth with pulp exposure when root canal therapy is not an option, tooth resorption exposed to the oral cavity, and penetrating malpositioned teeth.

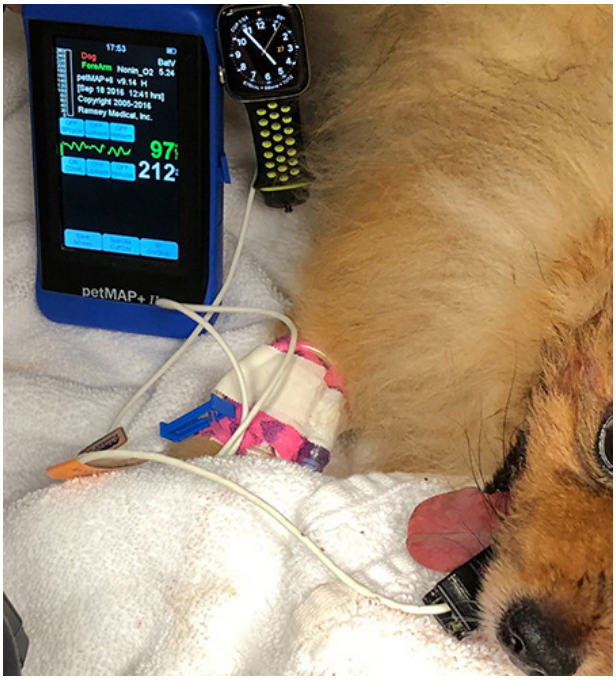

Figure 5. Recovery monitoring, including assessment of pulse oximetry and elevated heart rate.

Figure 6. Review of the COPAT visit with the client.

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Kyron Laboratories (Pty) Ltd. Co. Reg. No. 1990/004442/07
29 Barney Road, Benrose 2094 South Africa Tel. +27 11 618 1544