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The European Journal of Companion Animal Practice

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The language of EJCAP is English (UK). Where reprint papers have been translated, or where other versions of English were originally used, these have been translated to English (UK).

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The European Journal of Companion Animal Practice (EJCAP)

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Editorial

FECAVA was founded and EJCAP first published 21 years ago and both can now definitely be said to have come of age! One of the principal aims of the new Federation was to bring together, for the benefit of all members, the vast amount of expertise and knowledge available in Europe. Europe at 820 million has a population greater than North America's 520 million. It follows that the potential clinical base and pool of knowledge at least rivals that of North America. Because of language and cultural differences however, veterinarians in different parts of Europe had a limited idea of what advances were being made in other neighbouring countries. In order to address this problem FECAVA founded EJCAP where the best published work from all member countries could be published following selection and translation into English. More recently other scientific work originating in Europe has been made available to EJCAP readers. This includes Commissioned material, original work articles, papers based on FECAVA lectures, Book reviews, a Calendar of Continuing Education opportunities and news items, each helping readers to take advantage of the best in Europe.

This is the forty third issue of EJCAP and it will be the last to be published in hard copy format. To have the Journal available in both hard copy and online formats would have been the ideal arrangement but the cost of distribution of the printed Journal was becoming such a burden for some associations that the decision was taken that future issues will be available online only.

What has become increasingly apparent as we have worked towards the production of an online publication next year is the prospect of a much richer Journal, with lots of exciting add-ons and hyperlinks. Moreover, the online format will allow us to address one problem that the Journal has always presented for some of our readers - the fact that not all can benefit fully from a journal that is not produced in their native language. Online publication will allow the production of a journal with multilingual elements, tailored to meet the needs of all members. There can be no doubt that on-line publication is the way forward in this digital age.

I urge all readers to read Monique Megens introduction to the online Journal on page 131 of this issue and you will then understand why those of us involved in developing this project are convinced of the benefits of online publication.

My e-mail is always open to constructive suggestions as to how we can meet your own requirements as we move to the online format. Interactive questionnaires will also regularly appear in the online issues.

Be excited and ready to view the first online issue in April 2012

Keith Davies, Editor EJCAP

FECAVA NEWS

FECAVA News is brought together by Simon Orr, FECAVA President Elect

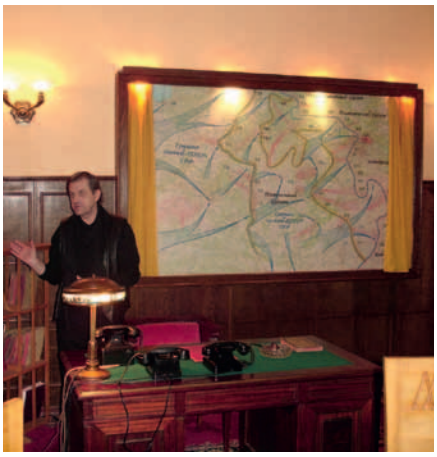
FECAVA Council visits Russia for the first time

The FECAVA Council, committee and working group meetings took place in Moscow from 14th – 16th April this year at the invitation of our Russian member, the Russian Small Animal Veterinary Association (RSAVA).

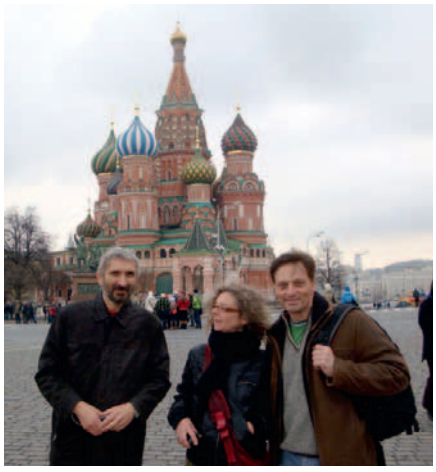
The Council was welcomed to Moscow by Dr. Serguey Sereda, the RSAVA President who expressed how important the support and collaboration of Europe is for Russia. He explained that RSAVA members presently faced immense difficulties due to recently enacted medicines legislation, which essentially meant that they could not legally use any anesthetics and analgesics. He asked for FECAVA's help in effecting sensible changes to this situation.

On Thursday 14th April, delegates were taken on a visit to Stalin's bunker to the east of Moscow, from where Stalin directed operations against the German armies as they approached the city of Moscow. An informative guide gave the audience some idea of the momentous events that took place in the second half of 1941 during Operation Barbarossa. Although meetings occupied most of the time from Thursday through to the Council meeting on Saturday, some managed to find time to visit the city of Moscow and see some of the famous sites including Red Square and the Kremlin.

FECAVA is very grateful to RSAVA for making the visit possible and for the tremendous organisation and hospitality offered during the meeting.



The tour guide standing behind Stalin's desk in front of a map showing the situation as the Germans approached the city.



From left to right - Dr. Miloš Urban (FECAVA Director for CSAVA), Ulrike Tewes (FECAVA Secretariat) and Dr. Wolfgang Dohne (FECAVA Director for BSAVA) in front of St. Basils Cathedral in Red Square

From left to right - Dr. Alexander Tkachov Jr. (FECAVA Director for RSAVA), Dr. Serguey Sereda (RSAVA President) and Dr. Johan van Tilburg (FECAVA President)

The FECAVA Board joined the FVE and UEVP delegates in Palermo

The FECAVA Board had a meeting on 9th-10th June in Palermo, which gave it a chance to network with the FVE and UEVP Boards and delegates attending their assembly meetings.

All the meetings, including the FECAVA Board meeting, took place in the rather grand Palazzo dei Normanni or Royal Palace of Palermo. However, not all attendees seemed very interested in what was being discussed!

The UEVP General Assembly meeting took place the day before the FVE meeting and the items of relevance to

FECAVA were discussed in both meetings and are summarised below.

An election was held for the UEVP Board and the following results were declared:
Re-elected as President
Zsolt Pinter (Hungary)
Re-elected as General Secretary
Andrew Robinson (UK)
Re-elected as Treasurer
Anne Ceppi (Switzerland)
Re-elected as Vice-Presidents
Andrew Byrne (Republic of Ireland)
Thierry Chambon (France)
Rens van Dobbenburgh (The Netherlands)

Zsolt Pinter
UEVP President

The FVE Assembly was opened and delegates were welcomed to Palermo, by FVE President Dr Walter Winding and Fedrazione Nazionale Ordini Veterinari Italiani President, Dr Gaetano Penocchio. FVE Executive Director, Jan Vaarten updated the Assembly on recent FVE activities and priorities, which had included:

a. The One Health initiative.
b. Strengthening links with the medical profession.
c. The Medicines and the Medicated Feed Directives.
d. Responsible use of antimicrobials, in particular the FVE response to the amendment to the European Parliament Antimicrobial Resistance Resolution and participation in EU AMR Day.
e. Animal Welfare issues including the BEVA / FEEVA work on transporting horses, the declaration on pig castration and the work on responsible animal ownership.

He also noted that FVE has undertaken considerable work in relation to veterinary education and research, including having responded to the consultation on the revision of the Recognition of Professional Qualification Directive, worked on the European Board of Veterinary Professional Development and been a part of the CALLISTO project on the transmission of zoonotic diseases from companion animals.

The President, Walter Winding, introduced the paper 'Report on reflections on the structure of FVE' noting that the FVE was looking at the relationship between the FVE and its sections and branches, to establish whether working practices and collaboration could be improved. The FVE was also considering its relationship with other European organisations such as FECAVA. The paper was not proposing a change of structure, but was a reflection on how the current structure worked and could be developed.

Simon Orr, the FECAVA Vice-President, noted that FECAVA has a good working relationship with FVE and ask that it be allowed to feed into any discussions that would take place in the future.

An election was held for the position of FVE President and four positions of Vice-President and the following results were declared:
Elected as President –
Christophe Buhot (France)
Elected as Vice- Presidents
Robert Huey (UK)
Karin Ostensson (Sweden)
Rafael Laguens (Spain)
Hans Joachim Gotz (Germany)

Christophe Buhot
FVE President

Christophe Buhot stated that it was an honour to be elected as President and informed the Assembly that during his term of office he wished to:

- Ensure that the FVE remained independent and proactive.
- Strengthen the diversity of knowledge and culture within FVE.
- Address the 'big five' issues: Antimicrobial Resistance, education, the Medicines Directive, the Animal Health Law and the Animal Welfare Law.
- Improve communications within FVE.
- Ensure the profession was recognised and the veterinary surgeon was acknowledged as the most qualified person to address animal health.

FECAVA Hygiene Poster receives endorsement at the FVE Meeting in Palermo

Nancy De Briyne, Deputy Executive Director of FVE, gave the FVE Assembly meeting in Palermo an update on the development of the Community Animal Health Law. She closed her presentation explaining that a previous EU Veterinary Week had been on the subject of Biosecurity. She then presented the FECAVA Hygiene poster and invited everybody to take a copy.

Nancy De Briyne, Deputy Executive Director of FVE. Photograph courtesy of Karin de Lange / Aksent

An update on the European Board for Veterinary Professional Development

The European Board for Veterinary Professional Development (EBVPD) held its inaugural meeting in Brussels on April 6th. The first task was the establishment of statutes together with a mission statement and strategy. The statutes are now drafted and the new Board agreed to meet again on 21st September 2011.

The Board comprises FVE, UEVP, FECAVA (as a co-opted member), the European Association of Establishments for Veterinary Educational Establishments (EAEVE) and the European Board for Veterinary Specialisation (EBVS). It is envisaged that other groups (e.g. the statutory bodies) will be involved in the near future. Andrew Byrne (FECAVA/UEVP) was elected by the Board as Chairman.

FECAVA and the CALLISTO PROJECT

FVE (the Federation of veterinarians of Europe) has asked FECAVA to take a significant role in a major project concerning zoonosis.
Zoonotic pathogens continue to pose a significant health risk to humans. In the past few decades we have witnessed several events where pathogens crossed the barriers from their regular animal host to humans via contact or vectors or via food, causing large outbreaks in the human population. About 60% of infectious diseases in humans originate in animals and about 75 % of emerging diseases are zoonotic. In addition, food animals are also at risk of emerging pathogens mainly originating from other animal species.

An increasing number and range of companion animals – defined as any domesticated or domestic-bred animals kept by humans for company, amusement or psychological support including dogs, cats, horses, birds, rabbits, ferrets, guinea pigs, reptiles and ornamental fish – are being kept in close interaction with human beings and food animals. Investigating and understanding the role of companion animals in the emergence of infectious diseases in humans and food animals and its implications for intervention strategies remains a relatively underrepresented area of attention in current research, public health and animal health policies. Moreover, the knowledge that is present is scattered amongst various specialists in different areas having different perspectives. This leads to the current situation where we lack a complete overview of the situation in terms of, for instance, incidence, main risk species and high risk areas and the developments herein.

Yet this information is necessary to develop evidence based, targeted actions to prevent reduce and eliminate the health risks for humans and food animals associated with keeping companion animals, in particular resulting from the pathogens that they harbour.

CALLISTO will contribute to this need by bringing together specialists from different fields of expertise, disciplines and sectors – ranging from veterinarians, virologists, bacteriologists, parasitologists, epidemiologists, ecologists and medical doctors to pet traders, farmers, animal welfare organisations, sociologists and health and food safety authorities – in a single network that will function as an interprofessional, interdisciplinary and multisectorial think tank.

The main objectives of the CALLISTO think tank are:

- To provide an overview of the role of companion animals as a source of infectious diseases for humans and food animals;
- To propose targeted actions that contribute to reducing the risk for infectious disease outbreaks in humans and food animals associated with keeping companion animals.

In pursuit of these main objectives CALLISTO will:

- Assemble a balanced multidisciplinary, multisectorial and interprofessional network of experts and representatives from the key stakeholder groups relevant to the main objectives of CALLISTO;
- Organise a series of meetings at different levels of integration, facilitating both interprofessional exchange of expert level knowledge and cross disciplinary and multisectorial integration of knowledge and perspectives;
- Produce and disseminate expert level opinion reports containing an overview of the current situation and proposed actions to reduce the health risks to humans and food animals associated with infectious diseases originating in companion animals.

In total, seven Working Groups will be involved in a 3 year during project. The role of FECAVA will be to chair Working Group 1 which concerns pets in the community. We will be responsible for spreading the message of the CALLISTO project to the public and more specifically to our clients all over Europe.

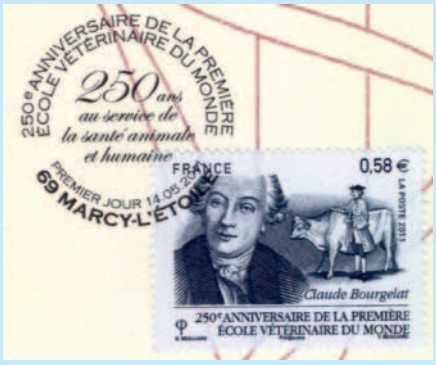
The responsibility and challenge in delivering this project is huge and we will need all our expertise in companion animal medicine to convince our clients and public opinion that living together with animals is a pleasure even though it can pose some risks and cause some problems. It will be our task to bring the correct information without frightening people.

The project will start January 2012.

Vet 2011 – La Poste issues a Commemorative Stamp

To celebrate the 250th anniversary of the world's first veterinary school the French post office, La Poste, has issued a commemorative stamp.

On August 4th 1761, a decree issued by Louis XV's Council of State granted Claude Bourgelat authorisation to open a veterinary school near Lyon. This was followed by Maison d'Alfort in 1764. From that time, students from all over Europe came to study and then in turn open veterinary schools in their respective countries, most of which still exist today.



You are invited to the largest companion animal conference in Europe – WSAVA / FECAVA / BSAVA Congress, 12-15 April 2012

In 2012 the **British Small Animal Veterinary Association** will host the **WSAVA/FECAVA/ BSAVA Congress**. This will include the world's most impressive selection of speakers, a huge variety of subjects for vets, nurses and practice staff, plus a superb exhibition and social programme.

At the 2011 BSAVA Congress there were **more than 8000 visitors**, including exhibitors. There were 5,816 delegates (an increase by 15% on 2010), including a record-breaking 634 visitors from overseas, with more than 50 countries represented. This figure is expected to rise when the BSAVA hosts the World Congress in 2012.

Reasons to attend WSAVA / FECAVA / BSAVA World Congress 2012

- The programme includes over 300 lectures presented by world class speakers, covering a wide range of topics, see the programme at www.bsava.com/congress
- The programme features interactive sessions, Controversies, How to… lectures, and Masterclasses
- Provides for all levels and abilities of veterinary practice staff and includes extended management streams
- The largest veterinary commercial exhibition in Europe with over 250 exhibitors, with all the latest innovations and industry expertise
- Amazing social events including the wonderful World Congress Welcome Party, fine dining at the Congress Banquet, and the unbeatable Party Night
- Centrally located in the UK - Birmingham has its own international airport and is one of Europe's most cosmopolitan cities, with wonderful shopping and entertainment, plus close to 'Shakespeare country' and some of the best of British countryside
- FECAVA and WSAVA members can register at the discounted BSAVA member rate.

Online registration began 1st August 2011. The Early Bird deadline is 12th January. For more information visit www.bsava.com/congress or email congress@bsava.com if you have a question.

The European Commission acts to protect Member States from tapeworm

On 14th July 2011, the Commission adopted a regulation permitting, from 1st January 2012, a pre-movement treatment for dogs travelling to listed Member States claiming echinococcus-free status. Finland, the United Kingdom, Ireland and Malta are the Member States currently on the list.
To be on the list, these Member States are obliged to introduce surveillance programmes and report the results to the Commission once a year. Positive findings need to be transmitted to the Commission and the other Member States immediately.

Before travel to one of the four Member States, a dog needs to receive a specific treatment administered by a vet. The details of the treatment should then be introduced by the vet in the pet's passport and the owner can travel with his pet from 24 hours to five days (120 hours) after treatment.

The regulation harmonises treatment requirements and travel times following treatment for the listed Member States, thereby facilitating pet owners' travel.

What is Echinococcus?

Echinococcus multilocularis is a tapeworm.

The typical transmission cycle of the parasite in Europe involves wild carnivores, such as foxes, as definitive hosts and several species of mammals, notably small rodents, as intermediate hosts. The rodents become infected by ingesting echinococcus eggs that are disseminated through foxes' or dogs' faeces.

Dogs can catch the worm by eating infected rodents. They may then serve as a source of infection for humans and a source of contamination of the environment. The human infection is called alveolar echinococcosis. It is a rare zoonotic disease and is considered as one of the most severe human parasitic diseases in non-tropical areas.

While Echinococcus multilocularis infection in animals occurs in the northern hemisphere, including the central and northern parts of Europe, it has never been recorded in certain areas of the European Union.

Background

According to the rules laid down in Regulation (EC) No 998/2003 (known as 'the Pet Regulation'), pet dogs, cats and ferrets travelling with their owner for non-commercial movements to another Member State must be accompanied by a passport, or when imported from a third country by a certificate, providing proof of a valid anti-rabies vaccination. The regulation also grants a transitional period (to expire on 31st December 2011) to Finland, Ireland, Malta, Sweden and the United Kingdom making the entry of pet animals into their territory subject to compliance with certain additional requirements in relation to rabies, echinococcosis or ticks.

Sweden is not on the list of Member States claiming echinococcus-free status because it reported its first echinococcus cases in wild carnivores in January 2011.

The Commission's action is based on the advice of the European Food Safety Authority. EFSA considered that the risk of the introduction of Echinococcus multilocularis into parasite-free areas through the movement of infected dogs is greater than negligible. That risk, EFSA concluded, could be mitigated if dogs from endemic areas were to be treated prior to entry into echinococcus-free areas.

Using its delegated powers conferred by Article 290 of the Treaty of Lisbon, the European Commission adopted the measures mentioned above. They will now be transmitted for scrutiny by the European Parliament and the Council – a procedure that will last about four months. If neither Institution opposes, the delegated regulation will be published in the Official Journal of the European Union and will enter into force on the twentieth day following that of its publication.

Using the same powers, the Commission also adopted another delegated regulation amending the technical requirements for the anti-rabies vaccination set out in Regulation (EC) No 998/2003. The new rule clarifies that the date of vaccination must not precede the date of microchipping or tattooing indicated in the passport or the accompanying health certificate (in case of movement from a third country).

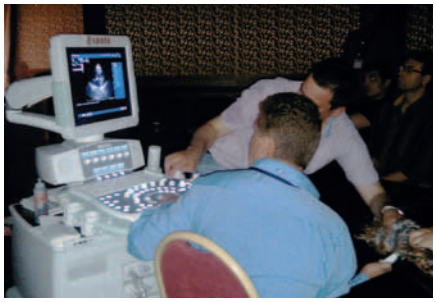
The BASAV Small Animal Veterinary Conference in Varna

From Denis Novak, SASAP President, FECAVA CE coordinator for EE

The Bulgarian Association of Small Animal Veterinarians (BASAV) organized the Varna Small Animal Veterinary Conference 2011 at the Melia Grand Hermitage Hotel, Golden Sands Resort in Varna on 2nd -5th June 2011. There were 241 delegates mainly from Bulgaria but also from Romania, Serbia, Greece, Slovenia, the Republic of Macedonia, Russia - and even one delegate from Australia.

Speakers were well known experts in veterinary medicine: Dr. Elke Rudloff, USA - Emergency Medicine; Prof. Howard Seim, USA - Soft Tissue Surgery; Prof. David Senior, USA - Urology; Prof. Ron Ofri, Israel - Ophthalmology and Dr. Otto Fisher, Austria - Dermatology.
The main programme was accompanied by a pre-congress day which included neurology lectures given by Dr. Petr Srenk from the Czech Republic and commercial presentations from industry.

The main sponsors of the Conference were Intervet/Schering-Plough Animal Health, Pfizer Animal Health and Eukanuba. Other exhibitors included Royal Canin, Purina, Biomed, Bayer Animal Health, Solingen and 5 local companies selling veterinary equipment and products.



The FECAVA Day practical seminar on ultrasonography

Dr. Denis Novak addresses the Varna Conference delegates

On Saturday 4th June and for the first time, BASAV organized a FECAVA Day parallel to the main programme. The idea was to have a practical workshop in ultrasonography and echocardiography. The two lecturers for the practical seminars on the FECAVA day were from Russia: Dr. Alexander Tkachov Jr. - Ultrasound and Dr. Andrej Kamolov - Cardiology.

The lectures were given in Russian, which was a problem for delegates who were not familiar with the language. Also, a hotel venue was probably not the best choice for such a workshop as many delegates were not able to have hands-on experience. I hope that this can be improved by developing guidelines for future FECAVA Day programmes and for practical sessions which should be used by local member associations in order to deliver a high quality CE programme.

As the FECAVA representative and CE coordinator for Eastern Europe I was honoured to give a presentation about FECAVA in general , detailing also its current work.

It is a clear that many delegates were familiar with FECAVA's role in the companion animal field. Certainly, there is a lot of room for improvement and for more proactive work with small animal veterinarians and FECAVA member Associations within the Balkan region.

The BASAV organising committee should be congratulated for producing a very good scientific and social programme and for setting a very popular registration fee which included attendance at all social events. A big thank you goes to all delegates who came to Varna to make it one of the best CE events in the region in 2011.

Isabelle Dietrich wins the ABCD & Merial Young Scientist Award 2011

From Karin de Lange, ABCD secretary

The ABCD and Merial Young Scientist Award 2011 was presented to Isabelle Dietrich MRes, a PhD student at the Centre for Virus Research of the University of Glasgow (UK), on 25 June in Vienna, on the occasion of the congress of the International Society of Feline Medicine.
Isabelle Dietrich (28) received the award for her work on a potential gene therapy for cats infected with the feline immunodeficiency virus (FIV), based on restriction of the virus with a synthetic feline TRIM5-CypA fusion protein. *"In our study, we confirmed that such a protein was highly efficient at preventing FIV infection in vitro"*. A TRIM-Cyp-based gene therapy approach for FIV-infected cats *"would offer an effective antiviral defense strategy with a very low potential for toxicity and the emergence of resistant viral variants, and would contribute significantly to animal welfare"*, she explained.

The award was presented by Professor Marian C. Horzinek, Founding Chairman of the European Advisory Board on Cat Diseases (ABCD), who congratulated the laureate. *"Isabelle Dietrich has contributed to the knowledge of feline infectious diseases by a series of studies of high quality and originality. Her research into the intracellular defense mechanism offers a novel insight into the potential control of an often devastating disease"*. Isabelle had been selected *"with flying colours"* from a pool of *"very good candidates"*, he added.

From left to right - Professor Marian C. Horzinek, Chair of the European Advisory Board on Cat Diseases (ABCD), Dr Jean-Christophe Thibault, Merial's Technical Director for Biologicals (Europe, Middle East and Africa) and Isabelle Dietrich MRes.

Isabelle's work was also *"of major importance"* in the field of human viral diseases like AIDS, recalled Jean-Christophe Thibault, Merial's Technical Director for Biologicals (Europe, Middle East and Africa), *"As a leading animal health company, Merial is very proud to be associated to this prestigious European award, in association with a recognised expert group such as the ABCD."* He also thanked the organisers of the ISFM congress, which was *"the most appropriate venue for presenting this award"*, created to *"highlight key research in the field of feline medicine"*.
The ABCD and Merial Young Scientist Award, created in 2008, is funded by Merial and is presented to a young scientist in veterinary or biomedical sciences, who has made an original contribution in the field of feline infectious diseases and/or immunology.

Applicants should have published their findings in a journal listed in *PubMed* or *Web of Science* or have had them accepted by another recognised assessing body.

Candidates should be based in Europe, have completed a veterinary or biomedical curriculum, and be under 35 years of age at the time of application. Applications in the fields of both basic and applied sciences are welcome.

For further information, please contact Karin de Lange, ABCD secretary, karin.delange@abcd-vets.org

WSAVA and OIE join forces to promote One Health

The World Organisation for Animal Health (OIE) and World Small Animal Veterinary Association (WSAVA) have signed a memorandum of agreement to promote increased collaboration between the two organisations in the area of One Health - a movement which aims to encourage human health and veterinary professionals to work together to eradicate disease.
Under the terms of the agreement, the WSAVA has been granted full observer status at the annual OIE General Assembly. The OIE is the intergovernmental organisation responsible for improving animal health and welfare worldwide and is responsible for the global surveillance of animal diseases, including zoonoses.

The organisations will collaborate on a range of activities including the development of global standards and guidelines to improve companion animal health and the continuing education of companion animal veterinarians. They will also implement practical measures including developing communication campaigns to increase awareness of infectious disease surveillance and reporting programmes.
The OIE is also the inaugural recipient of the WSAVA One Health Award, designed to recognise exemplary service by an individual, who has promoted the global One Health Concept, and, in particular, has highlighted an aspect of small companion animal relevance to the One Health Agenda. They will present the international lecture at the upcoming WSAVA 2011 Jeju World Congress in Jeju, Korea.

WSAVA Foundation launched

A WSAVA Foundation has been launched with a remit to improve global companion animal care through science and education. It held its first meeting early in 2011 and is identifying potential projects, including:

- initiatives to educate veterinarians and the public globally about disease prevention and improvement of health in companion animals
- creating standardization projects in key areas of companion animal health and welfare
- supporting the development of innovative clinical approaches for the diagnosis and treatment of clinical diseases in companion animals

The Foundation is also identifying sources of funding, grants and partnerships with the veterinary pharmaceutical and pet nutrition sectors and other potential donors.

WSAVA Nutritional Assessment Guidelines

Nutrition is critical because nutrients affect every living cell in the body; therefore WSAVA recognizes that nutrition for dogs and cats requires the same attention to detail as all other species cared for by our profession.

Our companion animals are often fed a single source of nutrition, either pre made or homemade diets. Careful assessment of their nutritional needs must be taken into consideration in order to maintain optimum health and performance, be part of a treatment regime for a diseased state, or maximize the quality of life in the patient with chronic disease.

To emphasize that point, our goal is that a nutritional assessment and specific nutritional recommendation be made on every patient on every visit. This will become known as the **5th Vital Assessment (5VA)**, following the **four vital assessments of temperature, pulse, respiration and pain** that are already addressed on each patient interaction. WSAVA will encourage every veterinary teaching institution in the world to begin to formalize this approach in their curricula as soon as possible.

Routinely doing a brief screening evaluation of the nutritional status during history taking and the physical examination can be seamlessly performed as part of every patient exam. An extended evaluation would follow, if one or more risk factors is suspected or identified on screening. Nutrition related risk factors could include age, changes in appetite, activity level, abnormal physical exam findings, body condition score, unexplained weight change and disease status.

Client compliance with nutritional recommendations offered by the veterinarian, veterinary nurses/technicians and their clinic team require everyone in the practice to believe in the critical importance of nutrition for their patients. A team approach to continuous nutritional education, implementation of appropriate protocols and focused client communication, utilizing these WSAVA Nutritional Guidelines, will be the key components to reach this 5VA goal.

The WSAVA Nutritional Assessment Guidelines can now be viewed on the new FECAVA website.

From left to right - Professor Michael Day (Chairman of the WSAVA One Health Committee), Professor Jolle Kirpensteijn (President of the WSAVA), Dr Bernard Vallat (Director General of OIE) and Dr Alex Thiermann (President of the Terrestrial Animal Health Code of the OIE)

Upcoming WSAVA Congresses:

- **2011 - Jeju, Korea October 14-17**
- **2012 - Birmingham, England April 12-15 (with Fecava Congress)**
- **2013 - Auckland, New Zealand March 6-9**
- **2014 - Capetown, South Africa September 14-19**

The WSAVA World Congresses will offer a comprehensive scientific programme delivered by global experts from around the world in a social atmosphere where veterinarians can share information, achievements and build a sense of fellowship. However, the Congress is, of course, more than an outstanding clinical experience – it also gives you an opportunity to explore a unique part of the world so reach for your guidebooks!

Notes for Contributors

These can be seen on www.fecava.com and are also printed on page 184 of this issue of EJCAP. There is an important change. Submissions should now be sent to:

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How to contact the FECAVA Office and Secretary

Our secretary is Ulrike Tewes.

You can contact Ulrike:
By phone : +32 (0)2 533 70 20
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The office is open from 8.30 am to 4.30 pm Monday to Friday.

EJCAP online - up-to-date in an interactive and engaging way

For 21 years FECAVA has published a high quality hard copy veterinary journal: the European Journal of Companion Animal Practice - EJCAP. Now EJCAP goes digital. Starting in 2012, FECAVA's scientific journal will only be available in digital format. And with this change come great opportunities.

Started in 1990 by 12 associations, FECAVA now represents the vets of national companion animal associations in 37 European countries who receive the journal twice a year in their mailbox and have access to an online special edition once a year. To the benefit of in excess of 30,000 vets EJCAP makes expertise and knowledge available to companion animal vets all over Europe. EJCAP comprises reprint scientific articles previously published in national journals translated into English, commissioned articles often written by European specialists, original work, book reviews, European veterinary news and much more. This will not change and we guarantee a lot more will be added!

The future is here and now

To strengthen FECAVA's ambitious vision to be the platform for the Companion Animal Veterinarian in Europe, we are preparing for a bright future and a considerable part of FECAVA's activity will be online. One of the first steps was taken in September 2011 with the launch of a new website meeting the new media expectations of the 21st century. Another important step, 21 years after the first hard copy was published, will be to go completely online with our journal in the spring of 2012. EJCAP online will be a multilingual journal with a lot of rich media, different to any other online journal in the veterinary field. The journal will look like a regular journal with pages you can turn and a summary of the article surrounded by relevant rich media. If you are interested you can download and read the whole article or if preferred easily print it.

Are you a busy practitioner who does not always have a lot of time to read scientific articles? Like many of us, you will be juggling your time, but want to stay up-to-date. For that reason, FECAVA is transforming EJCAP: it will be an interactive and engaging online journal where additional information using rich media is added to the scientific content. It will be easy to absorb with the same scientific standard as you expect from FECAVA.

Rich media

Scientific articles will be supported by interviews with one or more of its authors. More in depth information concerning the subject of the article and personal experiences of the author(s) will be shared.
VIDEO will make it possible to give practical instructions for surgical and other procedures or to educate your clients and in that way to convince them of the benefit of a certain procedure.
AUDIO can be used to demonstrate cardiac murmurs corresponding with the content of the specific article on

cardiology. **PHOTOS** will be interactive so you can zoom in and out, for example to study radiographs better.
SLIDE SHOWS will be added to articles.
Through **ANIMATIONS** certain processes such as surgical procedures, diagnostic protocols and disease mechanisms will be explained more explicitly.
Rich media will not interfere with the scientific content; it will support and add to the article and offer even more to the companion animal practitioner.

Multilingual – Spanish and English

Although vets can often read English, the language differences in Europe do not make EJCAP easy accessible for many vets. The language barrier limits the principal aim to bring together the expertise and knowledge available in Europe. One of the big advantages of going online is the possibility of having a multilingual journal. From the first online edition, EJCAP will be available in Spanish and English. It is expected that more languages will follow in the near future.

Frequency of publication and the special issue

The publication of the journal will initially occur 4 times per year, with three regular editions.
The fourth edition each year will concern a specific topic. Previous issues covered ophthalmology, dermatology, zoonoses, and dentistry. It is expected that the topic for December 2012 will be Diagnostic Imaging, a perfect subject for the use of rich media.

Exclusively available to you!

As a member of your national companion animal association you are automatically a member of FECAVA. Not sure whether your association is a member of FECAVA? Just check at our website: www.fecava.org.
Companion animal vets who are not a member of one of the 37 national companion animal associations cannot get a subscription. Your national association will inform you when a new online edition is available or you can register directly without any obligations at www.fecava.org and get the notification through FECAVA.

Gracias a AVEPA, una de las asociaciones fundadoras de FECAVA, la edición on line de EJCAP desde su primer número estará disponible también en español. Una interactiva y comprometida publicación on line, en la cual aparte del contenido científico, una interesante información adicional estará disponible para el clínico veterinario Español. Después de 21 años, el español es el primer idioma al cual EJCAP sera traducido. Esperamos en un próximo futuro que otros idiomas seguirán esta iniciativa.

REPRINT PAPER (CH)

Stabilisation of the emergency patient part II: Circulation**

Nadja Sigrist[(1)]

SUMMARY

Stabilisation of the emergency patient follows the ABC (airway-breathing-circulation protocol). Following the stabilisation of respiration and provision of oxygen-saturated blood, perfusion must be ensured. Perfusion is evaluated according to heart rate, pulse quality and rate, mucous membrane colour and capillary refill time, and temperature. Shock is defined as decreased perfusion leading to hypoxia. Depending on the cause and pathophysiologic processes, hypovolemic, obstructive, distributive or cardiogenic shock can be differentiated. All lead to a decrease in cardiac output, followed by decreased perfusion of tissues and subsequent cellular hypoxia. Therapy includes oxygen supplementation, fluid resuscitation with bolus therapy of isotonic crystalloid or colloid solutions, analgesia and haemorrhage control. Intensive monitoring is required for successful stabilisation.

Key words: shock, hypovolemia, perfusion, fluid therapy

This paper originally appeared in:
*Kleintierpraxis** **55**, 3, 2010, 140-154 #

Introduction

Stabilisation measures of emergency patients concentrate on the identification and immediate treatment of live-threatening problems based on their importance (ABCD: Airway – Breathing – Circulation - Disability) [Aldrich, 2005]. The respiratory tract, the heart and circulation and the central nervous system are the most important organs to protect.

The purpose of these organs is the oxygen supply of cells and requires adequate oxygen uptake by the lungs (see Part I: respiration) and appropriate perfusion of all tissues. Maintaining or normalizing the circulation is therefore given priority directly after or already during the stabilization of breathing. This requires a brief clinical examination of the patient, the correct interpretation of the findings as well as an appropriate therapy. In many cases, stabilization of circulation will include fluid therapy, therefore this issue will be discussed in detail in the following review article.

Definitions

Le Dran, a french physician, described the condition of an acute collapse after a major trauma as "shoc". Clinically, shock is defined as a condition of reduced or absent perfusion that leads to metabolic changes [Boag and Hughes, 2005]. At a cellular level, shock is defined as insufficient oxygen supply to the cells for the maintenance of cellular energy production [Shoemaker, 1994]. The cellular hypoxia is caused by decreased blood flow and not by a decrease in oxygen uptake (lung problems) or carrying capacity (anaemia). Decreased perfusion can be local (eg aortic thromboembolism) or generalized (eg haemorrhage leading to hypovolemia). When dealing with the stabilization of emergency patients, the generalized form of shock is more important. Regardless of whether the cause of shock is due to haemorrhage, a heart rhythm disorder, or sepsis, the insufficient supply of tissues with oxygen and other nutrients will lead to life-threatening cellular changes [Vallet *et al.*, 2005].

Evaluation of perfusion parameters in emergency patients

The primary survey of emergency patients should evaluate the perfusion status, including the following parameters [Aldrich,

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** Part I was published in EJCAP 21(1) April 2011 and Part III in this issue

2005]: Heart rate and rhythm, pulse rate and strength, mucous membrane color and capillary refill time (CRT), rectal temperature, peripheral temperature and consciousness (Table 1). The venous filling (jugular, peripheral) can also provide information regarding blood volume and its distribution [Boag and Hughes, 2005]. None of these parameters is a sole criterion of perfusion and thorough interpretation of circulation must include all parameters and consideration of their relationships. Determination of arterial blood pressure, central venous blood pressure, ECG rhythm, and blood gas analysis including lactate measurement may provide additional information [Boag and Hughes, 2005].

It is important that shock is distinguished from dehydration. Both describe a fluid deficit, however, the fluid has been lost in different compartments (intravascular vs. interstitial) and is therefore treated differently [Sigrist, 2005a]. Clinical signs of dehydration include dry mucous membranes, decreased skin turgor or enophthalmus. Severe dehydration may lead to hypovolemia with the classic signs of tachycardia, pale mucous membranes and prolonged CRT, but these are signs of shock and are treated accordingly.

Causes of shock

Based on the pathophysiologic processes that lead to decreased blood flow, shock is clinically divided into four types: hypovolemic, obstructive, distributive and cardiogenic [Hinshaw and Cox, 1972; Schertel and Muir, 1989]. The various causes and their pathophysiological consequences result in a reduced cardiac output (CO) followed by a decrease in perfusion. Depending on the definition of shock, hypoxemic and metabolic shock are differentiated on a cellular level [Malouin and Silverstein, 2009]. Veterinary emergency patients often show combinations of different types of shocks. Traumatic shock, septic shock and toxic shock are examples of combinations of the above types of shock [Otto, 2005]. Pain can lead to the same clinical symptoms as shock as well as to a decreased perfusion. Pain in combination with shock will also lead to a worsening of clinical symptoms [Rudloff and Kirby, 1994]. The classification of the different types of shock and possible causes are summarized in Figure 1.

Tissue hypoxia due to decreased perfusion

- **Hypovolemic (decreased blood volume)**
  - Absolute hypovolemia
    - Haemorrhage (internal and external)
    - Vomiting, Diarrhoea
    - Polyuric renal failure
    - Hypoadrenocorticism
    - Diabetes insipidus
  - Relative Hypovolemia
    - Peritonitis
    - Increased permeability leading to oedema
- **Obstructive (Obstruction of venous or arterial blood flow)**
  - Obstruction of venous return
    - Gastric dilatation-volvolus
    - Pericardial effusion with right heart tamponade
    - Severe heart worm disease
  - Peripheral arterial or venous obstruction
    - Aortic thrombosis (saddle thrombus)
    - Disseminated intravasal coagulation
    - Pulmonary thromboembolism
- **Distributive (generalised vasodilation)**
  - Anaphylactic shock
  - SIRS/Sepsis
  - Brain stem lesions
- **Cardiogenic (heart insufficiency)**
  - Decreased contractility
    - Dilative cardiomyopathy
    - SIRS, Sepsis
    - Traumatic myocarditis
    - Electrolyte disturbances
  - Decreased cardiac volume
    - Hypertrophic and restrictive cardiomyopathy
    - Endocardiosis
    - Endocarditis
  - Arrhythmias
    - Electrolyte disturbances
    - Brain stem lesions
    - Primary heart disease
    - Traumatic myocarditis

Figure 1: Categorisation and causes of shock

Hypovolemic shock

Hypovolemic shock results from a loss of circulating blood volume. The normal blood volume in dogs is 90 ml/kg BW and 60 ml/kg in cats. Losses of more than 15-20% lead to clinically apparent shock symptoms [Astiz, 2005]. The volume loss can be absolute or relative. An absolute volume loss is seen with haemorrhage and massive dehydration after fluid loss through vomiting, diarrhoea or polyuria. A relative volume depletion results from redistribution of fluid in third compartments (ascites, increased permeability leading to edema). Regardless of the cause, the loss of volume leads to a reduction in venous return to the heart and subsequently to a reduced CO.

Obstructive shock

As the name suggests, with obstructive shock obstruction of blood flow leads to a decreased perfusion. The obstruction of large venous vessels decreases venous return to the heart, which subsequently leads to a decreased CO. Causes of venous obstruction are gastric dilatation volvolus, severe heartworm infection, cardiac tamponade, tension pneumothorax or neoplasms and thrombi in the vena cava or large pulmonary vessels [Astiz, 2005]. Multiple arterial (micro-) thrombi (disseminated intravascular coagulation, aortic thrombosis) can also lead to decreased perfusion due to obstruction. However, the CO in these cases is normal.

Distributive shock

A distributive shock is caused by an abnormal distribution of blood in the microcirculation, caused by disturbances of the autonomic nervous system (therefore often referred to as neurogenic shock), loss of autoregulation, and metabolic disturbances on a vascular level [Moore and Murtaugh, 2001].

This results in a disproportionate distribution of blood with underperfused as well as overperfused tissues. Vasodilation is predominant in most cases, which results in a massive increase in blood vessel capacity with the same amount of blood volume. This leads to blood accumulation in the peripheral microcirculation and a relative hypovolemia with decreased venous return and subsequently insufficient CO.

Cardiogenic shock

The reduced CO in cardiogenic shock does not result from a lack of volume but rather by a reduced cardiac performance. Causes include endocardiosis, cardiomyopathy, arrhythmias, or decreased contractility.

Metabolic and hypoxemic shock

These types of shock lead to cellular hypoxia, regardless of the perfusion, are therefore less important for the normalization of perfusion in emergency patients and are discussed here only for completeness.

With metabolic shock the available oxygen is not converted to ATP due to dysfunction of the cell (mitochondrial enzyme damage, or lack of energy production). In hypoxemic shock, oxygen deprivation results from reduced lung function or decreased transport capacity due to anaemia [Malouin and Silverstein, 2009].

Other shock types described in the literature are combinations of the above types of shock. Examples include toxic shock (distributive, possibly cardiogenic), septic shock (distributive, hypovolemic, cardiogenic, and often a metabolic component), and traumatic shock (distributive, hypovolemic).

Pathophysiology

The patho- physiological changes in shock have been well studied especially in hypovolemic shock [Astiz, 2005]. The hypovolemia leads to a reduction in venous return and subsequently to decreased cardiac filling and correspondingly lowered cardiac output (Starling's law). The cardiac output (CO) is a function of the heart rate (HR) and stroke volume. The stroke volume in turn depends on the contractility of the heart muscle and the venous return [Guyton and Hall, 2000]:

$$CO = SV \times HR$$

The physiological response of the body to a reduced cardiac output is the baroreceptor reflex: the baroreceptors in the aortic arch and the carotid bifurcation are less stretched and pass this information to the vasomotor center in the brainstem. The decreased stretch of the pressure receptors leads to activation of the sympathetic and inhibition of the parasympathetic nervous system. The release of noradrenaline and other vasoactive substances leads to both an increase in heart rate and cardiac contractility and an increase in cardiac output [Moore and Murtaugh, 2001; Astiz, 2005]. In addition, venous vasoconstriction occurs, which increases blood return to the heart.

In addition, but delayed in time, there is a fluid shift from the interstitium into the intravascular space and both ADH as well as the renin-angiotensin-aldosterone system are activated with the aim of preserving water in the kidneys [Moore and Murtaugh, 2001] .

If CO cannot be normalized in this way, continuous activation of the sympathetic nervous system occurs, leading to pronounced arterial vasoconstriction in order to maintain blood flow to the heart, lungs and brain [Moore and Murtaugh, 2001]. The arterial vasoconstriction begins in the skin and muscles, but progressive vasoconstriction is also seen in vital organs such as the gastrointestinal tract, liver and kidneys. Vasoconstriction leads to decreased blood flow to these organs, and additional oxygen deficiency.

The baroreceptor reflex is restricted in distributive shock. Compensatory tachycardia and an increase in cardiac contractility result in a normal to high cardiac output, but the vasoconstriction can not occur. The prevailing, mainly nitric oxide-mediated vasodilation leads to a redistribution of blood to the microcirculation and hypotension [Astiz, 2005].

All cell and organ functions need energy (ATP). The production of ATP is most effective in an aerobic milieu. Under aerobic conditions 38 ATP molecules are produced from glucose and oxygen in the Krebs cycle [Guyton and Hall, 2000]:

$$\text{Aerobic: } 1\ Glc + 6\ O_2 + 38\ ADP + 38\ Pi \rightarrow 6\ CO_2 + 6\ H_2O + \mathbf{38\ ATP}$$

Under anaerobic conditions, the ATP production is extremely unproductive:

$$\text{Anaerobic: } Glc\ 1 + 2\ ADP + 2\ Pi \rightarrow 2\ \text{lactate} + \mathbf{2\ ATP}$$

This leads to accumulation of lactate and hypoxanthine as well as changes in the cell milieu (acidosis, Ca-accumulation), ischemia-induced release of inflammatory mediators and vasoactive substances, which further lead to maldistribution of blood flow, myocardial depression and activation of the coagulation cascade with formation of thrombi and coagulation abnormalities [West and Wilson, 1996; Haljamae, 1993]. Acidosis, energy depletion and inflammatory factors will lead to terminal shock with vasodilatation of the peripheral arteries and veins, arrhythmias and eventually respiratory and cardiac arrest [Wiggers, 1942].

Clinical signs of cardiovascular shock

The clinical signs of shock are given by the activation of the sympathetic nervous system and depend, particularly in the hypovolemic shock, on the shock stage (Table 1). A reduction in blood volume by 10-15% is associated with few clinical symptoms (such as seen with blood donation). With a loss of up to 20% tachycardia is seen. With a volume loss of 20-35% clinical signs of decompensated hypovolemic shock can be expected. Losses of more than 35-40% are fatal if not treated with appropriate therapy [Schertel and Muir, 1989].

Compensated shock: the first stage of shock is caused by the compensatory activation of the sympathetic nervous system and manifests itself in an increased contractility (clinically

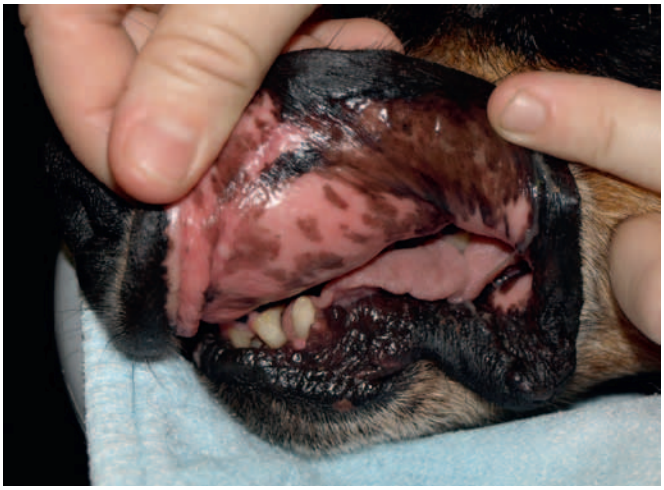

Figure 2a: compensated shock
Red mucous membranes and a short CRT are the clinical signs of compensated shock.

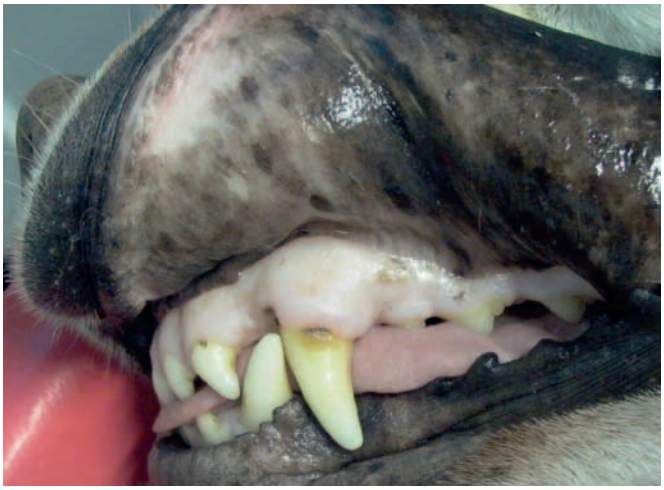

Figure 2b: decompensated shock
Pale mucous-membranes with a prolonged CRT are indicative of decompensated shock. Vasoconstriction leads to underperfusion of skin, mucous membranes and other organs.

not visible) and tachycardia [Moore and Murtaugh, 2001]. Overcompensation, also called the hypermetabolic state, with tachycardia, erythematous mucous membranes and a short capillary refill time (CRT) can be seen [Otto, 2009]. If no overcompensation takes place, mucous membranes and CRT are normal. The femoral pulse is normal or throbbing, and the blood pressure is normal or increased [Boag and Hughes, 2005].
Cats rarely show a compensated shock state [Otto, 2005]. Often a compensated shock state with hypermetabolism may be seen during shock therapy of decompensated shock. With fluid therapy, the mucous membranes are no longer pale but reddened and the CRT becomes short (Fig 2a). These animals are still in shock and need continued fluid therapy.
Differential diagnoses of compensated shock are distributive shock, sepsis, fever, excitement or stress.

Early decompensated shock: with beginning peripheral arterial vasoconstriction, which leads to hypoperfusion of the less important organs such as skin and mucous membranes in order to maintain the blood flow to the vital organs like heart and brain (centralization), decompensated shock results [Otto, 2005]. Due to vasoconstriction, pale mucous membranes and a prolonged CRT can be seen in addition to tachycardia. The pulse may be weak, the peripheral limbs are cooler and the animals may present with hypothermia [Moore and Murtaugh, 2001]. Blood pressure is normal in the early stages. Hypotension manifests only after a volume loss of 40% of the intravascular volume [Astiz, 2005].

Late decompensated shock: With ongoing arterial vasoconstriction, the animals show grey-white mucous membranes, prolonged or no longer measurable CRT, tachycardia, tachypnea, hypothermia, and stupor. Severe hypothermia or anaemia should be considered as differential diagnoses of this shock stage.

Terminal shock: Once vasoconstriction can no longer be maintained due to lack of energy, vasodilation with accumulation of non-oxygenated blood in the microcirculation occurs. Clinically, the mucous membranes become grey-purple with undefinable CRT, the animals are showing bradycardia or arrhythmias, are stuporous, hypothermic and hypotensive [Moore and Murtaugh, 2001]. This shock stage ends in cardio-pulmonary arrest.
Differential diagnoses are cardiogenic shock, other causes of bradyarrhythmias (heart problem, hyperkalemia) or brain stem lesions.

In distributive shock, no vasoconstriction occurs (primary problem is an uncontrolled vasodilation), which is why the division into shock stages is not possible and why it is difficult to estimate the extent of the shock level [Otto, 2009]. Cats rarely show injected mucous membranes associated with distributive shock and SIRS / sepsis and in a retrospective study stupor and bradycardia were found as the predominant symptoms of distributive shock [Brady *et al.*, 2000].

Diagnosis

In addition to the clinical examination, blood pressure measurement, blood gas analysis and lactate measurement may help to identify a perfusion deficit.
The arterial blood pressure is maintained for a relatively long time. However, a normal blood pressure does not necessarily indicate a normal blood flow. Because of vasoconstriction, the blood pressure is maintained for a long time even though the blood flow is diminished by the extensive vessel contraction [Cohn, 1967; Shoemaker and Czer1979]. More helpful may be the interpretation of the blood pressure curve: a high narrow curve, respectively a high systolic and low diastolic blood pressure may be indicators for vasoconstriction due to hypovolaemia. This can also be felt as a throbbing or "bouncing" pulse during the evaluation of pulse strength [Boag and Hughes, 2005].
An ECG analysis should be performed in patients with bradycardia or tachycardia and in patients with clinical signs of arrhythmias.
The determination of hematocrit and total protein should be part of the initial diagnostic workup of all emergency

Perfusion Parameter	Compensated	Early- decompensated	Late-decompensated	Terminal
Heart rate	Tachycardia	Tachycardia	Tachycardia → Bradycardia	Bradycardia
Pulse strength	Pounding	Weak	Weak	Weak-missing
Mucous membrane colour	Red	Pale	White-grey	Grey-purple
CRT	< 1 sec	> 2 sec	> 2-3 sec	Not measurable
Blood pressure	Normal-increased	Normal-decreased	Hypotension	Hypotension
Mental status	Normal	Decreased	Depressed	Stupor
Peripheral temperature	Normal	Beginning hypothermia	Hypothermia, cold extremities	Hypothermia, cold extremities
Urine production	Normal	Decreased	Decreased	Decreased

Table 1: Shock stages

patients. Anaemia as a cause of tachycardia and white mucous membranes can be excluded rapidly by determination of the microhaematocrit. Depending on the size and duration of blood loss, the hematocrit may be reduced, while it is still normal in acute bleeding due to lack of dilution. Fluid losses without red cell loss (vomiting, diarrhea, polyuria) lead to haemoconcentration.
Lactate accumulates in the body during anaerobic metabolism in shock and can be detected in blood [Weil and Afifi, 1970; Cady *et al.*, 1973]. Lactate levels > 2.5 mmol/L in combination with appropriate clinical symptoms are associated with decreased perfusion and the lactate levels correlate with the degree of shock [Boag and Hughes, 2005]. Lactate may be increased, however, by other diseases (neoplasia, diabetes mellitus), and with increased muscle activity and is a late marker of hypoxia [Boag and Hughes, 2005].

Treatment

The main components of shock therapy are fluid administration to restore the intravascular volume (except in cardiogenic shock), bleeding control, oxygen supplementation and analgesia [Mandell and King, 1998; Otto, 2005].

Oxygen supplementation

Shock is a state of oxygen deficiency, therefore animals in shock should be supplemented with oxygen, especially when an additional lung problem can not be excluded. Oxygen supplementation is initially easiest by using oxygen flow-by or a mask (see stabilization of emergency patients, Part I). For continuing oxygen therapy, it may be more convenient to place a nasal oxygen tube, or administer oxygen by an oxygen hood, made out of an Elisabethan collar and cellophane wrap. The oxygen saturation should be at least 95%.
The oxygen supply to the tissues depends not only on the perfusion and the arterial oxygen content but also on haemoglobin, which represents the major part of the transport capacity. In the case of massive bleeding blood transfusions or substitute products like Oxyglobin® (Biopure, USA) may be required for maintenance of oxygen transport capacity [Astiz, 2005]. In acute bleeding leading to a PCV < 20%, haemoglobin should be substituted in the form of whole blood, erythrocyte concentrate or Oxyglobin®. The goal of transfusion therapy is a PCV of 25-30%, where the rheology of blood is the most ideal [Cozette *et al.*, 1979]. Using fresh whole blood, 2 ml of blood per kg body weight are needed to raise the hematocrit by 1%, with packed red cells 1-1.5 ml / kg per desired % PCV raise are administered [Sigrist, 2005b]. If time permits, a cross test should be performed prior to the administration of blood products. In cats, the determination of at least the blood group is mandatory.

Control of haemorrhage

Visible bleeding should be stopped by pressure bandage or ligature of the vessel. In the case of coagulation abnormalities, either due to a primary problem (massive haemorrhage), complications (DIC, sepsis) or dilution (massive fluid therapy), plasma in a dosage of 8-15 ml/kg over max. 6 hours, sometimes 3 times a day, is indicated [Rudloff and Kirby, 1998]. The indications of haemoglobin transfusion are discussed below.

Fluid therapy

Venous access:
Patients with clinical signs of shock will need large amounts of intravascular fluids, requiring immediate venous access. Subcutaneous fluid will not be absorbed due to vasoconstriction of the skin or only very slowly. To ensure a quick infusion therapy, the largest possible venous catheter is selected. Short catheters are preferred over long central venous catheters because the flow rate of a catheter not only depends on the radius, but also on the length (Poseuille's Law) [Marino, 1997]. With collapsed veins a skin cut or even a mini-cutdown with preparation of the vein may be needed [Dethioux *et al.*, 2007]. Intraosseous fluid therapy may be an alternative to intravascular administration and may be easier especially in small and young animals. An intraosseous access is easiest achieved in the femur (intertrochanteric fossa). In young animals, a yellow or pink needle can be used while commercially available intraosseous needles are handy in larger or older animals.

Choice of fluid solution:
The optimal fluid for the treatment of hypovolemic shock is still controversial [Schierhout and Roberts, 1998; Choi *et al.*, 1999]. Intravascular fluid deficits (hypovolemic, obstructive and distributive shock) can be replaced with isotonic crystalloid solutions, colloids, hypertonic saline solution, blood products or combinations of these (Table 2) [Rudloff and Kirby, 1998].

The combination of a crystalloid (eg Ringer's lactate or 0.9% NaCl) and colloidal fluid allows the fastest and longest effective therapy of hypovolemic shock. Colloids remain in the vascular system due to their molecular size, and will draw water from the interstitium and keep the crystalloid solution longer in the intravascular space [Rudloff and Kirby, 1998]. Isotonic crystalloid solutions such as Ringer's lactate or 0.9% NaCl are distributed throughout the extracellular space and only ¼ of the amount applied is still available intravascularly after 2 hours. These fluids are therefore excellent for the treatment of patients who are both dehydrated and in shock (such as with acute gastroenteritis). Trauma patients are in most cases only hypovolemic and have no pre-existing fluid deficits, so the combination of Ringer's lactate with a colloid such as Haes is preferable.

Hypertonic saline solution leads to a very rapid redistribution of water from the interstitial into the intravascular space, increasing the blood volume very rapidly and effectively. However, this effect lasts only 15-20 minutes [Rudloff and Kirby, 1998]. The administration of hypertonic saline can be lifesaving in late decompensated shock, since an immediate effect is achieved and time is gained in order to apply other fluids. Because the interstitium becomes dehydrated during the application of hypertonic saline, these patients must then be rehydrated with an isotonic solution and the use of hypertonic saline in the already dehydrated patient is contraindicated [Rozanski and Rondeau, 2002]. The effect of hypertonic saline solution can be extended with simultaneous administration of Haes or dextran. The distribution and composition of various infusion solutions are provided in Table 2.

Fluid dose:

Due to the physiological understanding and the introduction of colloidal fluid solutions, the "shock dose" of 90 ml/kg/h is no longer indicated and may lead to both under- as well as over-infusion of patients. Since the exact amount of fluid cannot be accurately determined and the blood volume should be normalized as quickly as possible, fluids should be administered by bolus infusion. Clinical symptoms of compensated shock are seen with a volume loss of 15-20% and of decompensated shock at 20-35% volume loss [Moore and Murtaugh, 2001]. In dogs, this corresponds to amounts of 15-30 ml/kg, in the cat of 10-20 ml/kg body weight. This results in the proposed bolus dose of fluid therapy (see also Table 3). Emergency patients with signs of decompensated shock are treated with an initial bolus of 20 ml/kg (dog), respectively 10 ml/kg (cat), of an isotonic crystalloid solution (eg Ringer's lactate) together with a bolus of 10 ml/kg (dog), respectively 5 ml/kg (cat), of a colloid (eg Tetraspan®, B. Braun Vet Care GmbH, D or Voluven®, Fresenius

Table 2: Comparison of different fluids

Name	Compartment	pH	Na	Cl	K	Ca	P	Mg	Buffer	comments
			Mmol/L							
Crystalloid isoton										
0.9% NaCl	Extracellular	5	154	154						no Buffer
Ringer solution® (Braun)	Extracellular		147	156	4	2.2				no Buffer
Lactated Ringer's (Fresenius)	Extracellular	5-7	131	118	5.4	1.8			Lactate	
Plasmalyte-A®	Extracellular	6.5-8	140	98	5			1.5	Acetate, Gluconate	
Stereofundin® Iso	Extracellular		140	127	4	2.5		1	Acetate, Malate	
Crystalloid hyperton										
7% NaCl	Extracellular		1197	1197						hyperton
Crystalloid hypoton										
5% Glukose	Intracellular	4								Glucose 50g
Sterofundin® HEG5	Intracellular		70	66	2	1.3				Glucose 50g
Glukose5%-NaCl0.9% 2:1 Fresenius	Intracellular, interstitial	3-5	51	51						Glucose 33g
2.5% Glc/NaCl	Intracellular, interstitial									
Whole blood	Intravascular		140	100	4					COP 20
Plasma	Intravascular		140	100	4	2	2		Albumine	COP 20
Haes-steril® 6%	Intravascular	5.5	154	154					Haes 200/	COP 32
Voluven®	Intravascular		154	154					Haes 130/0.4	
Venofundin®	Intravascular	4-6.5	154	154					Haes 130/0.42	COP 37.8
Tetraspan®	Intravascular		140	118	4	2.5		1	Acetate, Malate, Haes 130/0.42	
Oxyglobin®	Intravascular									

P: Phosphor; COP: colloid-oncotic pressure; Glc: Glucose

Cardio-vascular Problem	Dose isotonic crystalloid	Dose colloid
Hypovolemic shock		
Compensated	Dog: 10-30 ml/kg Bolus# Cat 10 ml/kg Bolus#	--
	Dog: 15 ml/kg Bolus# Cat: 5 ml/kg Bolus#	Dog: 5 ml/kg Bolus# Cat: 5 ml/kg Bolus
Decompensated	Dog: 15-30 ml/kg Bolus# Cat: 10 ml/kg Bolus#	Dog: 5-10 ml/kg Bolus# Cat: 5 ml/kg Bolus
	10 ml/kg Bolus# + Hypertonic sodium: 4ml/kg	5 ml/kg Bolus
Haemorrhage*	Dog: 10 ml/kg Bolus# Cat: 5 ml/kg Bolus#	3-5ml/kg Bolus whole blood / pRBC according to needs Dog: Oxyglobin 5 ml/kg Bolus (max 30 ml/kg)
Cardiogenic shock + Hypovolemia	5-15 ml/kg Bolus slowly	1-3 ml/kg Bolus slowly
Coagulopathy		Plasma 8-15 ml/kg

#repeat as required
* Goal: systolic blood pressure 100 mmHg, or mean arterial blood pressure > 60 mmHg

Table 3: Examples of fluid therapy (Rudloff und Kirby, 1998)

Kabi AG, Switzerland). The boluses are given intravenously over 10-15 minutes. The patient is then re-evaluated. If perfusion abnormalities persist, the bolus is repeated. Depending on the cause and magnitude of shock, several boluses or various combinations (crystalloid and colloid solutions or blood products) will be necessary. It is important that the boluses are given as fast as possible (shock = lack of oxygen!) and not as "double maintenance" for several hours.
The dose of hypertonic saline (7-8%) is 4 ml/kg body weight. This, in comparison small amount, has the same effect as a large bolus of Ringer's lactate, but is much faster applied [Schertel *et al.*, 1997].
In case of suspected internal bleeding, lung contusions or hypothermia, a conservative fluid therapy should be applied. Small boluses (5-10 ml / kg Ringer's lactate and 3-5 ml / kg colloid) are chosen and the patient is monitored very closely [Adamantos and Hughes, 2008]. This conservative fluid therapy is referred to as "limited volume fluid resuscitation", the goal is a just sufficient perfusion, ie, a mean blood pressure of 60 mmHg, to avoid overinfusion and re-bleeding [Rudloff and Kirby, 1998; Hammond and Holt, 2009].

Continued fluid therapy:
Further fluid therapy after normalizing the intravascular volume depends on further fluid deficits and losses. After shock

Parameter	Normal value dog	Normal value cat
Heart rate	60-100 / Min	160-200 / Min
Mucous membranes	Pink, moist	Pink, moist
CRT	1,5 sec	1,5 sec
Pulse	Strong, regular	Strong, regular
Mean arterial blood pressure	80 mmHg	80 mmHg
Central venous pressure	4-8 cm H_2O	2-5 cm H_2O
Urine production	> 1ml/kg/h	> 1 ml/kg/h
Hematocrit	> 25%	> 25%
Albumin	> 20 g/l	> 20 g/l

Table 4: Goal of fluid therapy (Rudloff und Kirby, 1998)

treatment using fluid boluses, the dehydration is estimated again and the fluid loss is calculated according to the formula:

Dehydration (ml) = % dehydration x kg body weight x 10 [Rudloff and Kirby, 1998].

This interstitial deficit is replaced intravenously over 6-12 hours with an isotonic crystalloid solution. Maintenance requirements (2-3 ml/kg/h) and any future losses from vomiting, diarrhoea or polyuria are added to this amount. Depending on the disease, the supplementation of potassium, phosphorus, or glucose may be necessary.

Analgesia
Pain can cause the same clinical symptoms as shock, which may make interpretation of the perfusion difficult [Rudloff and Kirby, 1994; Day and Bateman, 2004]. All shock patients who may potentially be in pain (trauma, diarrhoea, vomiting, breathing problems) should be treated as early as possible with an appropriate analgesic. The ideal analgesic is potent but reversible, does not affect the circulation and respiration, has no side effects and can be titrated. This description most closely describes the µ-agonist opioids. Methadone 0.1-0.2 mg/kg i. v. or i. m. every 1-2 hours or fentanyl 2-5 ug/kg/h as a continuous rate infusion (CRI) are possible analgesics for emergency patients [Campbell, 2005]. µ-agonists can be titrated as well as antagonized and have no major side effects on circulation and respiration in the described dosages [Campbell *et al.*, 2003].
Other opioids such as buprenorphine (0.01 mg/kg i.v. / i.m. every 6-8 hours) or butorphanol (0.2 mg/kg i.v. or i.m. every 1-2 hours) are also possible, but cannot be repeated in the case of insufficient analgesia and are only limited reversible. The analgesic effect of butorphanol is much shorter (40 minutes) as the sedative effect, which is why a CRI (0.1 mg/kg/h) is recommended [Plumb 2004].
Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients in shock as they reduce renal blood flow and can lead to ulceration in the gastro-intestinal tract [Campbell, 2005]. Both the kidneys as well as the gastrointestinal tract are organs that are inadequately perfused during centralization in decompensated shock, and are therefore

much more sensitive to any possible side effects of NSAID's. NSAID's are ideal analgesics for trauma patients with soft tissue trauma once adequate renal blood flow (indicated by normal urine production) has been established [Campbell, 2005].

Support of heart function

The support of cardiac function has priority in cardiogenic shock. Adequate treatment requires the identification of the causative cardiogenic problem (contractility problem versus volume overload), which is usually only possible by means of cardiac ultrasound.

A reduced contractility as well as various arrhythmias may be appearent both in cardiogenic shock as well as other types of shocks (due to various inflammatory mediators) [Day and Bateman, 2004]. Dobutamine (5-10 µg/kg/min) increases the contractility of the heart and may increase cardiac output in diseases with reduced contractility (DCM, sepsis) [Plumb, 2004]. With an already increased contractility as seen as a normal compensatory mechanism of the heart in order to normalise cardiac output, dobutamine leads to an undesirable increase in the oxygen demand of the heart muscle and is therefore not indicated [Plumb, 2004].

The most common arrhythmia seen in shock patients are ventricular arrhythmias [Day and Bateman, 2004]. Ventricular tachycardia can cause hypotension due to the high heart rate and decreased contractility. Multi-focal premature beats, severe tachycardia or signs of decreased perfusion are indications for the medical treatment of extrasystoles [Day and Bateman, 2004]. Lidocaine (bolus 2 mg/kg followed by 40-80 µg/kg/min CRI) is the anti-arrhythmic drug of choice for ventricular arrhythmias. Causative factors such as hypoxia, hypovolemia or electrolyte changes should be corrected as well.

Vasopressors are generally not indicated in hypovolaemic and obstructive shock, since they lead to further vasoconstriction and centralization of the blood with subsequent ischemia of other organs. Vasopressors are used in distributive shock [Schertel and Muir, 1989]. Again, the goal of vasopressor therapy is not vasoconstriction but a normalization of vascular tone. The replacement of volume has priority and vasopressors are only indicated if the vascular volume is normalized (normal central venous pressure).

Dopamine (2-10µg/kg/h) leads to vasoconstriction and is therefore indicated in hypotension due to vasodilation (distributive shock) [Day and Bateman, 2004].

Other therapies

Trauma patients in shock are often hypothermic and need to be warmed up [Rudloff and Kirby, 1998]. Water bottles, warm water-filled disposable gloves, warmed fluid solutions, heat lamps or hot air supply by means of a Bair hugger are suitable to warm patients. The normalization of the temperature is very important, especially in cats, as perfusion parameters are not interpretable in very hypothermic animals.

Antibiotic therapy is usually not indicated because of shock. Exceptions are indications of interruption of the normal intestinal barrier, such as haemorrhagic faeces or melaena.

Steroids have been promoted for the treatment of shock a few years ago due to their membrane-stabilizing effect. Several clinical studies have shown no reduction and possibly even an increase in mortality and morbidity, indicating that the in vitro membrane stabilizing effect either seems to have no clinical effect or the side effects of steroids are greater than the potential benefits [Lefering and Neugebauer, 1995; Cronin *et al*, 1995; Wadell *et al*, 1998]. Steroids are therefore not indicated. The only exception is a patient with sepsis and hypotension (septic shock) despite adequate fluid therapy and vasopressors. In this case, steroids are supplemented in a physiological dose (Illness related Addison's disease) [Martin and Groman, 2004]. The incidence of septic shock with hypoadrenocorticism is low in the dog and not previously been described in the cat [Peyton and Burkitt, 2009].

Monitoring

Since the exact amount of fluid loss in shock patients can not be determined and further fluid losses may occur, repeated evaluation of perfusion parameters, both during the stabilization and in the subsequent phase, is very important. The goal of shock therapy is a normal blood flow and a normal oxygen supply to the tissues (Table 4). The blood flow can be verified by clinical parameters such as heart rate, pulse quality, mucous membrane colour, capillary refill time and urine output. These parameters are determined at regular intervals after each bolus and after normalization of perfusion.

Since shock is a state of cellular hypoxia and the clinical parameters indeed provide an indication of the perfusion but not to the cellular oxygen supply, ongoing search for other monitoring parameters is required. Lactate is a marker of anaerobic metabolism [Cady *et al.*, 1973] and increases with reduced perfusion. Normal oxygen supply to the tissues can be demonstrated by decreasing lactate levels and normalization of the acid-base balance (accumulation of lactate during anaerobic metabolism leads to metabolic acidosis). A decrease of CO2 can be measured by blood gas analysis, gastric tonometry or sublingual, however, this is rarely done in practice.

SvO2, the saturation of haemoglobin with oxygen in the blood of a central vein (ideally from the pulmonary artery) is a marker for the balance between oxygen supply and consumption [Scalea *et al.*, 1988]. In human medicine, SvO2 is an important parameter for the evaluation of fluid therapy in patients with septic shock and a rapid normalization of SvO2 by administering fluid therapy, blood products, and vasopressors as needed, leads to a reduction in mortality [Rivers *et al.*, 2001].

The monitoring of haematocrit and total protein is important especially in trauma patients, where internal, invisible bleeding can not be excluded, as the hematocrit may be normal initially and only decrease after normalizing the intravascular volume with fluids. Continued fluid therapy with colloids depends on the oncotic pressure estimated by the level of albumin. The oncotic pressure should be increased by means of synthetic colloids (Haes, 1-2 ml/kg/h) when albumin levels are < 20 g/ l or total protein is < 40-50 g/l [Rudloff and Kirby, 1998]. Aggressive fluid therapy may cause an iatrogenic hypokalemia. Hypoglycaemia should be considered in young animals presenting in shock.

The rapid and adequate normalization of circulation during the stabilization of an emergency patient is important to prevent secondary organ changes and complications. After stabilization

of respiration (see stabilization of emergency patients, Part I: respiration) and normalizing perfusion, the emergency patient is stable enough to allow a complete physical examination and a diagnostic and therapeutic plan can be established.

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Efficacy of Advance Veterinary Diets Atopic Care on the management of Canine Atopic Dermatitis (CAD): a randomized, doubled-blinded controlled clinical study

CAD is a chronic inflammatory disease of the skin causing pruritus. The prevalence is calculated at 10-15% of canine population (Hillier &Griffin, 2001), with special predisposition in some breeds such as West Highland White Terrier, French Bulldog o Shar Pei, where prevalence can reach 30%. Pathogenesys of CAD is complex and probably not identical in all cases. Recent studies show two main mechanisms of action of CAD: hypersensibility against environmental allergens and skin barrier alterations (Marsella & Samuelson, 2009; Oyoshi et al, 2009). Development and severity of CAD are related to the complex interaction between genetic, immunologic, environmental, pharmacologic and physiological factors, as well as the functional condition of the skin barrier.

The study evaluated the effect of Advance Veterinary Diets Atopic Care on pruritus, cutaneous lesions and steroid-sparing effect in dogs with non-seasonal, atopic dermatitis. The dogs enrolled were not previously medicated and had undergone an elimination diet. Dogs were randomly assigned to either a diet enriched with essential fatty acids, vegetal extracts and collagen peptides (A) or a commercial diet (B), in a multicentered double-blinded study. They all received prednisone initially at 0.5 mg/kg/day, which was reduced whenever possible according to a written protocol. Owners evaluated pruritus weekly using a visual analog scale. Veterinarians performed CADESI-03 at day 0, 28, and 56.

CADESI and pruritus scores at day 0 were not significantly different between groups. Mean pruritus scores were 7.09±0.5, 7.2±0.6; 2.64±0.4, 5.3±0.9; 0.45±0.2, 4.5±0.8; at days 0, 28, and 56, for diets A and B respectively. CADESI scores were 110.64±16, 99.7±16.7; 48.3±11.5, 78.2±17.7; 14.36±4.9, 56.60±4.8; at days 0, 28, and 56, for diets A and B respectively. The reduction of pruritus and CADESI scores was significant for dogs on diet A from day 0 to 28 (p=0.017 and p=0.014), and from day 0 to 56 (p= 0.001 and p=0.020), but not for dogs on diet B. Total prednisone administered (days 0-56) was 13.63 mg/kg ±1.5 and 22.61 mg/kg ± 2.3 for dogs in diets A and B respectively (p=0.004). At the end of the study none of the dogs on diet A received prednisolone, while 8/11 dogs on diet B still received prednisolone.

The results showed that the nutritional approach of Advance Veterinary Diets Atopic Care was helpful for dogs with atopic dermatitis, achieving a significant reduction of pruritus, skin lesions, and prednisone administered.

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REPRINT PAPER (CH)

Stabilisation of the emergency patient part III: Central Nervous System**

Nadja Sigrist[(1)]

SUMMARY

The emergency patient with decreased consciousness is identified by clinical examination of pupil size and reaction, additional brain stem reflexes, level of consciousness and motor activity. Priority stabilisation of respiration and perfusion is mandatory in the management of patients with neurological diseases and is part of the strategy aiming at preventing secondary neuronal damage induced by hypoxia, hypercapnia and decreased cerebral perfusion. The goal of the emergency stabilisation is maintenance of normal ventilation and oxygenation as well as keeping mean arterial blood pressure above 70 mm Hg. Hypertonic saline, Mannitol and sedation may be indicated with signs of increased intracranial pressure. Seizures must be treated immediately and some patients may require anaesthesia and positive pressure ventilation.

Key words: brain oedema, intracranial pressure, cerebral perfusion, status epilepticus, brain trauma

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Introduction

After stabilisation of the circulation and respiratory problems caused by disturbances of ventilation or oxygenation, the stabilisation of emergency patients concentrates on the central nervous system (CNS).
Disturbances in the central nervous system affect consciousness. The assessment of consciousness and neurological status is particularly important in the neurological emergency patient, but can only be assessed seriously after stabilisation of respiration and circulation, because shock and both hypoxia and hypercapnia can also be the cause of a reduced state of consciousness.

Pathophysiology

Like all organs, the function of the CNS depends on sufficient blood flow and oxygen and energy supply. The brain is a very active organ with a particularly high oxygen and energy demand. It consumes about 20% of the total body oxygen and more than 25% of glucose (Sokoloff, 1981]. Neurones are also not able to retrieve their energy anaerobically to a sufficient extent. Since the brain has only very limited storage capacity for glucose and oxygen, already a minimal lack of energy can lead to brain damage.
Cerebral blood flow depends on the ratio between cerebral perfusion pressure (CPP), and the cerebrovascular resistance. In a healthy brain, the cerebral perfusion pressure is monitored closely to maintain the oxygen and energy supply to the nerve cells [Guyton and Hall, 2000]. Through the so-called autoregulation, cerebral blood flow is kept constant despite changes in blood pressure and cerebral vascular resistance. Cerebral blood flow is effectively self-regulated with cerebral perfusion pressures between 50-150 mmHg. At CPP's above or below this range the cerebral blood flow becomes directly proportional [Busija et al, 1980]. In various diseases of the brain such as in traumatic brain injury, encephalitis, or seizures, autoregulation may be impaired focally or generally, which will also lead to a direct dependence of cerebral blood flow of mean arterial blood pressure (MAP):

CPP = MAP - ICP

The intracranial pressure (ICP) is built up by the skull and its contents (brain parenchyma, cerebrospinal fluid, blood volume)

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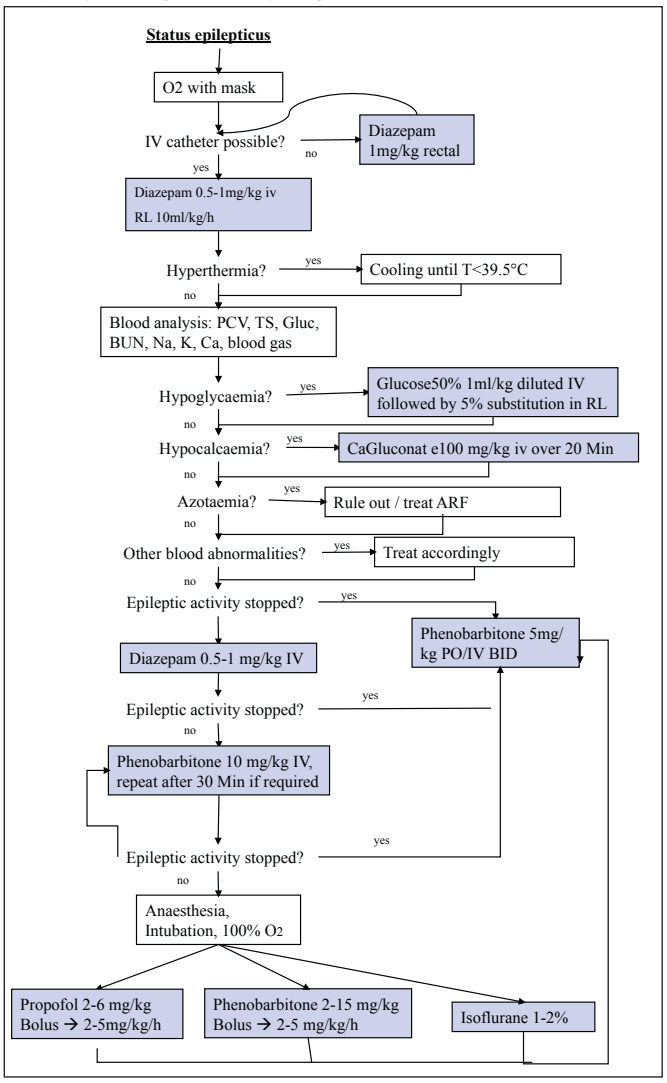
[Bagley, 1996]. Normal ICP in dogs and cats is 5-10 mmHg [Bagley, 1996]. ICP can rise due to volume increase by brain masses, cerebrospinal fluid and blood volume. An increase in ICP results in decreased perfusion pressure (CPP) and cerebral blood flow, decreased blood flow to and diminished supply of brain cells with oxygen and glucose. This leads to secondary changes and cell damage. Intracranial hypertension will lead to alterations of consciousness, respiratory and circulatory abnormalities, and may cause death of the patient by brain herniation.

Clinical symptoms and localisation

The initial brief neurological examination should assess the responsiveness of the patient, the pupil size and response, other cranial nerve functions such as the menace response, and the muscle tone of the limbs [Sigrist and Spreng, 2007]. The clinical symptoms of central nervous system disorders manifest in abnormalities of mentation, cranial nerve deficits, and abnormal posture reactions [Vite and Steinberg, 2003]. The consciousness may be hyperactive, normal, somnolent, stuporous or comatose [Jellinger, 2009]. In a stuporous animal a reaction can be triggered by noise or pain stimulus, while the comatose animal is unconscious and shows no reaction to stimuli [Pschyrembel, 1994, Jaggy and Spiess, 2007]. Hyperexcitability or seizures can also represent clinical signs of an intracranial problem.

Figure 1: Algorithm for seizure control
Adapted from Sigrist and Spreng, 2007



A complete neurological exam is essential to further localise the problem and stabilise the patient. Paretic or paralysed patients with a trauma history should be carefully manipulated until a spinal injury is excluded. The problem can be further localised on the basis of specific neurologic deficits [Vite and Steinberg, 2003]. The spinal reflexes are generally normal with an isolated central nervous system problem [Jaggy and Spiess, 2007]. If posture reactions are abnormal in all limbs, the problem can be localised cranial to C5 [Jaggy and Spiess, 2007]. Ataxia, hemi- or tetraparesis may be caused by lesions in the cortex, cerebellum, brainstem and spinal cord. Identification of walking abnormalities will help identify the localisation [Jaggy and Spiess, 2007]. With a cortical lesion, paresis or compulsive walking will be seen together with abnormal consciousness. Hypermetria, cerebellar ataxia and lack of the menace response are characteristic of a cerebellar lesion. Once cranial nerve deficits can be identified, the brainstem is included in the localisation. In the emergency patient, evaluation of the menace response (except for puppies younger than 4 weeks), pupillary reflex and pupil size and symmetry are particularly helpful. Both miotic and dilated, non-responsive pupils are a sign of a brainstem problem. Anisocoria indicates a lateralised or very focal problem [Oliver et al., 1997]. Horizontal nystagmus, triggered by lateral head movement, is a physiological reflex. The rapid eye movement should take place in the direction of head movement. The lack of a physiological nystagmus indicates a brainstem lesion with swelling, bleeding, or compression.

Decerebrate rigidity with limb extension and opisthotonus is seen with severe brainstem compression or herniation of the brainstem and / or the cerebrum, while an extension of the front limbs and flexion of the hind limbs (decerebellate rigidity) is seen with herniation of the cerebellum.

Respiratory and circulatory parameters can be altered by CNS lesions. Breathing can be changed in many ways and is unfortunately not specific for a certain localisation [Vite and Steinberg, 2003]. The Cushing reflex is seen with massive intracranial hypertension due to cerebral oedema or haemorrhage. The diminished blood flow to the brain results in CO2 accumulation in the brain which leads to activation of the sympathetic circulatory centre, followed by generalized vasoconstriction. The vasoconstriction results in increased blood pressure and a reflex bradycardia, the classic symptoms of the Cushing's reflex [Guyton and Hall, 2000]. Other clinical signs of intracranial hypertension are dilated, non-responsive pupils, stupor or coma and decerebrate rigidity [Vite and Steinberg, 2003].

The Glasgow Coma Scale Score is a simple scale to assess the degree of central nervous system problems [Teasdale and Jennet, 1974] and was adapted [Shores, 1983] and evaluated for veterinary patients [Platt et al., 2001]. The score is most often applied in the traumatic brain trauma patient, where it has prognostic significance, but can also be used to quantify CNS function in any emergency patient. The categories brainstem reflexes (pupillary size and response), motor function and consciousness are divided into six stages with points from 1-6

Mentation	Cranial nerves Pupillary and oculocephalic reflexes (OCR)	Motor activity	Points
Responsive	Normal pupils and OCR	Normal gait, normal spinal reflexes	6
Responsive but depressed	Reduced but present pupil reaction and OCR	Hemiparesis, Tetraparesis	5
Semicomatose, reactive for visual stimuli	Bilateral unresponsive miosis with present OCR	Lateral recumbency, intermittend extensor rigidity	4
Semicomatose, reactive for noises	Pinpoint pupils with decreased or missing OCR	Lateral recumbency, constant extensor rigidity	3
Stupor, reactive for pain	Unilateral unresponsive Mydriasis with decreased or missing OCR	Lateral recumbency, constant extensor rigidity with opisthotonus	2
Coma, no reaction	Bilateral unresponsive Mydriasis with decreased or missing OCR	Lateral recumbency, muscle flaccidity, decreased or missing spinal reflexes	1
Points of physical exam results of mentation, cranial nerve results and motor activity are added for the Glasgow-Coma-Scale Score (GCS-Score).			

Table 1: Modified Glasgow Coma Scale (Shores, 1983)

(Table 1). The higher the score (maximum 18), the better the prognosis. A score of <8 points in dogs with traumatic brain injury is associated with less than 50% chance of survival during the first 48 hours post trauma [Platt et al., 2001].

Differential diagnoses

Depending on the degree of consciousness abnormalities and additional clinical symptoms, various differential diagnoses should be considered [Vite and Steinberg in 2003]. Vascular, infectious / inflammatory, traumatic, congenital anomaly, metabolic, idiopathic, neoplastic and degenerative (acronym VITAMIN D) causes are distinguished [Vandevelde, 2007]. In emergency patients with CNS symptoms, traumatic brain injury, metabolic causes of seizures as well as differential diagnoses of reduced consciousness (Table 2) should be ruled out. Hypoglycaemia, hypocalcaemia and disturbances of sodium haemostasis, as well as many intoxications may lead to both decreased consciousness and hyperexcitability or seizures. Potential neurotoxins are summarized in Table 3 [Gfeller and Messonier, 1998, Peterson and Talcott, 2001].

Table 2: Causes of CNS symptoms in the emergency patient

Decreased mentation (consciousness)	Hyper-excitability	Seizures
Intoxication	Intoxication	Intoxication
Traumatic brain injury		Traumatic brain injury
Encephalitis		Encephalitis
Hypoxia		Hypoxia
Hypoglycaemia		Hypoglycaemia
Hyperglycaemia		
Hypocalcaemia	Hypocalcaemia (Tremor)	Hypocalcaemia
Hypercalcaemia		Hypercalcaemia
Hyponatraemia		Hyponatraemia
Hypernatraemia	Hypernatraemia	Hypernatraemia
Renal insufficiency		Renal insufficiency
Liver failure		Liver failure
Hypotension		Hypotension
Hypoventilation (Hypercapnia)		Thromboembolic disease, infarct
Thiamin-deficiency		Thiamin-deficiency
Hypothyroidison	Hyperthyroidism	
Heat stroke		

Diagnosis

Due to the different metabolic causes of CNS symptoms, a complete blood analysis with CBC, chemistry profile, and if indicated blood gas analysis, coagulation profile and urinalysis, should be performed. In the emergency situation, at least PCV / total protein, glucose, electrolytes including calcium, urea and creatinine, and possibly ammonia should be determined.
Blood pressure, pulse oximetry, ECG and end-tidal CO2 in

Table 3: Neurotoxins

Seizures/Tremor	Decreased mentation
Amphetamine	Amitraz
Lead	Barbiturate
Bromethalin	Benzodiazepine
Carbamate	Bromethalin
Drugs (LSD, Cocaine, Marijuana)	Drugs (Opioids, Ketamine, Cannabis)
Ivermectin	Ethanol, Methanol
Lidocaine	Ethylenglycol
Methaldehyde	Ivermectin
Methylxanthine	Methylxanthine/Theobromine
Mycotoxins	Opioids
Opioids (high doses)	Phenothiazine
Organophosphate	
Pyrethroid	
Zinc phosphide	

intubated patients are not only helpful for monitoring but also for the inclusion or exclusion of the differential diagnoses. Depending on overall condition and other clinical signs, chest radiographs and / or abdominal ultrasound may be indicated.
Depending on the differential diagnosis specific neurological investigations such as CSF analysis, electroencephalogram (EEG), magnetic resonance imaging (MRI) or computed tomography (CT) of the brain may be indicated.

Stabilisation

Stabilisation of emergency patients with CNS problems focuses on the normalisation of breathing and perfusion, followed by measures of intracranial stabilization [Syring, 2005]. The stabilization of breathing and perfusion has been described in the first two parts of this series [Sigrist, 2010a, b]. Specific aspects of oxygen supply and fluid therapy will be discussed in detail. The reduction of secondary damage to the brain by cerebral oedema and / or necrosis, which are favoured by hypotension, hypoxia, hypercapnia, hyperthermia and inflammatory mediators, is an extremely important treatment strategy in neurological emergency patients and is particularly important in patients with traumatic brain injury [Chestnut, 1995]. Normalising oxygenation and ventilation, maintenance of intracranial blood flow through adequate infusion therapy, reduction of cerebral metabolism and if necessary reduction of intracranial pressure and control of seizures are the main goals of treatment [Proulx and Dhupa, 1998, Syring, 2005]

Maintenance of oxygenation

Hypoxia must be avoided since hypoxia leads to an increase in intracranial pressure [Fortune et al., 1995] and is therefore an important mortality factor [Bratton et al., 2007a]. Oxygen supplementation is immediately instituted in every patient with central nervous system disease and can be applied with different techniques [Sigrist, 2010a]. Intranasal or intratracheal oxygen administration should be avoided in patients with intracranial disorders as irritation will lead to sneezing or intensive head movements with subsequent massive increase in intracranial pressure. The animal with persisting hypoxia (SpO2 <90% or PaO2 <60-80 mm Hg) despite oxygen supplementation, or hypoventilation (PCO_2> 40-50 mm Hg) should be intubated and mechanically ventilated, as both hypoxia and hypercapnia lead to intracranial hypertension [Fortune et al., 1995a].

Maintenance of intracranial blood supply

As discussed before, the intracranial blood supply depends on blood pressure and intracranial pressure. Various studies have shown that hypotension (systolic blood pressure <90 mm Hg) is associated with increased mortality [Chestnut et al., 1993, Bratton et al., 2007a]. The aim of fluid therapy is to maintain a cerebral perfusion pressure of at least 50 and a maximum of 70 mmHg [Syring, 2005, Bratton et al., 2007b]. Depending on the intracranial pressure, the loss of autoregulation requires a mean arterial blood pressure of at least 70-80 mm Hg in order to maintain normal cerebral perfusion pressure. Blood pressure optimisation is carried out primarily by the application of fluids that remain in the intravascular space. While the goal of the infusion therapy is clearly defined, a consensus regarding the ideal fluid solution in both veterinary and human medicine is lacking. The intact blood-brain-barrier is impermeable to electrolytes and colloids. However, in neurological emergency patients fluid therapy becomes more difficult as the blood-brain-barrier may show increased permeability, or may even be destroyed [Zhuan et al., 1995]. With a damaged blood-brain barrier, all fluid types may leak from the vascular system and lead to brain oedema. However, the blood-brain barrier is usually only locally destroyed and the benefits of aggressive fluid therapy outweigh a potential local increase of intracranial pressure. Given the possibility of a generalised increased permeability, the isolated use of isotonic crystalloid solutions is less favourable and hypotonic crystalloid solutions are ineffective at increasing the intravascular volume [Feldman et al., 1995]. Combinations of colloidal (5-10 ml/kg) with isotonic crystalloid solutions (10-20 ml/kg), administered as an IV bolus over 10-20 minutes, are given and repeated until normal perfusion parameters and the desired mean blood pressure are achieved [Proulx and Dhupa, 1998; Syring, 2005].
Hypertonic NaCl (3-8%) at a dose of 3-5 ml/kg is discussed as the fluid of choice for traumatic brain injury [Bratton et al. 2007c]. Due to the high osmolarity, hypertonic saline leads to a water shift from the interstitial and intracellular space into the intravascular space, leading to both an increase in blood volume and blood pressure as well as a reduction of cerebral oedema [Bratton et al. 2007c]. Hypertonic saline is therefore specifically indicated in patients with hypovolemia in combination with oedema [Syring, 2005]. Hypertonic NaCl further leads to an improved regional cerebral blood flow and oxygen supply to the tissues by reducing cell swelling, arterial vasodilation and reduction of inflammatory reactions [Doyle. et al. 2001, Bratton et al., 2007b]. Since it is a crystalloid solution, hypertonic NaCl is rapidly distributed in the extracellular space and the effect is therefore only very briefly. By combining it with colloids (dextran or HES) the effect can be extended [Qureshi and Suarez, 2000]. Contraindications for the administration of hypertonic NaCl are hypervolemia, pulmonary oedema, hypernatraemia and chronic hyponatraemia [Bratton et al., 2007c].
After stabilisation of blood pressure and intracranial perfusion, further fluid therapy depends on the needs of the individual patient [Sigrist, 2005].
The cerebral blood flow depends also on the tone of the cerebral vessels. Hypercapnia due to hypoventilation or seizure activity leads to vasodilation and increased intracranial pressure [Fortune et al., 1995a] and should therefore be monitored and possibly corrected by means of ventilation therapy. The target value of PaCO2 is 30-35 mmHg [Syring, 2005, Warner et al., 2008]. It is important to take into account that hypocapnia is also harmful [Muizelaar et al., 1991, Fortune et al., 1995]. Hyperventilation is therefore no longer recommended [Bratton et al., 2007d]. An excessive increase in cerebral blood flow followed by increased intracranial pressure and subsequent increased oxygen consumption can be seen with increased cellular metabolism due to hyperthermia, hypertension, pain, excitement and convulsions. Patients should therefore be kept quiet and receive adequate analgesia, may be sedated and cooled if necessary.

Analgesia and / or sedation should have no side effects on circulation and respiration. Butorphanol (0.1-0.2 mg/kg/h IV), buprenorphine (0.01 mg/kg IV) or fentanyl (3 - 5 µg/kg/h IV) can be used as analgesics, while butorphanol (0.1-0.2 mg/kg IM or IV), diazepam (0.2 mg/kg IV) or midazolam (0.1-0.2 mg/kg IM or IV) can be used for sedation [Haskins, 2006; Dyson, 2008]. Convulsions should be treated urgently (see below).
The temperature is kept in the normal range (37-38 ° C) by actively cooling or warming the patient. Moderate hypothermia (32-33 ° C) is used in human patients with massive increase of intracranial pressure [Bayir et al., 2009], but requires a very intensive monitoring of potential side effects and precise protocols and is therefore not recommended in veterinary medicine.

Reduction of intracranial pressure

An increase in the intracranial pressure is associated with increased mortality, which is why the reduction of the ICP, respectively its normalisation, is an important part of stabilisation [Miller et al., 1977].
Mannitol is an inert sugar with an osmotic effect that is not metabolised, filtered renally and excreted unchanged [Muizelar et al., 1984]. Mannitol increases plasma osmolarity and therefore attracts water from the cerebral interstitial space and has been used for years to reduce intracranial pressure. Besides the osmotic effect on the cerebral interstitium, Mannitol also has favourable effects on the rheology of blood, is a radical scavenger, and shows a cerebral vasoconstriction effect, while at the same time increasing the intravascular volume [Muizelar et al., 1983, Bratton et al. 2007c].
Mannitol not only reduces the intracranial pressure due to the hyperosmolarity but also increases blood pressure, both resulting in an improved cerebral blood flow [Bullock, 1995]. The goal of Mannitol treatment is a plasma-osmolarity of 320 mOsm (normal is 300 mOsm) [Bullock 1995], which is achieved with a dose of 0.25-1 g/kg, administered as a slow IV bolus over 10-20 minutes [Plumb, 2004 ; Bratton et al. 2007c]. Because of fast renal excretion and subsequent diuresis, the increase in blood-pressure by Mannitol is only short-working and it is important that the fluid losses are adequately replaced to prevent hypotension and re-reduction of the CPP. The potential problems of Mannitol extravasation with a damaged blood-brain barrier are negligible in comparison with the positive effect [Bullock, 1995], due to the diuretic effect and potential side effects such as kidney failure and disruption of the integrity of the blood-brain barrier, Mannitol should nevertheless not be given without clear evidence or high suspicion of brain oedema [Bratton et al. 2007c]. If a positive effect is seen after Mannitol administration, mannitol can be repeated every 6-8 hours if necessary [Syring, 2005]. Hypertonic NaCl (3-8%) is also used to decrease the intracranial pressure and is partially effective in patients who are resistant to the pressure-effect of mannitol [Horn et al., 1999]. Elevation of the head by15-30 ° without affecting the blood flow to the brain leads to an improved flow of cerebrospinal fluid, [Platt, 2009]. It is important to ensure that the jugular veins are not compressed (no blood withdrawal or jugular catheter).

Suppression of seizures

The pharmacological interruption of seizures and prevention of consequent damage to the brain are the primary treatment goals following stabilisation of respiration and circulation [Platt and McDonnell, 2000]. Different drugs with an anti-epileptic effect are used to treat seizures and are often combined due to their different onset of action, duration of effect and related side effects.
Diazepam 0.5-1 mg/kg IV is the first choice due to the rapid onset of action [Platt and McDonnell, 2000]. If intravenous administration is not possible diazepam can be given rectally (0.5-2 mg/kg as a suppository or using the intravenous solution) or intranasally (0.5-1 mg/kg of the IV solution) [Plumb, 2004]. The anti-epileptic effect of diazepam occurs within a few minutes but the duration of effect is relatively short [Plumb, 2004]. Diazepam may be repeated two times at intervals of 10 minutes or be given as a continuous rate infusion (CRI) (0.1-0.5 mg/kg/h diluted in 5% glucose) [Plumb, 2004]. Since diazepam is sensitive to light, absorbed by plastic and may lead to thrombophlebitis, a CRI of midazolam is preferable, but there is no established dosage in veterinary medicine. The recommended dose of midazolam for IV or IM application is 0.07-0.3 mg/kg [Platt, 2009]. Midazolam, like Diazepam, has an anti-epileptic effect by the inhibitory effect of stimulated GABA-A receptors [Scott et al., 1998].
To further suppress epileptic activity in the brain, patients with status epilepticus that responded to diazepam or midazolam, should also be treated with a longer-acting antiepileptic drug such as phenobarbitone. Phenobarbitone increases the threshold potential of seizures by the stimulation of inhibitory GABA-A receptors and the inhibition of AMPA receptors which will reduce glutamate release [Plumb, 2004]. Due to the reduced lipid solubility the time to onset of action may take up to 30 minutes [Plumb 2004]. The dosage of phenobarbitone is dependent on the pretreatment and the response to benzodiazepines. If seizures could be stopped with diazepam or midazolam, Phenobarbitone is given as a dose of 2-5 mg/kg BID. With status epilepticus unresponsive to benzodiazepines, the recommended loading dose of phenobarbital is 10-20 mg/kg IV [Platt, 2009]. If no effect is seen after 20-30 minutes, the dose may be repeated up to a maximum of 24-30 mg/kg/24 hours [Platt, 2009].
At the same time metabolic causes of status epilepticus such as hypoglycaemia, hypocalcaemia and other electrolyte changes, azotaemia, hypoxia or severe acid-base changes should be ruled out by blood analysis and treated accordingly if necessary [Sigrist 2007]. Hypoglycaemia should especially be ruled out in puppies. Glucose values <3 mmol/l (60 mg/dl) are treated by means of bolus of glucose (0.5-1 ml/kg of a 50% solution IV, at least two times diluted). The maintenance infusion should be substituted with 5% glucose after bolus therapy (a 5% solution can be reached by adding 50 ml 50% glucose in 500 ml Ringer lactate or NaCl). Hypocalcaemic animals are substituted with calcium. In the case of status epilepticus due to hypocalcaemia calcium is given IV with ECG monitring over 15-20 min (e.g. calcium gluconate 100 mg/kg).
Levetiracetam (Keppra®, UZB Pharma AG Zurich) is a newer antiepileptic drug that is widely used in human medicine. Levetiracetam also appears to be effective and well tolerated in

the dog [Dewey et al., 2008; Volk et al., 2008]. Pharmacokinetic studies to establish an ideal dose in animals with status epilepticus are lacking though.

If the status epilepticus cannot be controlled with diazepam and a loading dose of phenobarbitone, other possible treatment options exist (Figure 1). The patient is placed under general anaesthesia using pentobarbitone, propofol or gas anaesthesia [Claassen et al., 2001]. Pentobarbitone acts like other barbiturates as a GABA-mimetic, inhibits glutamate release and therefore appears to have an anti-epileptic effect in addition to inducing anaesthesia [Plumb, 2004]. Side effects are hypotension through vasodilation and reduced cardiac contractility, hypoventilation, hypothermia, and accumulation leading to a prolonged recovery period and seizure-like activity during recovery [Plumb, 2004]. Pentobarbitone is administered to effect (3-15 mg/kg IV) and repeated as needed. Propofol also acts on the GABA-A receptor, suppresses the central nervous system metabolism and also appears to have anti-epileptic effects [Steffen and Grasmück, 2002], but EEG-controlled studies are lacking in veterinary medicine. Propofol is used as a bolus (1-4 mg/kg) or as a CRI (0.1-0.6 mg/kg/min) [Platt, 2009]. Both propofol and pentobarbitone can be combined with a midazolam drip in order to achieve a dosage as low as possible. The animals should show no more seizures, neither generalised nor locally. With both pentobarbitone and propofol it is debatable whether the central antiepileptic effect is sufficient to suppress the central seizure activity and not only muscular activity. Anaesthetised animals should therefore also receive phenobarbitone (5 mg/kg IV BID). Ideally, the suppression of seizure activity is confirmed by EEG [Claassen et al., 2002]. The recovery period is also monitored by EEG analysis since excitation from the side effects of anaesthetics cannot always be distinguished from epileptic seizures.

Patients are usually anaesthetised for 12-24 hours. This requires intensive monitoring. In order to avoid aspiration, patients should be intubated. Positive pressure ventilation may also be necessary under certain circumstances. However, in most cases, the animals breathe spontaneously and are supplemented with oxygen (by means of an oxygen tube into the endotracheal tube) without being connected to a respirator. The endotracheal tube should be suctioned every few hours or changed to prevent an obstruction or the ascent of bacteria. Intravenous fluid therapy follows the patient's needs. Animals in status epilepticus are usually not in shock, but may be, depending on the cause and are dehydrated because of the increased metabolism resulting in increased fluid requirements. Normally, maintenance dose of these animals is at least 5 ml/kg/hr of an isotonic crystalloid solution (e.g., Ringers lactate).With clinical signs of dehydration or desired fluid diuresis (intoxications, renal failure) this dose can be doubled [Sigrist, 2007].

Temperature control

Animals in status epilepticus often present with hyperthermia. Active cooling can occur with wet towels, ice packs, cold infusions, by wetting the fur, or if necessary, bladder or abdominal lavage with cool infusion solutions [Platt and McDonnell, 2000]. Active cooling should be stopped at a temperature of 39.5 ° C to avoid subsequent hypothermia.

Steroids

Steroids are rarely indicated for central nervous system problems [Platt et al., 2005]. With traumatic brain injury or cerebral oedema, clinical studies showed no beneficial effect of steroids [Bratton et al., 2007e]. High dose methylprednisolone results in increased mortality in both patients with traumatic brain injury [Roberts et al., 2004] and in patients with acute trauma to the spinal cord [Carlson et al. 2003]. Steroids have various side effects such as hyperglycaemia, immunosuppression, gastric ulceration, and delayed wound healing and are therefore not indicated in emergency patients with disorders of mentation [Marshall et al., 1977]. In particular, the induction of hyperglycaemia has a negative impact on prognosis.

Glucose control

Hyperglycaemia leads to reduced neurological outcome and increased mortality both experimentally and in human studies [Natale et al., 1990, Cherian et al., 1998]. The only (retrospective) study in dogs and cats with traumatic brain injury did not find any correlation between glucose values and outcome [Syring et al., 2001].

Decontamination

In case of suspected poisoning with neurotoxins (Table 3) the decontamination of the gastro-intestinal tract is an important part of emergency treatment [Sigrist, 2007]. The induction of vomiting is generally not indicated as altered consciousness or seizure activity will increase the risk of aspiration pneumonia [Rosendale, 2002]. Gastric lavage under anaesthesia is indicated if the toxin has been ingested less than 2-4 hours ago and severe poisoning is very likely. Animals should be intubated and the cuff inflated for a gastric lavage to prevent aspiration of irrigation fluid. The stomach is repeatedly rinsed with 5-10 ml / kg warm water until clear liquid is retrieved. The risks of gastric lavage, such as anaesthesia risk and aspiration pneumonia, must be weighed against the benefits. In animals that are intubated for other reasons (coma, convulsions), the benefit of gastric lavage outweighs the risks in most cases, and can also be carried out if the toxin ingestion is longer than four hours ago.

After gastric decontamination, the administration of activated charcoal (1-4 g / kg PO) to bind remaining toxin is probably the most effective decontamination strategy [Rosendale, 2002]. Activated charcoal may be administered orally or by gastric tube. Activated charcoal binds most of the neurotoxins and also oral medications such as phenobarbital. Laxatives such as sorbitol or lactulose can accelerate toxin elimination through the gastrointestinal tract.

Monitoring

Animals with central nervous system problems should be monitored regularly. Respiration, oxygenation, perfusion parameters including blood pressure and temperature are checked continuously in some patients. Haematocrit, total protein, glucose and electrolytes should be checked at least daily. After hyperosmolar therapy with mannitol or hypertonic

saline, electrolytes (sodium, potassium, and chloride) should be measured 30-60 minutes after administration. If abnormal findings are found, electrolytes are initially checked every hour followed by every 2-3 hours. In hypoglycaemic patients glucose is checked every hour after replacement until the glucose level has stabilized. The neurological status, in particular pupil size and response, or the GCS score respectively, is also verified several times a day (depending on the condition of the patient every 1-6 hours). Stuporous, comatose or anaesthetised patients are monitored with heart rate / rhythm, respiratory rate, temperature, mucous membrane colour and capillary refill time, SpO2, blood pressure and end-tidal CO2. The care of these patients also includes the application of eye ointment and oral hygiene, change of side every 2-3 hours, soft padding and control of urination. Arterial blood gas analysis, or at least a venous blood gas for PCO2 determination should be measured every 3-6 hours in stuporous and / or intubated patients to detect ventilation or oxygenation problems in time to fix them.

The measurement of intracranial pressure is one of the most important parameters in monitoring a patient with traumatic brain injury. The measurement of ICP's is recommended in human medicine in patients with traumatic brain injury and a GCS score <8 and CT signs of swelling, bleeding, contusion or herniation [Bratton et al., 2007f]. Various methods of ICP measurement exist, with the ventricular catheter as the most accurate and least expensive method [Bratton et al. 2007g].

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ORIGINAL WORK (B)

Canine nasal adenocarcinoma with atypical intracranial extension: computed tomography and magnetic resonance findings

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SUMMARY

This case report describes the computed tomography (CT) and magnetic resonance imaging (MRI) characteristics of a canine nasal tumour with atypical intracranial extension in a 10-year-old female large Münsterländer with progressing complaints of difficulties opening her mouth, dullness and weight loss. A presumptive diagnosis was made based on CT and MRI. Due to the poor prognosis, the owner opted for euthanasia of the dog. The mass was histopathologically examined and diagnosed as a nasal adenocarcinoma with intracranial extension and surrounding soft tissue involvement.

Keywords: nasal adenocarcinoma, intracranial, CT, MRI

Introduction

Nasal and paranasal tumours are uncommon in dogs; they account for up to 2.5 per cent of all canine tumours [1,2]. Among nasal tumours, adenocarcinoma is the most common [3]. Animals with nasal tumours have a wide range of clinical signs such as sneezing, nasal discharge, epistaxis, dyspnoea and facial deformity. Dogs with nasal adenocarcinomas have also been presented with neurological abnormalities without clinical signs related to abnormalties in the nasal cavity [4,5,6]. To detect changes in the nasal cavity, CT is superior to conventional radiography [7,8,9] and it provides similar information as MRI for the evaluation of canine intranasal neoplasia without intracranial extension [9]. MRI is superior in visualising brain pathology because of its multi-planar capabilities, increased sensitivity and better soft tissue characterization. In this case report the CT and MR imaging characteristics of a nasal adenocarcinoma with intracranial extent are described and discussed.

Case presentation

A 10-year-old female large Münsterländer weighing 27 kg, was admitted to the Department of Medicine and Clinical Biology of Small Animals, Ghent University with progressing complaints of difficulties opening her mouth, dullness and weight loss. From three weeks prior to presentation, opening her mouth was painful and she was unable to eat and drink in a normal way. Atrophy of the masticatory muscles appeared. Several antibiotics, non-steroidal and steroidal anti-inflammatory drugs were prescribed without clinical improvement. Physical examination revealed no abnormalities. Neurological examination revealed severe dullness, exophthalmia of the right eye, peripheral blindness in the left eye, painful reaction when trying to open the mouth and on palpation of the right masticatory muscles. Bilateral atrophy of the masticatory muscles was present. Due to abnormal consciousness, the exophthalmia and the pain, a right forebrain lesion with possible retrobulbar expansion was suspected.

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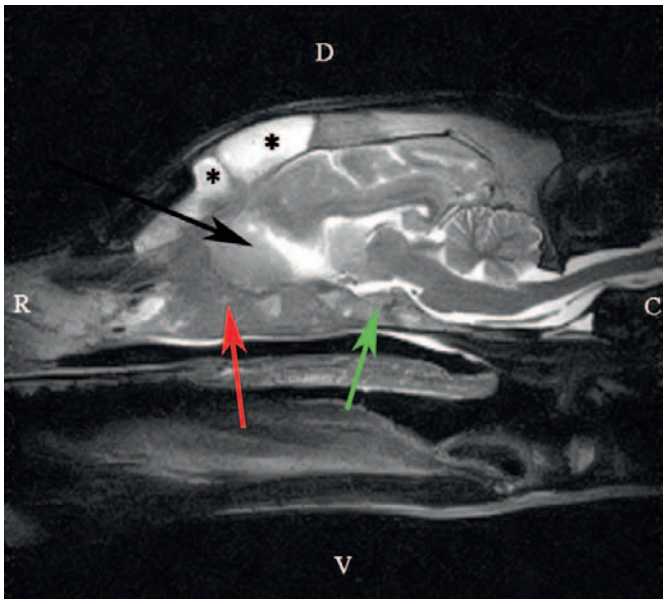

Fig. 1 Sagittal T2W image of the head. An irregular, ill-defined heterogeneous mass is visible in the olfactory bulb and frontal lobe (black arrow), more ventral (green arrow) and more caudal on the transition between the hard and soft palate (red arrow). An hyperintense signal is visible in the frontal sinus (*).

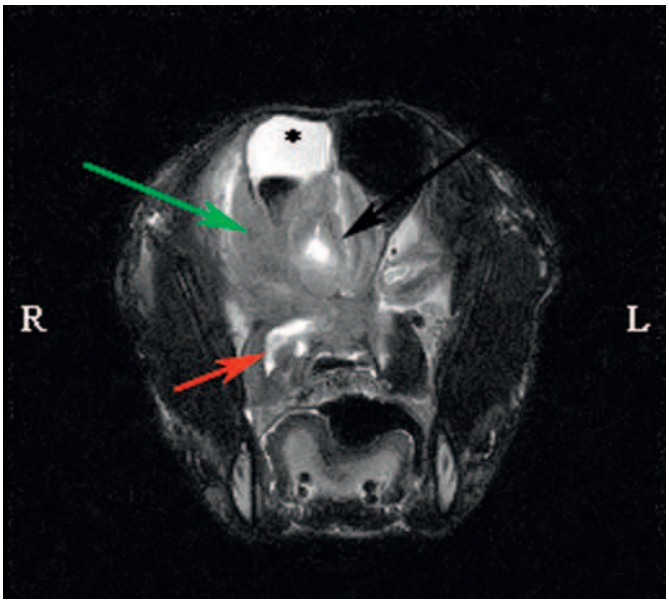

Fig. 2 Transverse T2W image at the level of the frontal lobe of a dog. A midline shift to the left is visible (black arrow). A hyperintense signal is visible in the right frontal sinus (*). An abnormal high signal is visible in the region of the medial pterygoideus muscle (red arrow) and the temporal muscle on the right side (green arrow).

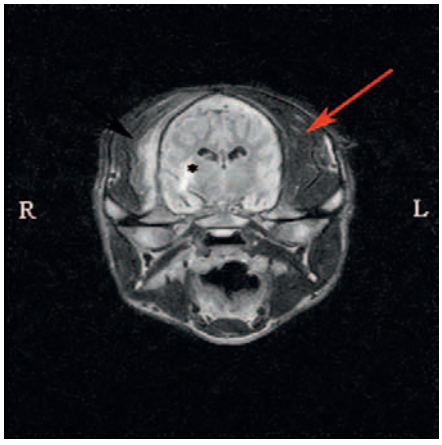

Fig. 3 Transverse FLAIR image at the level of the temporal lobe. Atrophy of the masticatory muscles (black arrow) is visible on the right side. Normal size of the masticatory muscles (red arrow) is visible on the left side. An hyperintense signal is visible in the temporal lobe (*), oedema is present.

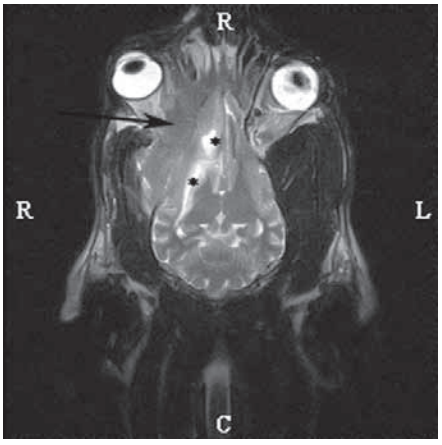

Fig. 4 Dorsal T2W image of the head. A retrobulbar heterogeneous mass is visible on the right side (black arrow) with exophthalmia of the eye. Multiple hyperintense regions (*) are visible in the right part of the cerebrum.

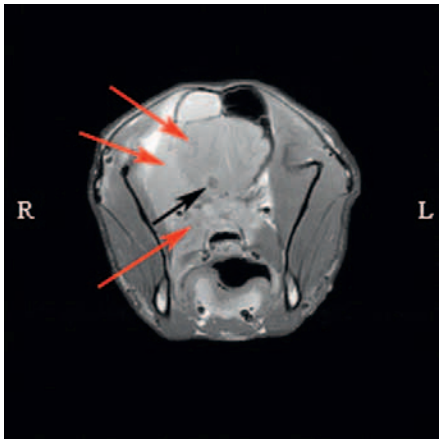

Fig. 5 Transverse post contrast T1W image at the level of the frontal lobe. Heterogeneous contrast enhancement is visible in the mass (red arrows). Rim enhancement (black arrow) of the hypointense lesions is visible.

To identify the lesion, an MRI (0.2 Tesla scanner; Airis Mate; Hitachi Medical Corporation) of the brain was performed with the dog in dorsal recumbency and the head in a human knee coil. The MRI procedure was performed under general anaesthesia. The dog was premedicated with a combination of 0.02 mg/kg acepromazine (Placivet; Codiphar) and 0.1mg/kg morphine (Morphini HCl; Sterop), both administered intravenously (IV). Anaesthesia was induced with 0.2 mg/kg midazolam (Dormicum; Roche) IV, preceding propofol (Propovet; Abbott Animal Health) administration to effect (total dose of 50 mg) IV and maintained with isoflurane (Isoflo; Abbott Animal Health) vaporized in oxygen using a rebreathing system. Images were obtained in three planes. Sequences included T1-weighted (T1W), T2-weighted (T2W) spin echo (SE) and fluid attenuated inversion recovery (FLAIR). T1W SE were also aquired after intravenous paramagnetic contrast medium (0.3 ml/kg; Magnevist; Bayer HealthCare Pharmaceuticals Inc.) injection. On the sagittal T2W images an irregular ill-defined heterogeneous mass was visible. The mass invaded the conchae, lamina cribrosa, olfactory bulb, frontal, parietal and temporal lobes on the right side. There was a ventral extension visible in the nasal recess and caudal on the transition between the hard and the soft palate (Fig 1). Normal outline of several bones of the skull was absent. The mass contained multiple hyperintense

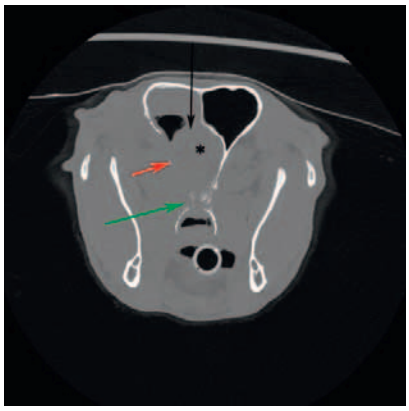

Fig. 6 Transverse CT image at the level of the olfactory bulb (*). Destruction of the lamina cribrosa (black arrow), nasal bone (red arrow) and ethmoid bone (green arrow) is visible.

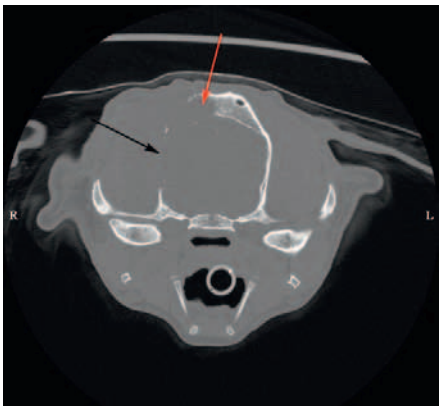

Fig. 7 Transverse CT image at the level of the parietal lobe. Destruction of the frontal bone (black arrow) is visible. The right frontal sinus is filled with a soft tissue density (red arrow).

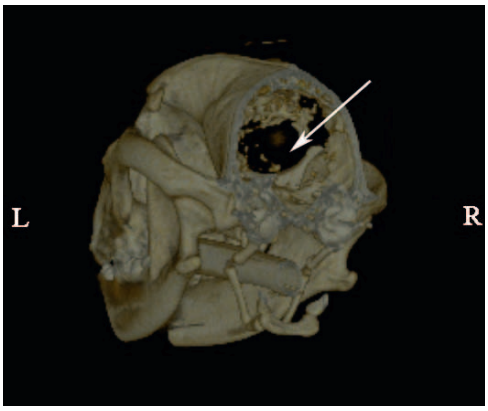

Fig. 8 3D reconstruction (OsiriX) of the head. Destruction of the bony structures on the right side is visible (white arrow).

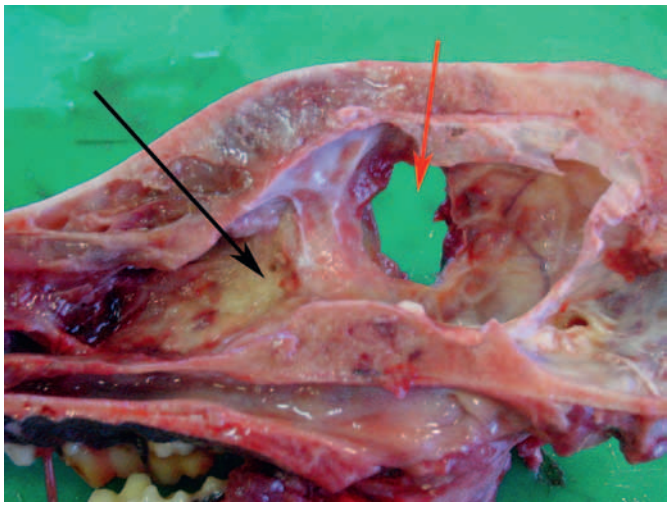

Fig. 9 Postmortem image of the right side of the skull. A pale soft mass (black arrow) is visible. An osteolytic lesion at the right side of the skull is visible (red arrow).

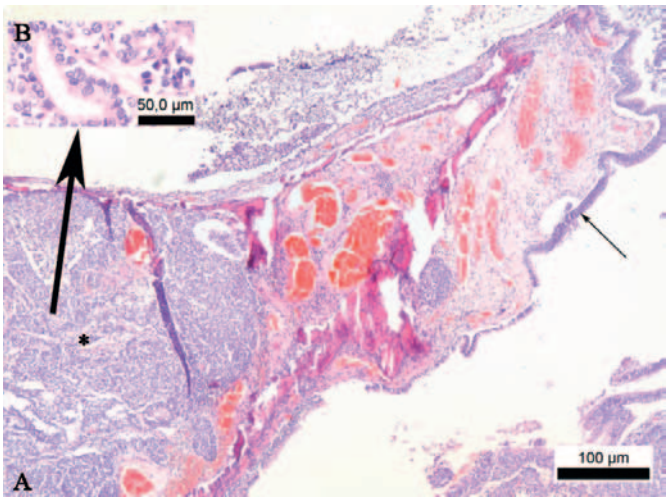

Fig. 10 Histopathological image of the nasal adenocarcinoma. Haematoxylin and eosin staining. A) Normal nasal mucosa (small arrow) and a densely cellular neoplasm (*) B) Detail of the neoplastic tissue. Neoplastic cells have a predominantly tubular arrangement.

signals on T2W images and hypointense signals on T1W images. A hyperintense signal was visible in the frontal sinus on T2W and T1W images. Transverse images revealed a midline shift to the left, an abnormal high intensity signal in the region of the right temporal and medial pterygoideus muscle and atrophy of the masticatory muscles (Fig 2). On FLAIR images multiple hyperintense regions were visible in the muscles, olfactory bulb, frontal and temporal lobe (Fig 3). Dorsal T2W images revealed a heterogeneous mass in the right retrobulbar region causing exophthalmia of the right eye (Fig 4). Post contrast images revealed heterogeneous contrast enhancement of the mass and rim enhancement of the hypointense lesions on T1W (Fig 5).

Because there was bone involvement visible on MRI an additional CT examination was performed to see the extension more clearly. A multi-slice helical CT scanner (GE Lightspeed QX/I; General Electric Co.) was used with the patient in dorsal recumbency. Images were obtained before and immediately after administration of 2 ml/kg intravenous contrast medium (Ultravist 300; N.V. Shering S.A.). Extensive destruction of the skull was visible on the right side from the region of the parietal lobe affecting two thirds of the nasal bone. Thinning and partial destruction of the pterygoid and presphenoid bone was present. The right part of the nasal cavity was filled with a soft tissue opacity (Fig 6). A partial destruction of the turbinates and destruction of the lamina cribrosa was also visible (Fig 7). Homogeneous moderate contrast uptake was visible in the mass. When using the 3D reconstruction tools of a DICOM viewer (OsiriX) the extent of the bone destruction becomes clearly visible (Fig 8). After discussing these findings with the owner, euthanasia was preferred because of the poor prognosis.

At postmortem examination, there was a multilobular retrobulbar mass visible in the right nasal cavity and sinuses. The mass was pale, soft and not encapsulated with infiltrative growth into the ethmoid, bulbus olfactorius, surrounding bones and soft tissues. The right parietal bone showed a 4 by 4.5 cm osteolytic lesion associated with invasive tumour growth (Fig 9). Microscopically, the tumour cells were arranged in simple columnar tubular

structures, and closely-packed simple non-secreting acini, within a fine fibrovascular stroma (Fig 10). The neoplastic cells were small cuboidal to medium-sized columnar, with basal or central round to oval nuclei and a moderate amount of granular eosinophilic cytoplasm. The mitotic index was low (1/high-power field). Extensive haemorrhages, multifocal necrosis and neutrophilic infiltration were noted. Findings were consistent with a nasal tubulopapillary adenocarcinoma with infiltration of the surrounding soft tissues, rostral part of the brain and skull.

Discussion

Because of the predominance of the neurological signs in this dog a lesion in the forebrain and/or retrobulbar region was suspected. Previous articles [10,11,12] elected MRI as the imaging modality of choice for intracranial lesions. When a mass lesion is found on MRI, primary and metastatic tumours, granulomas associated with granulomatous meningoencephalitis (GME) or cryptococcocis, infectious/inflammatory diseases such as toxoplasmosis or distemper, haemorrhages, abscesses, cysts, etc [13] can be included as differential diagnoses. Characteristics such as anatomical location, axial origin, shape and margins of the lesion, signal intensity and pattern, mass effect and contrast uptake could provide a good idea of the nature of the lesion [11]. The involvement of the nasal structures and the osteolytic content raised the suspicion of a primary nasal tumour with a secondary intracranial extension. Nasal tumours tend to extend intracranially through the cribriform plate or other cranial bones (frontal or presphenoid bones) [14]. They can also extend more caudally through the frontal sinuses, nasopharynx and the caudal recesses [15]. Malignant nasal tumours can invade the cranial cavity and cause neurological signs but minimal or no clinical signs of nasal disease. Because of this, diagnosis is quite difficult [4,5]. The CT features of nasal tumours are described previously and include soft tissue attenuating material in the nasal cavity which may extend into the ipsilateral frontal sinus, pterygopalatine fossa and cranial vault with destruction of turbinates, nasal septum and other surrounding bones including the cribriform plate. The presence of a mass effect, destruction of vomer, the cribriform plate, paranasal bone, invasion of the sphenoid sinus by a mass and nasopharyngeal invasion are associated with a diagnosis of neoplasia on MRI [16]. High signal intensity on T2W and T1W images in the frontal sinuses is typical for retained secretions because they contain high protein, fat and blood products. Accumulation of secretions caudal to a nasal mass is consistent with obstructive rhinitis and frontal sinusitis [9]. Hyperintense T2W regions in the mass are suspected cystic lesions which can be confirmed by rim enhancement after contrast uptake. The increased signal intensity in the extracranial soft tissues on T2W images and contrast enhancement indicate tumour invasion or increased vascular permeability from secondary tissue reaction [4]. Abnormal signal intensity could also be a sign of muscle atrophy.

Our MR and CT-findings corresponded with those found for nasal adenocarcinomas [10,11]. Tissue biopsy is necessary for definitive diagnosis [10]. Histological features of nasal adenocarcinomas include glandular patterns (papillary, tubulopapillary and acinar), cuboidal to columnar cells with round or oval nuclei and presence of secretory products [17].

Choosing the right imaging modality for a patient is challenging and is based on a detailed history, clinical examination of the animal and suspected diagnosis. Lesions and their extension seen on both imaging modalities are an important value in further treatment and prognosis of the disease.

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REPRINT PAPER (A)

A quick guide through the feline lymphoma complex

B. Wolfesberger[(1)]

SUMMARY

Lymphoma represents the most common malignant tumour in cats. Genetic factors, retrovirus infections, chronic inflammation, immunosuppression and passive smoking are discussed as possible causes. Clinical signs at presentation normally depend on the anatomic site of the tumour. The alimentary form occurs most frequently with an increasing incidence, followed by extranodal, nodal and mediastinal lymphoma. Cytology is an important diagnostic tool and samples can be obtained by ultrasound-guided fine-needle aspiration and thoracocentesis. In most cases, tentative diagnosis is confirmed by the results of the cytological examination. However, a histopathological examination is essential for establishing a state-of-the-art diagnosis. At present, the pathohistological classification systems are being reorganized, replacing the older WF (Working Formulation) with the newer REAL/WHO (revised European-American Classification of Lymphoid Neoplasms/World Health Organisation) Classification. The latter evaluates not only the morphology but also the immunophenotype of neoplastic cells.

The cornerstone of the treatment of feline lymphoma, an almost exclusively systemic disease, is chemotherapy, which in general is tolerated well by cats. Radiation therapy has proven successful especially in nasal lymphoma. Its usefulness in all other forms is not known yet. In addition, the impact of surgery as part of therapy is still unclear, with insufficient studies performed.

Prognosis for nasal or nodal lymphoma appears to be fair to good, with cats showing prolonged survival times of about one to two years. Mediastinal, spinal, renal and alimentary lymphoma has a less favourable prognosis, and median survival times of less than six months are quite common.

Keywords: feline lymphoma, anatomic classification, staging, pathohistological classification, chemotherapy, radiotherapy.

List of abbreviations used - see end of paper

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Introduction

Lymphoma is the most common hematopoietic tumour in humans and its term was introduced by the British doctor Thomas Hodgkin in 1832. Based on his name, lymphoid tumours were accordingly divided into Hodgkin and Non-Hodgkin lymphoma in human medicine. While in human medicine both neoplasia types play an important role, Non-Hodgkin lymphoma is far more common in veterinary medicine. Later, a description of lymphosarcoma followed by Virchow in 1863 and in 1871 Billroth suggested using the term "malignant lymphoma" to describe lymphoid tumours.

There is no benign lymphoma, as all are malignant tumours. Therefore, today these terms are used as synonyms in human and veterinary medicine. Lymphoma is a cancer developing

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in lymphocytes of the immune system, which can involve any organ or tissue. Lymphoma is the most common malignancy in the cat, representing up to 41 % of all malignant feline tumours [MacVean *et al.*, 1978].

Aetiology

Genetic factors

The feline leukaemia virus (FeLV), a retrovirus, is a possible tumorigenic agent, disturbing either the tumour suppressor genes or the proto-oncogenes by insertional mutagenesis [Fujino *et al.*, 2008]. The relative risk of developing lymphoma was shown to be 62 times greater in cats infected with FeLV and 77 times greater if the cat was infected with both FeLV and feline immunodeficiency virus (FIV) [Shelton *et al.*, 1990]. Interestingly, although 60-70 % of cats were feline leukaemia virus positive between 1960-1980, this FeLV-associated lymphoma rate decreased lately, in contrast to the general lymphoma incidence, which increased by about 20 % [Louwerens *et al.*, 2005]. Simultaneously, the age class of affected animals changed from younger (<6 years) FeLV-positive cats to older (>10 years) FeLV-negative cats [Vail *et al.*, 1998], although one has to bear in mind that in 22 % of cats, FeLV-negative ELISA tests showed a positive FeLV polymerase chain reaction (PCR) in lymphoma tissue [Gabor *et al.*, 2001].

Tumour suppressor genes are also discussed in transforming normal cells to neoplastic ones. The cyclin-dependent kinase inhibitor $p27^{Kip1}$ is considered as a tumour suppressor gene and was found to be reduced in both B and T-cell feline lymphomas [Madewell *et al.*, 2001]. Proto-oncogens (e.g. Ras from rat sarcoma; includes N-ras, H-ras, K-ras), which can be converted by mutation into active oncogenes leading to a permanent growth-stimulating signal in the cell are a possible cause of tumorigenesis. However, in a study of 15 feline lymphoma patients only one cat showed a mutation in N-ras [Mayr *et al.*, 2002], so that the importance of this particular proto-oncogene seems questionable in cats.

Telomeres, the regions at the end of chromosomes in normal cells, are shortened after each replication cycle and therefore limit cells to a fixed number of mitosis. Almost all neoplastic cells express the nuclear enzyme telomerase, which is able to elongate telomeres, a process that leads to immortalization. In a study of Cadile *et al.* [2001], the four examined feline tissue samples (peripheral lymph node, nasal, mediastinal and intestinal lymphoma) all demonstrated telomerase activity; however, telomerase activity appears to be rather an indicator of immortality [Kim *et al.*, 1994], an essential step in the development of malignant tumours, than the primary cause of tumorigenesis.

Immunosuppression

Cats infected with the feline immunodeficiency virus have a six-fold higher risk of developing lymphoma [Shelton *et al.*, 1990], most likely due to an indirect effect of immune dysfunction, although a direct role was also discussed in one case where integrated provirus was found in tumour DNA [Beatty *et al.*, 1998].

Feline patients receiving immunosuppressive therapy with cyclosporine after renal transplantation had 6.1 times higher odds to develop a tumour compared with the control group; 24 % (11 of 45 cats) were diagnosed with post-transplant malignant neoplasias, four of them representing lymphomas [Schmiedt *et al.*, 2009].

In human patients, an increased incidence of lymphoma has been found after treatment of inflammatory bowel disease with immunosuppressive drugs like azathioprine or methotrexate [Farrell *et al.*, 2000]. To date no studies concerning IBD therapy and risk of lymphoma development have been performed in cats.

Chronic inflammation

Inflammatory bowel disease (IBD) as a cause of lymphomagenesis is still controversial in human medical literature as some studies demonstrated a higher risk for IBD patients [Jones and Loftus, 2007], while this could not be observed in other studies.

Sound proof is also still lacking in feline IBD patients. One cat, diagnosed with lymphoplasmacytic enteritis, developed alimentary lymphosarcoma 15 months later [Hart *et al.*, 1994]. One cat, which was diagnosed with intestinal lymphoma, had concurrent lymphoplasmacytic gastritis and two cats showed concurrent colitis [Carreras *et al.*, 2003]. Three cats had been treated for IBD for 5, 14 and 24 months prior to the diagnosis alimentary lymphoma [Zwahlen *et al.*, 1998].

Bacterial pathogens causing chronic inflammatory diseases seem to play an important role in malignant transformations. Only recently, an association between *Campylobacter jejuni* infection in humans and mucosa-associated lymphoid tissue (MALT) lymphoma of the intestines has been discussed. A causative link between *Helicobacter pylori* infection and development of gastric MALT lymphoma has already been firmly established in human medicine [Du, 2007]. A significant association between the presence of the spiral organism *Helicobacter heilmanii* and lymphoma or gastritis was recently described in cats [Bridgeford *et al.*, 2008].

Passive smoking

Cats living in households where at least one package of cigarettes was smoked daily, had a significant threefold increase in risk for developing lymphoma [Bertone *et al.*, 2002].

Diagnostic approach and staging

After full clinical assessment, abdominal ultrasonography and thoracic radiographs are essential steps to evaluate the extent of the disease.

For a more specific evaluation of nasal cavities, brain or spine, the performance of myelograms, computed tomography or magnetic resonance imaging is also indicated.

A complete blood count with thrombocyte count, biochemistry profile with calcium, urinalysis and tests for FeLV and FIV should be performed. Additionally, serum cobalamin concentrations should

be assessed as 78 % of tested cats had low concentrations [Kiselow *et al.*, 2008]. Evaluation of bone marrow aspirates is necessary to complete clinical staging [Table 1, Mooney *et al.*, 1987].

Fine needle aspiration of suspected masses, thoracocentesis, abdominocentesis and cerebral fluid puncture are elegant, cheap and low-risk procedures to obtain sufficient material for cytological examination. An experienced veterinary cytopathologist is able to differentiate between neoplastic and inflammatory disease in most cases. Therefore, cytological analysis is the first important step to confirm the tentative diagnosis of lymphoma.

Histological classification systems

Diseases need to be described, defined and named before they can be diagnosed, treated and studied; hence a worldwide consensus classification system of lymphoid diseases is essential to categorize its different entities [Swerdlow *et al.*, 2008]. Histopathology is critical to this process. To perform state-of-the-art diagnostics in feline lymphoma, it is most important that tissue biopsies of every patient are evaluated by histopathologists.

In 1994, a new histopathological classification system named the REAL classification (Revised European-American Classification of Lymphoid Neoplasms) was instituted by the human medicine International Lymphoma Study Group. Pathologists did not try to stratify lymphomas on the basis of their histological grade (as done in the Kiel and Working Formulation classification of human and veterinary medicine) but used morphology, immunophenotype, genetic abnormalities, clinical presentation and course to differentiate the heterogeneous group of distinct lymphoid diseases. It appeared that lymphomas were unrelated to each other and that they could not be considered as a single illness with a spectrum of histological grade and clinical behaviour. The successor version of the REAL classification is the WHO (World Health Organization) classification, which was developed over seven years, first published in 2001 and updated 2008 for human medicine [Swerdlow *et al.*, 2008]. It emphasises that each disease must be assessed individually, that clinical groupings for protocol treatment are not feasible and that therapies for one lymphoma type is not necessarily applicable to other lymphomas, even if they originate from the same cell lineage. In the WHO classification, each lymphoma is a distinct disease entity, and therefore it is necessary that both clinicians and pathologists learn the histological and clinical spectrum of each of these diseases [Jaffe *et al.*, 2008].

Table 1: Clinical Staging System for Feline Lymphoma according to Mooney et al. (1987)

Stage I	Single tumour (extranodal) or single anatomic area (nodal) includes primary intrathoracic tumours
Stage II	Single tumour (extranodal) with regional lymph node involvement Two or more nodal areas on the same side of the diaphragm Two tumours (extranodal) with or without regional lymph node involvement on the same side of the diaphragm A primary resectable gastrointestinal tumour with or without mesenteric lymph node involvement only
Stage III	Two tumours (extranodal) on opposite sides of the diaphragm Two or more nodal areas on opposite sides of the diaphragm All extensive, primary, unresectable intra-abdomial disease Paraspinal or epidural tumours, regardless of other tumour sites
Stage IV	Stages I to III with liver and/or spleen involvement
Stage V	Stages I to IV with tumours with initial involvement of the central nervous system and/or bone marrow

In veterinary medicine, the older classification system of the National Cancer Institute (NCI), the Working Formulation (WF) classification, was already compared to the more recent REAL classification system in cats by Valli *et al.* [2000].

To classify the specific tumour correctly in the future and determine the cell line origin of the neoplastic cells, immunophenotyping will be essential. Immunophenotypes can be routinely evaluated by immunohistochemistry on histological sections [Zwahlen *et al.*, 1998; Pohlman *et al.*, 2009] or at research institutions by flow cytometry.

Sometimes, diagnosis of lymphoma can be very difficult when using the usual histological and immunophenotypic assessment. For these cases, demonstration of a clonal population of lymphocytes is an elegant method that suggests malignancy. Clonality is not synonymous with neoplasia, but an important hallmark of cancer. Much research has been done to develop molecular clonality assays to improve diagnostic tools for feline lymphoproliferative diseases [Moore *et al.*, 2005; Werner *et al.*, 2005; Henrich *et al.*, 2009].

Anatomical Classification

Alimentary (intestinal, gastrointestinal) lymphoma

The term "abdominal form" is occasionally used and includes all gastrointestinal forms plus kidney, liver, spleen, and pancreatic lymphoma. Sometimes renal lymphoma has been described as a separate form.

Epidemiology

Alimentary lymphoma manifests as an infiltrative process, which most commonly affects the small intestine (50-80 %), the stomach (25 %), the ileocaecal junction and the large intestine with or without mesenteric lymph node involvement. The reported frequency of the alimentary form ranges from 18-68 % of all lymphomas [Gabor *et al.*, 1999; Valli *et al.*, 2000; Kristal *et al.*, 2001; Teske *et al.*, 2002; Kiselow *et al.*, 2008]. Its overall rate has been steadily increasing since 1995 and today

alimentary lymphoma appears to be the most common form of feline lymphoma [Louwerens *et al.*, 2005].

Clinical presentation

Common clinical signs include loss of body mass, anorexia, lethargy, diarrhoea, vomiting [Zwahlen *et al.*, 1998; Kiselow *et al.*, 2008; Krick *et al.*, 2008]; in some cases, haematochezia, tenesmus [Slawienski *et al.*, 1997] and pica [Mahoney *et al.*, 1995] were observed. In most cats, a palpable mass (52-85 %) or thickened bowel loops could be detected on physical examination [Mahoney *et al.*, 1995; Slawienski *et al.*, 1997; Zwahlen *et al.*, 1998].

Diagnostic approach and staging

Loss of structure of gastric wall layers, gastric or intestinal wall thickening, decreased echogenicity and loss of motility are typical ultrasonographic findings in alimentary lymphoma [Penninck *et al.*, 1994; Hittmair *et al.*, 2000]. Cytological examination of ultrasound-guided fine-needle aspirations often indicates lymphoid neoplasia but for definitive diagnosis of the various lymphoma subtypes a histopathological evaluation is warranted. Samples can be obtained by surgery, laparoscopy or endoscopy. Endoscopy is an appealing method as it avoids surgery, and it was previously considered as the gold standard for alimentary lymphoma diagnosis. However, a study from Evans *et al.* [2006] revealed that although gastric lymphoma could be diagnosed on the basis of endoscopic biopsies, these biopsy specimens were of no diagnostic value for the differentiation between IBD and lymphoma in the small intestine. Full–thickness biopsies obtained by exploratory laparotomy or laparoscopy rendered superior and more reliable results. It is essential to obtain an adequate sample to get reliable histopathological results.

Recently, the REAL/WHO classification was specifically used to describe feline gastrointestinal lymphoma [Pohlman *et al.*, 2009], subclassifying for example the low-grade diffuse small lymphocytic tumour into the B-cell small lymphocytic and epitheliotropic T-cell lymphoma, or the high-grade immunoblastic lymphoma of the Working Formulation into diffuse large B-cell immunoblastic nuclear type, T-cell lymphoblastic and large granular lymphocyte lymphoma (Table 2). Large granular lymphocyte lymphoma is the one kind of lymphoma which is very difficult to diagnose on routine HE-stained tissue sections and it is believed that cytology is more sensitive for the identification of the characteristic azurophilic cytoplasmic granules [Roccabianca *et al.*, 2006].

The question whether alimentary lymphomas present more often as B-cell tumours or as T-cell malignancies is still under discussion. Some studies found more T-cell tumours [Zwahlen *et al.*, 1998; Carreras *et al.*, 2003; Kiselow *et al.*, 2008], while a higher incidence of B-cell lymphomas was observed in other studies [Gabor *et al.*, 1999; Waly *et al.*, 2005]. These contradictive results may be due to the fact that the examiners did not classify the tumours according to their location. In a study of Pohlman *et al.* [2009], all gastric and nearly all (88 %) large intestine lymphomas were of B-cell origin, while the majority of small intestinal tumours originated from T-cells (52 %); a smaller number of small intestinal lymphomas derived from B-cells (38 %) and only a few were nonreactive for B- and T-cell markers. Irrespective of the identified immunophenotype, all cats tested FeLV-negative on an ELISA. In contrast, two of six paraffin-embedded feline lymphomas showed a positive FeLV status by PCR [Jackson *et al.*, 1996]. Large granular lymphocyte lymphoma showed either a T-cell phenotype or lacked T- and B-cell markers, which is highly suggestive of a cytotoxic T-cell or a natural killer cell origin of this distinct type of lymphoma [Darbes *et al.*, 1998; Endo *et al.*, 1998; Roccabianca *et al.*, 2006].

REAL/WHO	WF
T-cell lymphoblastic	Lymphoblastic, high grade
Diffuse large B-cell lymphoma of immunoblastic nuclear type	Immunoblastic, high grade
Large granular lymphocyte	Immunoblastic, high grade
Diffuse large B-cell lymphoma of centroblastic nuclear type	Diffuse large, intermediate grade
B-cell lymphocytic intermediate type	Diffuse small cleaved, intermediate grade
T-cell-rich large B-cell	Diffuse mixed, intermediate grade
B-cell small lymphocytic	Diffuse small lymphocytic, low grade
Epitheliotropic small T-cell lymphoma	Diffuse small lymphocytic, low grade

Table 2: Comparison of the new REAL/WHO (revised European-American Classification of Lymphoid Neoplasms/World Health Organization) and the older Working Formulation (WF) classification system in feline gastrointestinal lymphoma according to POHLMAN et al. (2009)

Therapy and prognosis

Cats with alimentary lymphoma often have additional tumours at distant sites [Mahoney *et al.*, 1995; Zwahlen *et al.*, 1998]; this emphasizes the systemic nature of tumours originating from lymphoid cells and that the main pillar of treatment continues to be chemotherapy. There are limited studies in which only alimentary tumours were included [Mahoney *et al.*, 1995; Slawienski *et al.*, 1997; Zwahlen *et al.*, 1998; Fondacara *et al.*, 1999; Carreras *et al.*, 2003].

Effectiveness of various treatment protocols was assessed by calculation of the median survival time. Median survival time (MST; also called median overall survival or median survival) is the time (from diagnosis or from start of treatment) when half of the patients have died.

Treating cats with alimentary lymphoma, mostly using the COP protocol (cyclophosphamide, oncovin=vincristine, prednisolone), resulted in a median survival time (MST) of 1.6

months [Mahoney *et al*., 1995] or 4.5 months [Teske *et al*., 2002], while a MST of 2.8 months was observed in cats treated according to the VCM protocol (vincristine, cyclophosphamide, methotrexate) [Jeglum *et al*., 1987]. Using the VELCAP protocol (41 % alimentary lymphoma), the assessed MST was of 2.1 months [Hadden *et al*., 2008].

An Animal Medical Center protocol for cats with colonic lymphoma, consisting in a combination therapy with vincristine, L-asparaginase, cyclophospamide, doxorubicin, methotrexate and prednisone administered over two years, rendered a MST of about 3.3 months, a period of time which did not differ significantly from that of untreated cats [Slawienski *et al*., 1997].

The same drug combination was used in a study by Zwahlen *et al*. [1998] including 21 cats with alimentary lymphoma. The treatment resulted in a MST of 9.3 months. Unfortunately, no histopathology was performed; therefore it is not known whether these improved results are due to the fact that more low-grade cases were included in this study compared to others. In six cats treated with prednisone prior to chemotherapy, median survival time was not different from that of cats without cortisone pretreatment [Zwahlen *et al*., 1998].

In feline lymphoma therapy, it is still under debate whether the addition of the more expensive and time-consuming treatment with doxorubicin (requiring application as intravenous infusion over 20 minutes) holds any advantage for the patients. Complete remission after single-agent chemotherapy with doxorubicin was achieved only in 26 % [Kristal *et al*., 2001] or 32 % of patients, respectively [Peaston *et al*., 1999]. In a study from Moore *et al*. [1996], cats treated according to the COP protocol during one month were randomly assigned to two groups. One group was maintained on the COP protocol, while the other group received a doxorubicin monotherapy. Although the doxorubicin group showed longer median remission duration, with 281 days compared to 83 days in the COP group, the doxorubicin group included only one alimentary lymphoma out of seven patients. The longest remissions were observed in two cats treated with the COP protocol. No survival data were described in this study. In cats treated with COP plus/minus doxorubicin, a significantly longer median remission duration was observed in the doxorubicin group, but no significant difference in survival times was seen between the two groups [Vail *et al*., 1998].

In all probability, the varying results of the discussed chemotherapy protocols are due to the fact that in none of the described studies a subclassification into the different types of alimentary lymphoma was carried out and that therefore, no comparison between these subgroups could be made regarding survival times. Strictly speaking, one cannot compare the results of those studies at all, as we do not know the tumour subtypes.

Lymphocytic lymphoma (small-cell, well-differentiated, low-grade) of the gastrointestinal tract was examined by Fondacara *et al*. [1999]. Treating cats only with oral drugs (prednisone 10 mg/cat once daily and chlorambucil 15 mg/m^2 for 4 days every 3 weeks) resulted in an excellent MST of 1.4 years. Evaluation of 41 cats with low-grade lymphoma (68 % limited to the gastrointestinal tract) treated with prednisone (5-10 mg per cat once or twice daily) and chlorambucil (2 mg per cat every second or third day) also resulted in a high MST of 1.9 years [Kiselow *et al*. 2008]. This confirms the hypothesis that low-grade lymphoma patients treated with prednisolone/chlorambucil have a good prognosis. However, there were also three cats with small lymphocytic alimentary lymphoma, treated with cyclophosphamide, vincristine and prednisone, which stayed alive for 35, 50 and 641 days, respectively [Mahoney *et al*., 1995]. The tumours had not been classified according to the new REAL/WHO classification system, which differentiates between the low-grade diffuse small lymphocytic tumour and the B-cell small lymphocytic and epitheliotropic T-cell lymphoma [Pohlman *et al*., 2009]. Most likely, these different subtypes react differently to chemotherapeutic drugs. Feline epitheliotropic intestinal lymphoma, also classified as intestinal T-cell lymphoma, showed a MST of 11 months after treatment (chemotherapy or prednisone monotherapy). Individual long term responders, which were still alive after 28 months, were observed [Carreras *et al*., 2003].

The large granular lymphocyte lymphoma seems to be a comparatively aggressive disease entity with poor response to therapy, therefore carrying a grave prognosis. After treatment with a combination chemoprotocol (L-asparaginase, vincristine, cyclophosphamide, methotrexate, prednisone), the median survival time of cats with large granular lymphocyte lymphoma (most commonly affected organs: mesenteric lymph nodes, small intestine and liver) was 1.9 months [Krick *et al*., 2008]. Data of different chemotherapy protocols with subclassified lymphoma subtypes and median survival times are summarised in Table 3.

Neither clinical stage nor FeLV status [Mahoney *et al*., 1995] was found to be associated with outcome, and patients achieving complete remission did not live longer than cats showing partial remission [Zwahlen *et al*., 1998].

Low morbidity was observed during chemotherapy with mild gastrointestinal symptoms like inappetence, vomiting and diarrhoea being the most common clinical signs. Only in rare cases, these symptoms were persistent being most likely due to the progression of the disease rather than to the treatment itself [Zwahlen *et al*., 1998]. Neutropenia was most commonly reported, while thrombocytopenia and fever was observed in rare cases only. Most cats on long-term treatment showed alterations of the hair coat with loss of guard hairs and broken whiskers [Mahoney *et al*, 1995].

It is still unclear whether surgical intervention alone or performed prior to chemotherapy results in better survival times. No significant difference in survival after surgical procedures (mass resection or surgical biopsies) was found in a study by Slawienski *et al*. [1997]. Zwahlen *et al*. [1998] did not see any difference in survival times either between patients treated with chemotherapy alone versus chemotherapy and surgery. However, this result is not surprising as surgery consisted only in biopsy and not mass reduction. Mahoney *et al*. [1995] treated 24 patients with chemotherapy only and four patients with

Chemotherapy protocol	Lymphoma subtypes	MST (months)	References
COP	all	1.6	Mahoney *et al.* (1995)
COP	all	4.5	Teske *et al.* (2002)
VCM	all	2.8	Jeglum *et al.* (1987)
VELCAP	all	2.1	Hadden *et al.* (2008)
AMC	all	3.3	Slawienski *et al.* (1997)
AMC	all	9.3	Zwahlen *et al.* (1998)
Chlorambucil/prednisone	Lymphocytic lymphoma	17	Fondacara *et al.* (1999)
Chlorambucil/prednisone	Lymphocytic lymphoma	23	Kiselow *et al.* (2008)
VCM + L-asparaginase, prednisone	Large granular lymphocyte lymphoma	1.9	Krick *et al.* (2008)

Table 3: Survey of various chemotherapy protocols for treatment of analysed lymphoma subtypes and median survival times (MST) of cats diagnosed mostly with alimentary lymphoma

surgery and chemotherapy, resulting in a MST of 5 weeks versus 17 weeks, respectively. Although there is quite a difference between these survival times, it is of no statistical significance, presumably because of the low number of patients in the surgery group.

One cat with colonic lymphoma treated with a subtotal colectomy with clear margins survived 3.7 years without receiving any additional therapy [Slawienski *et al.*, 1997]. Another cat with a 4 cm ileocaecal mass was treated only with surgery and died 5 years later without a recurrence, although the margins of the surgery were not even clean [Valli *et al.*, 2000]. Therefore, besides chemotherapy, surgery could be considered as a treatment option for patients with stage II intestinal lymphoma. The benefit of radiation therapy in feline alimentary lymphoma has not yet been studied.

Mediastinal (thoracic) lymphoma

Thymus, sternal or mediastinal lymph node involvement characterises this lymphoma.

Epidemiology

A prevalence of 6-36 % was reported [Gabor *et al.*, 1998; Teske *et al.*, 2002; Louwerens *et al.*, 2005]. Most affected cats are young (< 2 years) and FeLV-positive; paraneoplastic hypercalcaemia is only rarely observed.

Clinical presentation

Cats commonly present with dyspnoea, depression, anorexia and regurgitation [Grufydd-Jones *et al.*, 1979; Court *et al.*, 1997]. Dyspnoea can result from the pressure of the mass in the thoracic cavity or from secondary pleural effusion, which is common. In rare cases, sympathetic nerve involvement may cause Horner´s syndrome. Pressure exerted on the cranial vena cava may provoke head oedema.

Diagnostic approach and staging

A mediastinal mass with or without pleural effusion is commonly seen on chest radiographs. Computed tomographic evaluation of mediastinal masses was not helpful to specify tumour-type [Yoon *et al.*, 2004]. To confirm the presumptive diagnosis, cytological examination of the thoracic fluid or the mass is often sufficient. Analysis of pleural fluid identified neoplastic lymphoblasts in 79 % of feline mediastinal lymphomas [Davies and Forrester, 1996]. Pathohistological examination revealed that these tumours are mostly of T-cell origin [Vail *et al.*, 1998; Gabor *et al.*, 1999]. Primary intrathoracic tumours belong to stage I lymphomas; however, to complete the staging process abdominal ultrasound and bone marrow biopsy are required (Table 1).

Therapy and prognosis

By treating cats with mediastinal lymphoma according to the COP protocol, complete remission could be achieved in 92 % of the patients, with a median remission duration of 6 months [Cotter *et al.*, 1983] and a median survival time of 6.4 months [Teske *et al.*, 2002]. COP protocol therapy with or without doxorubicin resulted in a survival time of 2.3 months [Vail *et al.*, 1998], while survival times of 6.6 to 84 months were reported of patients on a multi-agent long-term chemotherapy [Simon *et al.*, 2008].

Combining chemotherapy with radiation therapy in order to induce faster remission or to treat chemoresistant cases could be an option in the management of mediastinal lymphoma. However, the optimum radiation protocol has not been established yet [Meleo *et al.*, 1997].

Nodal lymphoma

This type of lymphoma is characterised by peripheral lymph node enlargement, with abdominal or thoracic lymph nodes not being included.

Epidemiology

Nodal lymphoma is quite seldom seen in cats, only 5-17 % of cats showed exclusively peripheral lymph node involvement [Gabor *et al.*, 1998; Louwerens *et al.*, 2005]. In human medicine, lymphomas are classified into Hodgkin's lymphoma (with large Reed-Sternberg cells as hallmark) and Non-Hodgkin's

lymphoma. In cats, Hodgkin's-like lymphoma with mostly one cervical mass has only been described in rare cases [Walton *et al.*, 2001; Steinberg and Keating, 2008].

Clinical presentation

In most cases, nodal lymphomas presented as one or two palpable masses in the ventral cervical, submandibular or prescapular region [Day *et al.*, 1999]; in one cat, the neoplasia was located in the inguinal region [Walton and Hendrick, 2001]. Apart from that, no other striking clinical signs were observed in affected cats. The majority of masses were reported to be fast growing [Day *et al.*, 1999].

Diagnostic approach and staging

Enlarged peripheral lymph nodes can easily be palpated during clinical examination. Fine needle aspiration to obtain samples for cytological evaluation is the first step to confirm neoplastic disease. Biopsy (core biopsy or excisional biopsy) or surgical removal of the entire lymph node is necessary for pathohistological confirmation and classification of the neoplasia. Thoracic radiographs, abdominal ultrasound and bone marrow biopsy are the diagnostic procedures required for the staging of the tumour (Table 1).

Therapy and prognosis

It has been discussed that feline Hodgkin's-like lymphoma may be a less aggressive form of the tumour, as cats receiving no chemotherapy at all (n=11) survived from one week to four years, compared to cats receiving chemotherapy (n=4), which showed survival time between six months and 1.3 years [Walton and Hendrick, 2001]. After treating cats with lymphoma in peripheral nodes (most likely non-Hodgkin's lymphoma as no Hodgkin's-like appearance was described) following the COP protocol, complete remission was achieved in 80 % of the patients, with a median remission duration of 28 months [Cotter *et al.*, 1983] and a median survival time of 20.8 months [Teske *et al.*, 2002].

There is some evidence that surgery alone could be an effective treatment for cats with nodal lymphoma. A case was reported where a single mass in the region of the parotid gland recurred 6 months after initial removal, was again excised and recurred after 9 months; the mass was operated again with no recurrence observed 13 months after the third surgery [Steele *et al.*, 1997]. In two cats, no recurrence occurred after excising a single mass in the neck [Day *et al.*, 1999]. A third cat showed a recurrence 6 months after surgical removal of the single tumour, which was excised again and recurred after 6 months. The mass was again removed and a COP protocol was started; 18 months after diagnosis no recurrence was observed. Local radiation therapy can be considered if only one mass is present. However, at present it is not known whether radiation therapy is more advantageous than conventional chemotherapy or surgery.

Peripheral lymph node hyperplasia

The most important differential diagnosis for nodal lymphoma is the histologically similar looking distinctive peripheral lymph node hyperplasia of young cats. The aetiology of this mostly transient hyperplasia is still unknown; retrovirus infection has been discussed as a possible cause. In one study, 67 % of affected cats were FeLV-positive, but only one of these cats developed lymphoma [Moore *et al.*, 1986]. In another study including six cats, lymphadenopathy resolved without any treatment in five animals. The sixth cat was euthanized due to wrong diagnosis. All six patients had tested negative for FeLV, although two cats had transient FeLV infection because FOCMA (feline oncornavirus-associated cell membrane antigen) antibodies were found [Mooney *et al.*, 1987b].

Extranodal/atypical/unclassified form

Lymphomas are tumours of the immune system and can originate from lymphatic tissue, such as lymph nodes, spleen and bone marrow or in atypical locations such as the nasal cavity, central nervous system, kidneys, liver, skin, eyes, and actually in any tissue. The most common extranodal lymphomas were found in the nasal cavity, the central nervous system (CNS) and the kidney [Vail *et al.*, 1998; Valli *et al.*, 2000].

Nasal lymphoma

Epidemiology

The most common nasal disease described in cats is neoplasia, with 70 % diagnosed as lymphoma [Henderson *et al.*, 2004]. A prevalence ranging from 2 to 13 % was reported for nasal lymphomas [Valli *et al.*, 2000; Teske *et al.*, 2002]. Patients were mostly FeLV-negative.

Clinical presentation

The most common clinical signs in cats with nasal lymphoma include nasal discharge (bloody or mucopurulent), sneezing, increased upper respiratory noise, ocular discharge, epistaxis and facial deformity [Henderson *et al.*, 2004; Little *et al.*, 2007; Sfiligoi *et al.*, 2007].

Diagnostic approach and staging

In order to assess location and extension of the primary tumour, skull radiographs and computed tomography scans should be performed; the latter is also necessary to plan radiotherapy. Rhinoscopy is an elegant method to obtain multiple biopsies for pathohistological evaluation to confirm tentative diagnosis. Tumour cells were all [Sfiliogi *et al.*, 2007] or predominantly [Little at al., 2007] of B-cell origin.

Sometimes a mass can be dislodged during nasal flushes and used for pathohistological examination [Henderson *et al.*, 2004]. To obtain a flush biopsy the cat is anaesthetized and intubated. One nasal cavity is flushed with saline in a retrograde manner using, for example, a bulb syringe, while the contralateral nostril is occluded. The specimen is flushed through the pharynx out of the oral cavity [Vail, 2007].

Nasal lymphoma has often been categorized as a localized disease. If only local radiation therapy is planned, a thorough staging of the tumour has to be performed to rule out any systemic dissemination (Table 1). In a study of Little *et al.* [2007], 67 % of the necropsied cats showed an extension of the neoplasia beyond the nasal cavity and in 31 % of completely staged cases multiorgan involvement was present.

Therapy and prognosis

Considering these findings, it seems suboptimal to restrict therapy for cats with nasal lymphoma to local treatment, although there are no studies supporting that a combined radiation and chemotherapy yields better results than radiation therapy alone. A multi-institutional retrospective study of 97 cats with nasal lymphoma showed no significant difference in survival times between patients treated with chemotherapy alone (10.7 months, n=18), radiation therapy alone (47.7 months, n=19) or combined radiation and chemotherapy [15.8 months, n=60; Haney *et al.*, 2009]. In another study, patients were treated with various megavoltage radiation and chemotherapy (COP or LCHOP protocol) resulting in a median survival time of 31.4 months [Sfiligoi *et al.*, 2007].

Median survival time after treating nasal lymphoma in cats with a COP-protocol was 3.3 months [Henderson *et al.*, 2004], 11.9 months [Teske *et al.*, 2002] and 15.2 months with a COP-protocol with or without doxorubicin [Vail *et al.*, 1998]. Survival time was reduced to 28 days if cats received no treatment or only prednisolone monotherapy [Henderson *et al.*, 2004].

Bony destruction and facial deformity, which can be severe, were no prognostic factors. In contrast, tumour transgression of the cribriform plate was proven to have a poorer prognosis [Sfiliogi *et al.*, 2007].

CNS lymphoma

Epidemiology

After meningioma, lymphoma was the second most brain tumour [Troxel *et al.*, 2003] and the most common spinal neoplasia in cats [Marioni-Henry *et al.*, 2004]. It seems that, in the past, affected cats were younger, often FeLV-positive (84-100 %) and predominantly affected by extradural spinal lymphoma [Spodnick *et al.*, 1992; Lane *et al.*, 1994], whereas more recently, the mean age of cats with lymphoma has been increasing and intradural lesions have become more common [Marioni-Henry *et al.*, 2004]. However, the latest study found extradural and intradural components (in 88 % of the cases), with 57 % of cats being FeLV-positive [Marioni-Henry *et al.*, 2008].

Clinical presentation

The most commonly affected site was the lumbosacral region resulting in paresis or paralysis of the hindlimbs, a typical clinical sign at presentation. However, in 40 % of cats the lymphoma extended to multiple other regions of the spinal cord, while the brain was involved in 50 % of the cases [Marioni-Henry *et al.*, 2004]. Other common clinical signs of patients with spinal and intracranial lymphoma were nonspecific like anorexia, lethargy and loss of body weight. Cats with lymphoma of the brain also showed ataxia, altered consciousness and aggression [Troxel *et al.*, 2003].

Diagnostic approach and staging

In patients with suspected spinal cord lymphoma, plain radiographs seldom showed a soft tissue mass or lytic vertebral lesion. Advanced imaging techniques such as myelography, computed tomography or magnetic resonance imaging were needed for visualization of masses [Marioni-Henry *et al.*, 2008]. Cerebrospinal fluid analysis demonstrated a nonspecific increase of neutrophils and protein in most cats, but positive findings of specific neoplastic lymphocytes were also observed in a variable number of cases, i.e. in 83 % [Singh *et al.*, 2005], in 67 % [Spodnick *et al.*, 1992], in 35 % [Lane *et al.*, 1994] or in 9 % of affected cats [Marioni-Henry *et al.*, 2008].

In order to assess involvement of other organs beside the CNS, complete staging of the tumour must be performed (Table 1). On post-mortem examination of cats with spinal lymphoma, the most common extraneural locations of the neoplasia were bone marrow and kidneys [Spodnick *et al.*; 1992; Marioni-Henry *et al.*, 2008].

Therapy and prognosis

Nine cats with intracranial lymphoma received palliative therapy with systemic corticosteroids; median survival time was 21 days with a range of nine to 270 days [Troxel *et al.*, 2003]. Four cats with extradural spinal lymphomas were treated with chemotherapy (combination of vincristine, L-asparaginase and prednisone) after local radiotherapy (three cats) or surgery (one cat). Only one patient improved long-term, being still alive after 13 months, while the other three cats died within five months [Lane *et al.*, 1994]. After a single dose of radiation and COP chemotherapy, one cat was euthanized after 38 days, another one survived for two months after decompressive surgery and chemotherapy [Marioni-Henry *et al.*, 2008]. Six cats treated according to the COP protocol showed a median remission duration of 14 weeks with complete remission and of six weeks with partial remission. Of three cats treated with prednisone monotherapy, one showed no response to treatment, while partial remission of four and 10 weeks was achieved in the other two animals. In one cat, which had been treated surgically (dorsal compressive laminectomy) and had received postoperative COP chemotherapy, complete remission of neurologic signs for 1.2 years was observed. After recurrence, therapy with doxorubicin (30 mg/m^2) again led to total remission, but the cat died in a car accident [Spodnick *et al.*, 1992].

Renal lymphoma

Epidemiology

About 5 % to 10 % of cats showed primary renal involvement [Jeglum *et al.*, 1987; Gabor *et al.*, 1998; Valli *et al.*, 2000] but in 31 % of the cats the kidneys were affected in addition to other organs [Gabor *et al.*, 1998].

Clinical presentation

On physical examination, renomegaly is the most conspicuous finding. Depending on the severity of azotaemia, unspecific clinical signs like inappetence, vomiting, polyuria and polydipsia are frequently observed.

Diagnostic approach and staging

Abdominal radiographs or ultrasound examination findings confirming renomegaly should always raise suspicion of renal lymphoma. Ultrasonography has shown an association between hypoechoic subcapsular thickening and renal lymphoma [Valdes-Martinez *et al.*, 2007]. To confirm the tentative diagnosis, fine needle aspiration of the kidney was described as a useful, non-invasive diagnostic tool [Borjesson, 2003].

Samples for histopathological examination can be obtained by transabdominal core biopsy, laparoscopy or laparotomy. The majority of tumours were of B-cell phenotype [Gabor *et al.*, 1999].

Therapy and prognosis

As renal lymphoma is always bilateral, nephrectomy does not represent a treatment option [Mooney *et al.*, 1987]. Chemotherapy has the advantage of being a systemic treatment, which is especially beneficial as cats with renal lymphoma often show involvement of the central nervous system [Mooney *et al.*, 1987]. For treatment, different chemotherapy protocols have been used yielding similar survival results. Median survival times of cats with renal lymphoma were five months after treatment with a VCM protocol [Jeglum *et al.*, 1987], 4.8 months with a COP plus/minus doxorubicin [Vail *et al.*, 1998] and 5.6 months [Mooney *et al.*, 1987] on a treatment consisting of an induction therapy (vincristine, L-asparaginase, cyclophosphamide, methotrexate) and a maintenance protocol (vincristine, methotrexate and cytosine arabinoside). Cats with only slightly increased renal parameters survived longer than those with moderately to severely elevated levels, but some of the cats with nearly normal values did not survive longer than patients with severely increased renal parameters. Some patients with extremely elevated kidney parameters (creatinine 5.9-14.4 mg/dl) responded well to chemotherapy. Therefore, severely increased renal parameters should never be reason to exclude a cat from therapy [Mooney *et al.*, 1987].

Conclusion

In the future, it will be of utmost importance for feline lymphoma management to obtain a correct, accurate and specific diagnosis, with veterinary histopathologists, cytopathologists and oncologists working together and speaking the same language worldwide. This is an essential premise to evaluate different therapeutic measures and to advance research in the clinically relevant field. Therefore, a state-of-the-art diagnostic approach is mandatory.

Diagnosing lymphoma only by fine needle aspiration without histopathological examination and immunophenotyping does not provide adequate information. The first important step must be evaluating tumours histopathologically in a uniform manner, preferably applying the new REAL/WHO classification system, which provides important information about morphology and immunophenotype of neoplastic cells. Additional research will be necessary to detect biological variabilities in order to understand in what ways the respective lymphoma diseases differ from each other at a molecular level. This knowledge will be essential to initiate innovative therapeutic approaches with the potential of improving prognosis and survival in feline lymphoma patients.

List of abbreviations used

AMC = Animal Medical Center;
CNS = central nervous system;
COP = cyclophosphamide, oncovin (vincristine), prednisolone or prednisone (prodrug);
DNA = deoxyribonucleic acid;
ELISA = enzyme-linked immunosorbent assay;
FeLV = feline leukaemia virus;
FIV = feline immunodeficiency virus;
FOCMA = feline oncornavirus-associated cell membrane antigen;
HE = haematoxilin-eosin;
IBD = inflammatory bowel disease;
LCHOP = L-asparaginase, cyclophosphamide, hydroxydaunorubicin = doxorubicin, oncovin = vincristine, prednisone;
MALT = mucosaassociated lymphoid tissue;
MST = median survival time;
NCI = National Cancer Institute;
PCR = polymerase chain reaction;
REAL/WHO = revised European-American Classification of Lymphoid Neoplasms/World Health Organisation;
VCM = vincristine, cyclophosphamide, methotrexate;
VELCAP = vincristine, elspar = L-asparaginase, cyclophosphamide, adriblastin = adriamycin = doxorubicin, prednisone;
WF = Working Formulation;
WHO = World Health Organisation

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REPRINT PAPER (GR)

Animal welfare issues on the use of rabbits in an animal assisted therapy programme for children

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SUMMARY

Animal Assisted Therapy (AAT) is a method of complementary treatment in the rehabilitation of many human illnesses and conditions. Although the dog is the most widely used therapy animal that is used in AAT programmes, the rabbit can also be used as an alternative animal species and complementary therapy for many diseases. It is an intelligent, human friendly and playful small animal, easily socialised and transported. Also, the rabbit has very good communication through its body language. A special bond also exists between children and rabbits, and in the animal world of children, the rabbit is a very popular animal mainly because of children's literature. As a result, rabbits elicit positive feelings in children and enhance their imagination. Based on previous experience from an AAT programme with rabbits in a children's hospital, the rabbit can be easily accepted by children with emotional or physical problems. In order for an AAT programme with a rabbit to be a success, it is very important to guarantee the good health and normal behaviour of the rabbit, as well as its proper welfare. The contribution and participation of a veterinarian during the design and the implementation of the programme are also very important for assuring the success of an AAT programme with rabbits.

Keywords: animal assisted therapy, children, rabbit, welfare

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Introduction

Animal assisted therapy (AAT) is a therapeutic intervention in which the physical and/or emotional needs of an individual are met through the use of an animal. It is based on the growing knowledge of benefits that animals can provide to sick, handicapped, old or socially-isolated individuals. The Delta Society is a human services organisation that is dedicated to improving people's health and well-being through positive interactions with animals. In an attempt to promote the standardisation of terminology, the society has defined AAT as a goal-directed intervention in which an animal that meets specific criteria is used as an integral part of the treatment process. AAT is directed and/or delivered by a health or human services professional with specialised expertise [Delta Society 1992].

The incorporation of an animal in therapy is beneficial, because animals have a natural tendency to create a bond with people. A good therapy animal will seek affection and interact with the patient. Thus, animals promote a warm and safe atmosphere that can be therapeutically beneficial for a patient and help the patient accept interventions that are offered by the care provider [Carmack 1991, Anonymous 1996, Dimitrijevic 2009].

The 1998 Prague Declaration of the International Association of Human-Animal Interaction Organisations urges all persons and organisations that are involved in animal-assisted activities and/or AAT and all bodies that govern the presence of such programmes in their facilities to consider and abide by the

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following points: (a) only domestic animals which have been trained using techniques of positive reinforcement, and which have been, and will continue to be, properly housed and cared for, are involved, (b) safeguards should be in place to prevent adverse effects on the animals involved, (c) the involvement of assistance and/or therapy animals is potentially beneficial in each case and (d) basic standards should be in place to ensure safety, risk management, physical and emotional security, health, basic trust and freedom of choice, personal space, appropriate allocation of programme resources, appropriate workload, clearly defined roles, confidentiality, communication systems and training provision for all persons involved [IAHAIO 1998].

Compared to service animals, which must be trained to do work or perform tasks for the benefit of a disabled individual, therapy animals are usually the personal pets of their handlers, who use them to provide AAT to patients [Anonymous 2009]. Although the dog is the most widely used therapy animal in AAT, other species, such as cats, horses or birds may, also, be used depending on the medical condition that requires curative treatment. During the last few years, there is an increasing trend to have a rabbit as a pet animal. This increasing use of pet rabbits prompted us to think about the possibility of using rabbits in AAT programmes. The aim of the present article is to present the role of rabbit as a therapy animal and to highlight the main rabbit welfare issues. These welfare issues, which have been taken from the published veterinary literature and our personal experience, should be considered when a rabbit is used in an AAT programme.

The use of rabbits in AAT programmes

Depending on the illness, the rabbit could be considered as an appropriate animal species to incorporate in an AAT programme. It is an intelligent, human friendly and playful small animal, easily socialised and transported [Adbill and Juppe 2000, Kaminski et al. 2002]. Furthermore, the rabbit has very good communication through its body language. A unique bond also, exists between rabbits and children In the animal world of children, the rabbit is a very popular animal, mainly through children's literature, as well as songs, drawings and zoo and pet farm visits [Mallon 1992].

In view of the above mentioned characteristics of the rabbit, we decided to use rabbits as complementary therapy for children with emotional or physical problems, as well as for abused and neglected children. This decision was taken despite the fact that the available literature on the use of rabbits in AAT programmes is limited. The AAT programme was organised and implemented in the Department of Oncology of the P & A Kyriakou Children's Hospital in Athens, Greece. Preliminary results of this study clearly show that there is a positive feedback from all children that participated in the programme and their accompanying persons [Loukaki et al. 2009].

Animal welfare issues in the use of Rabbits in an AAT Programme

An AAT programme is mainly managed from an anthropocentric point of view. In most cases, the focus of AAT is the patient and the therapeutic result, irrespective of whether it is beneficial or not, and this depends on the physical and mental health of the participating therapy animal. When rabbits are used in an AAT programme, there is a moral and legal obligation to safeguard the welfare of these animals. Discomfort and distress before, during and after their use may seriously affect the animal itself and, consequently, the expected results for the patients.

Defining animal welfare is a complex issue and different definitions have been proposed at various times. One of the first definitions was published as a minimal standard for farm animals by the Brambell Committee in 1965. This definition has since become known as the "five freedoms": freedom from thirst, hunger and malnutrition; freedom from discomfort; freedom from pain, injury or disease; freedom to express normal behaviour; and freedom from fear and distress [Brambell Committee 1965]. Others have proposed that the ability of an animal to cope with its environment, and thus exert control over its life, may be more important than any of the five freedoms of animal welfare [Webster 1994]. This definition is in line with Broom and Johnson's definition of animal welfare who defines it as "its state as regards its attempts to cope with its environment"[Broom and Johnson 1993].

Since "pet" rabbits retain many of their wild-type behaviour traits and express them when they are given the opportunity, it is very important for those planning an AAT programme with rabbits to consider their behaviour and biology in the wild, especially when designing rabbit housing and care programmes [Lehmann 1991, Stauffacher 1992]. In fact, the Delta Society emphasizes that AAT may be inappropriate for the animal when (a) injuries from rough handling or other animals may occur, (b) basic animal welfare, which includes veterinary care and access to water and exercise areas, cannot be assured, and (c) the animal doesn't enjoy visiting the human patient [Zamir 2006]. It is also important to determine whether the animal can be appropriately monitored for signs of stress. Monitoring signs of stress is probably the most important consideration for any species that is used as therapy animal, because the AAT environment can be stressful for them. Critical for the success of an AAT programme is whether an animal has the capacity to recover from its perception of encroachments, cope comfortably in the AAT environment and enjoy the human interaction. The main animal welfare issues for rabbits in an AAT program are their housing and husbandry conditions, human-animal interactions and veterinary care.

Housing and husbandry conditions

The rabbits which are used in an AAT programme are usually pet animals brought in by the pet's owner or the vet or the person organising the therapy, to the hospitals or the institutions where the patients reside. Depending on the internal regulations of the institution where the patients are living, rabbits may be with their owner, the vet or the person organising the therapy, or the companion of the rabbit housed in the same building where the AAT sessions take place. If transportation is needed, the rabbit could be confined in a proper cat carrying cage or basket for the journey. If no suitable carrying cage is available, the rabbit can be transported in a secure cardboard box with holes punched in the walls for ventilation.

An acclimatisation period should be provided after its arrival at

the location of the AAT, depending on the journey time and the frequency of each journey. Once the rabbit is no longer stressed and becomes familiar with the journey between its home and location of the therapy, the acclimatisation period could be shortened.

Special concern should be given to provide proper housing for the rabbits based on their behavioural and physical requirements. The cage should be a pleasant place to spend time for the rabbits and the bigger, the better. A general rule of thumb in selecting the cage is to choose one that is at least four times the stretched out size of the adult rabbit [Royce 1996]. If rabbits are kept in a hospital or institution where the AAT programme is taking place, they can be housed either individually or in groups in either cages or floor pens. In the case of group housing, the group must be stable and harmonious. Male rabbits are difficult to house in groups as they fight vigorously. If group housing is not possible, frequent human contact should be provided. The guidelines for the accommodation and care of animals that are used for experimental and other scientific purposes of the European Commission could be used for rabbits that participate in an AAT programme. [European Commission 2007].

Environmental enrichment items within the cage will increase the rabbit's behavioural repertoire and reduce stereotypic behaviours. Hay and grass cubes will prevent boredom and provide roughage. A wide range of enrichment items is commercially available for rabbits and it includes mirrors, plastic or rubber objects and stainless steel rattles and balls (Morton et al. 1993, Johnson et al. 2003). Each enrichment item should be carefully evaluated to ensure that there is sufficient evidence of use, they are not toxic and are not capable of causing any injury.

Human-rabbit interactions

Although rabbits usually enjoy interacting with humans, they need to be handled with great care, because they are easily frightened [Brewer 2006]. Therefore, proper handling by humans is very important for these animals. Rabbits that are used as therapy animals are routinely manhandled during an AAT session and, as a result, a small number of animals get injured. Even when gently handled, rabbits can become anxious when they are exposed to strangers who caress them. Therefore, before using a rabbit in an AAT programme, it is very important to train it for each project, such as daily presentation to a large number of people especially children, unusual noises and smells, and transportation.

Human-rabbit interactions are less likely to cause stress to the rabbit during husbandry or AAT when the behaviour of the staff and patients is compatible with the animal's natural behaviour. Rabbits can recognise and discriminate between different humans. Therefore, positive contact with familiar humans in the form of handling, training and general habituation to human contact will reduce stress when they are handled during an AAT session [Davis and Gibson 2000]. Rabbits that are to be used in an AAT programme should also be exposed to the staff that will run the programme before its start. Based on our experience, special concern should be given when incorporating rabbits into an AAT programme for children. Most rabbits do not like to be held or handled and may try to escape a well meaning child's arms by biting and scratching. In addition, a rabbit's back may be easily broken as a result of improper handling [Royce 1996].

Before starting any AAT session, it is important to inform the patients about the animal species that will be used in the session. This can be done using photo - graphs or videos depending on the age of patients. The animal's natural behaviour and needs and ways of safe contact with the animal should be properly explained to the patient by the participating animal care givers or veterinarian. Introducing the animal to the group gives the opportunity to the animal to become familiar with the new environmental conditions. For this purpose, another 'vital ingredient' in the AAT programme is the pet helper. This individual should be very skilled, because he/she acts as the interpreter between the possibly terrified animal and the frightened patients [Kobayashi et al. 2009].

Veterinary care

All rabbits that are to be used in an AAT programme must have a veterinary check in order to ensure that they are in good physical and mental health before incorporating them into a therapeutic process. In addition, a clinical examination should be performed on the rabbit(s) before each AAT session. Special concern should, also, be given to the temperament of the rabbit towards humans.

To avoid aggression and any troublesome behaviours, as well as for medical reasons, rabbits must be spayed or neutered. Studies have shown that 50 to 80% of unspayed female rabbits develop uterine and/or mammary tumours by five years of age [Green 1958, Toft 1992].

Special concern should be given to the possibility for disease transmission from the rabbit to the patients and from the patient to the rabbit, as well as the development of allergic reactions in patients who are participating in the AAT programme [Morrison 2001, Mani and Maguire 2009].

Assessment of rabbit welfare

When using rabbits in an AAT programme, It is important to establish a mechanism for assessing its welfare during the programme and the early recognition of behavioural changes which are often signs of poor welfare. Behavioural signs of stress in rabbits may be subtle and may not be immediately obvious to an untrained human observer. Thus, the assessment of rabbit welfare should be conducted by a person with considerable knowledge on the biology and normal behaviour of rabbits, including its ability to cope and adapt with its environment [Fraser 1993]. Behavioural and physiological changes, such as unexplained aggression, hiding, chewing cage bars, excessive grooming or reduced grooming, increased or decreased food consumption and unusual movements, such as repeated circling within the cage, could be expressions of stress, fear or depression [Mayer 2007]. Therefore, an assessment of the rabbit's behaviour should be made before, during and after the AAT session by a well-trained person.

Based on our experience, rabbits should be interchanged in an AAT programme, so that they are not separated from their home/group for long periods. For this reason, the use of two different rabbits in the same AAT programme is preferred. Rabbits should not be used if they need to cope with adverse environmental conditions, such as heat or large temperature differences (outside housing in winter and working in heated

rooms). Special attention should be made for signs of stress-related behaviour, such as freezing from fright. If such signs appear, the therapy session must be stopped.

In order to guarantee the proper use of rabbits in an AAT programme, specific institutional guidelines should be in force. In addition, the institution, in collaboration with a veterinarian, should establish a code of good practice for its AAT programms that includes animal welfare issues. This code should include the following requirements: (a) rabbit welfare must be a priority for the therapist, (b) the rabbit to be used in the programme must never be forced "to have to leave home in order to go to work" or to perform actions that it is reluctant to perform, (c) the rabbits should be given time to acclimatise before each AAT session, and (d) rabbits must be protected from individuals that are carrying transmissible diseases to rabbits [Preziosi 1997].

Conclusions

AAT is a novel therapeutic interventional programme with important benefits in the management of patients with chronic diseases and a prolonged hospitalisation. Although the dog is the most widely therapy animal, a rabbit can, also, be used in most AAT programmes, as it is an intelligent, human friendly small pet animal that can be easily socialised. In most cases, an AAT programme is mainly managed from an anthropocentric point of view and ignores the important role of the animal's physical and mental health in the treatment. Therefore, special concern should be given to animal welfare in an AAT programme. The assessment of rabbit health and welfare before, during and after an AAT session is very important and should be performed by a person, preferably a veterinarian, with considerable knowledge of the biology and behaviour of this animal. Behaviour of the rabbit should be evaluated regularly in an AAT programme and during an AAT session. As soon as behavioural changes are observed and compromised welfare is recognised, the treatment should be postponed. Institutes that have an AAT programme with rabbits should create a code of good practice in order to guarantee the rabbit's welfare in the programme

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COMMISSIONED PAPER

Clinical use of non-steroidal anti-inflammatory agents (NSAIDs); The current position

Stuart Carmichael[(1)]

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently the fastest growing class of drugs in both human and veterinary medicine [1]. This is mainly due to their effectiveness as convenient anti-inflammatory, analgesic and anti-pyretic agents across a range of species. They are used to provide surgical analgesia peri-operatively and in the control of soft tissue pain and inflammation, however their greatest use is in the management of osteoarthritis. Recently there has been a great deal of interest in using them in the management of cancer patients. In the UK the market value for NSAIDs in small animal use has more than doubled in the last decade, from an estimated £17 million in 2001 to £38 million currently in 2011. The market value for small animal pain management in USA in 2008 was estimated as being worth $200 million with 94% occupied by NSAIDs [2]. The number of animals receiving NSAID medication was estimated at 26 million dogs and 6 million cats with the main indications identified as osteoarthritis (44.6%); peri-operative use (24.1%) and non-surgical soft tissue trauma (11%).
There are an increasing number of licensed NSAID drugs appearing in the veterinary market in response to this growing clinical demand. These are a combination of generic versions of existing established products and a range of newly developed NSAIDs. It is useful to consider the development and appearance of NSAIDs into the clinical market as occurring in phases or generations (Table 1). The first generation drugs (aspirin; phenylbutazone; meclofenamic acid) were the first agents used and these were generally replaced by the second generation drugs (carprofen; meloxicam; etodolac) which dominate the market at present. More recently a third generation of new products has being introduced (firocoxib; robenacoxib; cimicoxib; mavacoxib; deracoxib and tepoxilin) which offer new opportunities for clinical management. This article will concentrate on the newer NSAIDs available and how these can enhance current clinical practice.

How NSAIDs work; Cox inhibition

NSAIDs achieve their beneficial clinical results through inhibition of cyclo-oxygenase enzyme (COX) [3]. Cyclo-oxygenase enzyme plays a key role in the Arachidonic Acid(AA) cascade, resulting in the production of an array of pro-inflammatory prostanoids (Fig 1). Arachidonic acid is produced when the phospholipid cell membrane is degraded as a normal physiological process, which is accelerated in the presence of injury or inflammation. The action of cyclo-oxygenase on AA results in the production of the prostanoids of PGE_2, PGI_1 (prostacyclin), $PGF_{2\alpha}$ and PGD_2 in addition to thromoxane, TXA_2. These can act in certain locations and tissues to initiate and prolong inflammatory processes, enhance pathological consequences and cause pain. NSAID drugs can modify these actions by blocking the action of cyclo-oxygenase enzyme.
However many of the products resulting from this cascade have important constitutive functions under normal circumstances and reducing the availability of these by using a NSAID can result in problems in certain areas recognized as the toxic effects of the drug. These effects are most commonly manifested as gastro-intestinal problems but damage can also be seen in the renal mechanism and in the liver.

(1) Vets Now Referrals, Penguin House, Castle Riggs, Dunfermline, Fife GB-KY11 8SG E-mail: stuart.carmichael@vets-now.com

Generation	Drugs
First Generation	Aspirin
	Phenylbutazone
	Meclofenamic Acid
Second Generation	Carprofen
	Etodolac
	Meloxicam
	Tolfenamic Acid
	Ketoprofen
Third Generation	Tepoxilin
	Deracoxib
	Firocoxib
	Mavacoxib
	Robenacoxib
	Cimicoxib

Table 1 Introduction of NSAID drugs

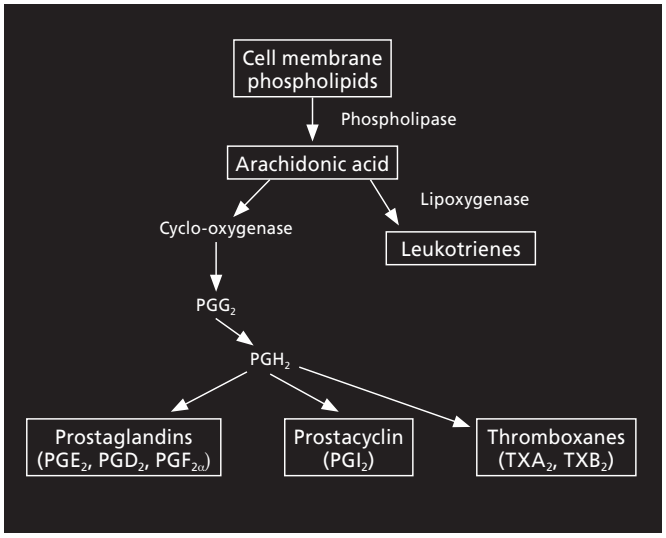

Figure 1. Phospholipid cell membrane releases Arachidonic Acid which through the action of cyclooxygenase enzyme results in the formation of pro-inflammatory prostanoids.

COX -1 and COX-2

A key advance in better understanding the actions and toxic effects of NSAIDs resulted from the discovery that cyclo-oxygenase was produced as at least 2 iso-enzyme forms, COX-1 and COX-2. These are produced from two entirely different genes [4] and expression occurs under different circumstances with COX-1 being more ubiquitous and having a physiologically constitutive function. The COX-2 iso-enzyme is not widely expressed under normal physiological conditions but appears with injury or inflammatory reactions in which it plays a central role [5]. This led to COX -1 being labeled 'Constitutive' and COX-2 being termed 'Inducible'. The logical progression from this knowledge was that it would be more sensible to produce and use NSAIDs which only blocked COX-2 and had a minimal effect on COX-1. It is certainly true that most of the toxic side-effects observed when using NSAIDs are due to the removal of COX-1 activity but experimental studies using exclusive COX-2 inhibitors were very disappointing and often these agents had fatal consequences. Therefore the 'good COX / bad COX' approach was not the complete answer. COX-2 has some very important physiological functions that we now understand, including repair of existing gastric lesions, CNS nociception, essential renal function, reproductive function and probably many that we are yet unaware [4;6;7;8]. A further COX iso-enzyme has been identified, COX-3 [9], whose function is still uncertain although it has been suggested that it may play a role in central pain transmission in dogs [10]. It seems that rather than each iso-enzyme having clearly defined roles and actions there is likely to be an overlap of COX iso-enzyme function required for normal physiological activity and this may vary depending on the site that they are functioning in at a point in time [11].

Targeting COX Activity for Clinical Use

Classification of NSAIDs based on their activity levels against COX-1 and COX-2 respectively is useful in differentiating their activity and, more importantly, understanding the risk of toxic side-effects. Individual drugs can be described as COX 1 or 2 sparing, preferential or selective. It has been proposed that it may be more useful to use consistent terms such as preferential, selective or specific, based on actual values rather than more subjective descriptions although there is as yet no clearly accepted scheme for this [12]. The usual way of determining this is by identifying the action against COX-1 (IC50) and dividing by the activity against COX-2 (IC50) to give a number. Alternatively this can be expressed as a ratio. The higher the number then the higher the relative activity against COX-2. Drugs with high values should be less likely to show COX-1 dependent problems such as gastro-intestinal toxicity and this has been demonstrated to be the case in human medicine [13]. Unfortunately the actual ratio can vary depending on the study quoted as there is, at this point in time, no consistent method of determining it. However broadly, Aspirin is regarded as COX-1 selective; carprofen, meloxicam as COX-2 preferential and newer agents firocoxib and rabenocoxib as COX-2 selective (Table 2).

Developing 3rd Generation NSAIDs

Many of the new generation of NSAIDs developed are coxib class determined by their chemical structure. Coxib class NSAIDs are usually COX-2 selective drugs specifically designed to try to reduce toxicity profile. These are the first NSAID drugs developed due to their COX-2 selectivity and are specifically designed in humans to reduce gastrointestinal toxicity. It is important to remember this in relation to the potential of renal toxicity and effect on other major organs and each individual

Table 2 COX 1: COX-2 Activity Description

COX-1: COX-2 Ratio	Description
< 1	COX-1 Selective
1< but < 100	COX-2 Preferential
100< but < 1000	COX-2 Selective
1000<	COX-2 Specific

Generic	Trade Name	COX-1:COX 2	Dose	Admin	Range of tablets	Injectable	Cat
Firocoxib	Previcox (Meriel)	COX-2 Selective	5mg/kg sid	Chewable tablets	57mg 227mg	No	No
Robenacoxib	Onsior (Novartis)	COX-2 Selective	1mg/kg sid	Flavoured tablets	5, 10, 20, 40mg	Yes	Yes 6mg tab
Cimicoxib	Cimalgex (Vetoquinol)	COX-2 Selective	2mg/kg sid	Ce Chewable tablets	8, 30, 80mg	No	No
Mavacoxib	Trocoxil (Pfizer)	COX-2 Preferential	2mg/kg monthly	Triangular tablet	6, 20, 30, 75, 90mg	No	No

Table 3 New Coxib class NSAIDs- characteristics

drug should be monitored to evaluate other potential problems particularly as COX-2 is essential to renal function and in other key areas. COX-2 selective drugs can cause significant side-effects in the same way as COX-1 selective in particular circumstances and acute renal failure, thromoembolic disease and gastrointestinal problems have all been seen as a direct result of their use [14;15]. These findings are consistent with COX-2 having an important constitutional role in the body. Recently this class of drugs were also associated with fatal cardiovascular complications in humans due to artherosclerosis which is not a major problem in dogs [16]. There are a crop of newly available coxib class NSAIDs for use in companion animals in Europe namely firocoxib (Previcox®; Meriel); robenacoxib (Onsior®, Novartis) and cimicoxib (Cimalgex®; Vetoquinol). The characteristics of each of these will be described individually in addition to another interesting NSAID that has been introduced, mavacoxib (Trocoxil®; Pfizer) (Table 3).

Firocoxib

Firocoxib (Previcox®; Meriel) is a highly COX-2 selective NSAID developed for use in the dog. It is available in chewable tablets in two sizes, 57 and 227mg (Table 3). Recommended dose is 5mg/kg once daily. There is currently no injectible form available but the drug is rapidly absorbed after oral ingestion achieving peak plasma concentration in one hour after administration. In an experimental model of induced synovitis, dogs treated with firocoxib had lameness scores that were significantly better than placebo or carprofen at both 3 hours and 7 hours post administration and similar to dogs treated with vedaprofen (Quadrisol®; Intervet) [17]. Extensive clinical trials have indicated that it has a good safety profile [18;19;20] and good efficacy when compared with both carprofen [21] and etodolac [19]. In both of these studies, which were conducted over a period of 30 days treating dogs with clinical osteoarthritis, firocoxib was demonstrated to be superior to both carprofen and etodolac as evidenced by owner and veterinary assessment of clinical signs and force plate analysis of weight-bearing [19;21]. Firocoxib was also shown to be well tolerated in a study in dogs over 7 yrs of age with osteoarthritis where treatment effects were monitored for 90 days. In a much longer study, extending over 52 weeks also involving client owned animals with clinical osteoarthritis, a drop out rate of 5.1% was reported due to GI signs, compared to 2.9% drop out in an earlier 40 day study [18;22]. Improvement rates of 82% at 15d, 84% at 90days and 96% at the conclusion of the study were reported. It would seem that firocoxib is an effective COX-2 selective drug with a high safety profile as evidenced by published results.

Robenacoxib

Robenacoxib (Onsior® ; Novartis) is a new COX-2 selective NSAID with indications in both the dog and cat. It is available in a wide range of flavoured tablet strengths for dogs and as a 6mg flavoured tablet for cats. Recommended dose is 1mg/kg once daily for both species. Tablets should be given without food in the dog as combining with a meal reduces absorbtion and availability. Better efficacy was reported if food was withheld for 30 mins before or after administering tablets. In cats the recommendation is to give tablets with a small meal. There is also an injectable product available. Robenacoxib attains peak plasma levels quickly but has a relatively short plasma half life. There is evidence that there is rapid passage into inflamed osteoarthritic joints and that concentrations within joints were three times that of plasma 10 hours after administration [24]. The drug demonstrates tissue selectivity, being concentrated at the site of inflammation, a characteristic that was predicted for drugs displaying specific biochemical behaviour [24;25]. Robenacoxib was demonstrated to posses these in trials done in the cat [26]. The advantage of such a quality may be that a higher concentration of the drug in the target inflamed tissue would lead to sustained and enhanced action while the relatively low plasma concentrations may serve to avoid exposing normal organs to high levels of the drug. Resulting slow clearance would explain an observed long duration of action in inhibiting PGE2 [26;27]. Another interesting feature described is that while the COX-1 binding of robenacoxib shows almost instant de-binding, the COX-2 de-bind is much slower with a half-life of 25minutes [27]. All of these properties would predict enhanced action at the site of a problem with a good safety profile. Robenacoxib displayed a good combined safety index in laboratory Beagle dogs [28] and non-inferiority, both in efficacy and adverse effects, when compared with carprofen in a study in client owned dogs suffering from osteoarthritis over a 12 week period [29]. In the cat high safety index was demonstrated in 28-48 day administration study [30] and similar efficacy to ketoprofen was seen in a shorter study using an acute pain and inflammation model over 5-6 days [31]. Although this is a relatively recent entrant into the market there is already evidence of good efficacy and safety in both dog and cat and an interesting variation in mode of action proposed.

Cimicoxib

Cimocoxib (Cimalgex® Vetoquinol) is a new coxib that has just appeared on the market. It is available as a range of chewable tablets for dogs given at a dose of 2mg/kg once daily. There is very little published data available at the present time but two field studies are described.

These field studies involved dogs of different age groups, genders and breeds. A study in dogs (average age 8.8 years old) with chronic osteoarthritis lasted for up to 90 days. Dogs were given either cimicoxib or firocoxib once daily. Effectiveness was determined based on examinations by a veterinarian and assessments by the animal's owner. A second study involved dogs (various ages from four months upwards) undergoing either orthopaedic or soft tissue surgery. The dogs received either cimicoxib or carprofen. The first dose was given two hours before surgery, and treatment was continued for several days. Pain was assessed by the veterinarian (up to 24 hours after surgery and at the end of the follow-up treatment). The owner also noted pain-related observations. Given daily, Cimalgex reduced pain and inflammation and lameness in dogs with chronic osteoarthritis, and was as effective as firocoxib. Cimalgex was also shown to be as effective as carprofen, in the management of peri-operative pain due to orthopaedic or soft tissue surgery during the first 24 hours after surgery. At present it is suggested that great care be taken in dogs less than 6 months old and that use in puppies up to 10 weeks of age should be avoided.

Mavacoxib

Mavacoxib (Trocoxil®; Pfizer)is a coxib by chemical structure but is a preferential COX-2 inhibitor rather than a selective one. It is unique among the NSAIDs currently available in having a very long half-life of 40days, meaning that dosing is once monthly. Trocoxil is available in a variety of tablet strengths (6,20,30,75 and 90mg) to be administered at a dose of 2mg/kg. The tablets are triangular in shape and chewable. They can be given with food as this increases bioavailability but it is important to ensure that the tablet(s) are ingested. Dose regime suggested is a 'jump start' one with the second dose given at 14 days and then monthly dosing thereafter for a total treatment of 7 doses maximum. Treatment can be resumed after a break of one month. This drug is indicated where continuous treatment in excess of one month is required, usually in osteoarthritic dogs. It has not got a license for use in cats. Both safety and efficacy were comparable to carprofen at this dose level which was determined by field trial studies [32;33].

Initial studies in laboratory beagles had indicated a dose of 4mg/kg but this was modified after field trial in dogs with osteoarthritis to 2mg/kg when half-life was found to be longer in target breeds. Interestingly no increased toxicity was seen in these trials where the higher dose of 4mg was used. Toxicity was mainly gastro-intestinal and there were some initial concerns about toxicity as the active drug could not be withdrawn as is common practice when this occurs. In reality the adverse events lasted no longer than the same events seen with carprofen despite the fact that the drug was still active in the system. As this type of toxicity is often predisposed to by other inciting factors, these must be looked for and, if present, removed or corrected eg hydration in dehydrated animals. The advantages, rather than disadvantages, of having continual suppression of prostanoids in the clinically affected animal are interesting. Trials demonstrated a clear improvement at each time interval in dogs treated with mavocoxib with changes seen from the second day after treatment started. This has been a consistent feature of long term administration of NSAID [34;35] but it is clearly much easier to achieve this with mavocoxib.

Using NSAIDs Safely and Successfully

General

With an increasing set of drugs and a wide range of application it can be confusing to the veterinarian trying to plan what medication to use in what situation. When faced with a choice of selecting a particular NSAID there are factors to be considered and these can be prioritized as follows:

1. Safety
2. Effectiveness
3. Ease of administration
4. Cost

Using NSAIDs safely

Safety of a particular drug and avoidance of adverse effects is the factor that most influences choice. Most veterinarians are aware of the relatively high occurrence of problems with regular NSAID use and these concerns restrict both the use of drugs and the period they are used for. Side effects reported with all NSAIDs are mainly gastrointestinal (64%) with renal events (21%) and hepatic problems (14%) the other main toxicities reported [36]. The majority of these are not serious and reversible with early attention. Almost all of the second and third generation of NSAIDs that we have available are much safer than their predecessors offering greater comfort in this area. The coxib group have been developed with their COX-1 sparing profile to try and minimize gastro-intestinal adverse events. Sadly although there are some individual dogs which are very sensitive to NSAID use, many of the problems seen are due to misuse or poor communication with the owners. Common mistakes seen include

1. using the incorrect dose (overdose)
2. using in combination with another NSAID
3. using in combination with corticosteroids

Using an incorrect dose can be due to a genuine mistake or increasing the dose above the recommended one in the mistaken belief that this will improve the effect by vet or owner. These are both avoidable with appropriate understanding and communication. Cumulation of drug due to reduced clearance or altered metabolism can be more difficult to avoid completely but can be predicted by knowing of other health issues or screening patients who are believed to be at risk for problems by blood sampling or performing other diagnostic tests pre-treatment. The challenge is to make these drugs and their benefits more available to risk groups such as geriatrics rather than to deny them access.

When using NSAIDS peri-operatively to control surgical pain it is imperative that the patient is adequately hydrated throughout the procedure. Failure to achieve this can lead to problems with renal perfusion and subsequent serious renal damage or death.

NSAIDs must never be used in combination and never used with corticosteroids.
Monitoring for any signs of problems is an important part of using these drugs. A clear set of instructions to owners explaining the risk and advising them what to look out for can avoid serious complications. Most adverse events, especially gastrointestinal ones, can be contained and resolved if the animal is presented early. The majority of gastrointestinal problems occur early, usually within the first two weeks of treatment. Vigilance should be higher during this period for any signs of vomiting or diarrhoea.

Coping with Gastrointestal (GIT) events

In the majority of cases early recognition with withdrawal of the NSAID and supportive therapy is adequate to allow an early return to normal. In more severe events gastric ulceration and perforation can result. Unfortunately side-effects have been reported even with the third generation coxibs. Sadly in the events documented it seems that the main reason for serious adverse events with these drugs was again down to inappropriate use [36;37]. It is much better to try and avoid these consequences rather than treat them and this emphasizes the importance of owner vigilance and making early contact with the veterinarian if there are concerns about toxicity. Advised practice in cases showing possible adverse events is to withdraw NSAID, ensure that animal is properly rehydrated and try to establish if there are any other reasons for the signs. Various medical interventions are available if gastric ulceration is suspected but few are very effective at quickly resolving an NSAID induced ulcer [2]. H2-blockers such as Cimetidine can be used to try and decrease the acidity in the gastric lumen, which can reduce secondary damage, but cimetidine will not prevent the formation of an ulcer. Omeprazole (protein-pump inhibitor) may be a more practical and effective choice as it is a much more potent antacid and is given once daily. Misoprostal, which is a synthetic PGE1 analog which can be used to prevent ulceration but requires dosing 3-4 times daily and side-effects are common. In the absence of any satisfactory method of either preventing or healing drug induced ulceration best practice is to try to avoid their formation by using NSAIDs sensibly and only using gastro-protectives in extreme circumstances or proven intolerance cases. Even in these cases, results can be unpredictable.

NSAIDs in the management of Osteoarthritis

Osteoarthritis is the most common cause of chronic pain in small animals and one of the most common indications for NSAID use. NSAIDs are becoming increasingly important in the management of osteoarthritis with the realization of how important control of pain is to deliver an improved outcome. This is coupled with increasing disappointment over the results of so-called chondro-protective drugs in alleviating the clinical signs. Recently the understanding that peripheral and central sensitization in the sensory system in chronic osteoarthritis could play an important part in suffering and disease progression has prompted increased interest in the actions of COX-2 in the nervous system, in particular, the CNS. COX-2 seems to play an important role in sensory perception in OA and sensitization [38] and COX-2 inhibition has been demonstrated to decrease central sensitization [39]. There is also speculation that prolonged and effective suppression of peripheral and central pain mechanisms may lead to altered disease progression [40;41].
These findings have altered the basic management of osteoarthritic cases and produced new challenges in this area. In simple terms NSAIDS are being used increasingly and for more prolonged periods. Several studies have indicated that prolonged use of NSAIDs has resulted in improved outcomes compared with shorter periods of treatment [34;35], presumably in line with the reasons identified above, and this is becoming more common practice. This raises concerns about possible toxicity but as yet, there has been no evidence that prolonged use has resulted in increased or new adverse events (Pfizer; Trocoxil Study). Many of the newer drugs have long-term license indications.
There are three major situations that veterinarians have to deal with when using NSAIDs to manage OA.
The first one deciding what NSAID to use, which is becoming increasingly complicated with a greater variety of choices. The newer second and third generation drugs all demonstrate good safety profiles and have good evidence of efficacy therefore choice is really based on personal preferences. Most of these also come in formulations that are easy to administer and are in once daily dose regimes, both of which increase compliance. The coxibs hold promise with increased GI safety profiles and all of these are perfectly suitable for first line use. Drugs like mavacoxib offer an easier method of delivering prolonged therapy in cases which are stable and would benefit from this approach. Increasingly NSAIDs are not used as single agents to treat OA but as part of a multi-modal approach supplying analgesia along with alterations in diet, lifestyle, exercise and mobility in addition to possible surgical intervention. [2] This approach recognizes the complex nature of a chronic lifelong disease like OA and produces better and more sustained results.

The second main challenge is that presented by an animal that shows a poor response to NSAID treatment, the slow responder. This situation has to be dealt with logically and a multimodal approach assists with this. In this situation a number of questions have to be posed and answered.

1. Is the joint too altered to respond to medication? In these cases there may be a surgical salvage solution if a single joint or pair of joints is involved eg Total Hip Replacement.
2. Could the animal have a poor response to that NSAID? Although all of the modern NSAIDs show good efficacy in the test populations it is widely accepted that there are individually determined variations in response. This means that one NSAID may work better than another in an individual case. Unfortunately there is no way to find this out other than by using trial and error. However this may be the simplest way to resolve the problem and obtain a good response.
3. Has the NSAID had long enough to have an effect? This is a common situation where a drug is removed too quickly before it has had time to make a difference. Again a multimodal approach can help and promote a degree of patience. Clearly it depends on the degree of pain or suffering but that is not the usual reason for poor response being recognized. Usually the expectations for improvement are wrong and false hopes of a complete recovery in a short period of time lead to frustration and disappointment.

NSAID	COX Selectivity	Route	Dose	Licence for
Meloxicam	COX-2 Preferential	Inj Oral Suspension	0.2mg/kg 0.1 then 0.05mg/kg	Once indefinite
Robenacoxib	COX-2 Selective	Inj Tablet (6mg)	2mg/kg 1mg/kg	Once Up to 6 days
Ketoprofen	none	Inj Tablet (5mg)	2mg/kg 1mg/kg	Up to 3d Up to 5d
Tolfenamic Acid	none	Inj Tablet	4mg/kg 4mg/kg	2days 3 days

*Table 4 NSAID use in cats**

** Data from ISFM and AAFP Guidelines*

The third dilemma is a more difficult one, and is dealing with an animal in need of pain relief which shows early adverse effects or obvious intolerance of NSAIDs. In these cases in helps to have an understanding that although there has been a reaction to the NSAID used there is a chance that another NSAID may be better tolerated and that the class should not be dismissed as a therapeutic option. Care and patience are required with substitution of a replacement drug. New third generation NSAID afford additional options with their increased GI safety profile. It is also important to keep in mind that most toxicity is the result of overdosage. This could be relative and reducing the dose or increasing the dose interval may resolve the problem. Persistent intolerance can be difficult to manage but once again a multimodal approach may give solutions while still allowing the treatment objectives to be preserved.

In both of the situations discussed above, poor response and intolerance, the understanding that all NSAIDs do not behave the same way in individual cases is key and can give an easy solution. Another key understanding is that of the possible dangers posed by swopping one NSAID for another in this process. These dangers which can be the result of complimentary toxicities, for example COX- 1 induced gastric ulceration induced by drug 1 replaced by COX-2 selective which may impair ulcer healing. A 'wash-out' period is used to minimize this possibility [42]. The amount of time that should elapse between withdrawal of one drug and commencing treatment with the substitute is still contentious and really depends on the situation. The accepted wisdom is that this period should be sufficient to allow any pathology to resolve completely. In reality if the reason for changing is a poor response, the dangers are much less and a prudent 3-5 day interval is suggested. If the reason for changing is the occurrence of an adverse event then much more care should be exercised and a longer interval used. Analgesia should be provided by a another means during this period and once again using a multi-modal approach facilitates this.

NSAIDs in Cats

With several NSAIDs now being licensed for use in cats there is increasing interest in using the class of drugs in this species as effective analgesics. This interest has been accelerated by the relatively new realisation that osteoarthritis and degenerative joint disease are very common occurrences, particularly in older cats [43;44;45]. This has accentuated the need for safe and easy to use NSAIDs in this species. The cat provides additional challenges with a high incidence of renal disease a concern for toxicity, difficulty in ensuring accurate dosage because of the smaller bodyweights and difficulty in administering medication [46]. There are three Second Generation NSAIDs which are licensed for use in the cat and which have clinical evidence of both safety and efficacy. These are meloxicam, ketaprofen and tolfenamic acid. The only Third Generation product to have an indication in cats at this time is robenacoxib (Table 4). It is outwith the scope of this article to expand in detail on the use of these drugs in cats but there is an excellent set of guidelines which have been produced by the ISFM and AAFP for long term use of NSAIDs in cats to which the reader is directed [46].

Concluding summary

NSAIDs carry considerable advantages in the management of both acute and chronic pain in both dogs and cats as a result of their mode of action and the fact that they are easy to use. Recent introduction of a new range of third generation coxibs increase the choice available to the veterinarian. A full understanding of the drugs and the diseases they are used to treat allows safe and effective use avoiding unnecessary adverse events. Clear communication to the owners is a key part of this. This is especially important for the increasing numbers of older cats and dogs who may benefit from the proper use of NSAIDs to alleviate pain and suffering as a result of chronic disease.

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ORIGINAL WORK (UK)

Intracranial germ cell tumour in an Airedale Terrier

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SUMMARY

A 30-months-old neutered male Airedale Terrier presented with depressed mental status and anisocoria. A space-occupying suprasellar lesion was visualised by magnetic resonance imaging. The lesion appeared isointense relative to the brain parenchyma on T1-weighted images and hyperintense on T2-weighted images and had a moderate homogeneous enhancement. The dog was euthanased and the histopathologic diagnosis was a suprasellar germ cell tumour.

Key words: Airdale Terrier, intracranial germ cell tumour, immunohistochemistry, magnetic resonance imaging.

Introduction

Germ cell tumours are a group of primitive gonadal neoplasms but they may also occur in extra-gonadal sites [1, 2]. In man and in dogs, these tumours have been rarely observed in the central nervous system, often in the suprasellar region [1-12]. Intracranial germ cell tumours (IGCT) have been described in young adult Doberman Pinschers, although this neoplasm has also been reported in other breeds [3,4,6,7,12]. This is the first report of an IGCT in an Airedale Terrier. In human patients, magnetic resonance imaging (MRI) has been reported as the investigation of choice for the presumptive diagnosis of IGCT and for planning the surgical approach [13]. In dogs there is sparse data on MRI features of IGCT [12]. The present report describes the clinical, MRI and histopathologic features of IGCT in a young Airedale Terrier.

Case report

A 30-months-old neutered male Airedale Terrier was referred for investigation of progressive drowsiness and anisocoria noted one week before presentation. On neurological examination the dog had low neck carriage and depressed mental status. Direct and consensual pupillary light reflex was considered normal in the left eye and absent in the right eye. In particular, the right pupil appeared constantly dilated. Palpebral, corneal and gag reflexes, facial sensation, menace response, eyes movements, spinal nerve reflexes, proprioception and muscle tone were normal. Fundoscopic examination of both eyes revealed no gross abnormalities. The neurological findings supported involvement of the brain and the parasympathetic portion of the right oculomotor nerve. Haematology, biochemistry and cerebrospinal fluid profiles were normal. The dog had reduced total L-Thyroxine (6.44 nmol/l; reference 15.0 to 50.0 nmol/l) and low-normal basal cortisol (24.8 nmol/l; reference 27.5 to 125 nmol/l). Thyroid-stimulating hormone was also low-normal (0.036 ng/ml; reference 0 to 0.6). MRI scans (Vet-MR Grande, Esaote S.p.A, Genova, Italy) of the dog's brain were obtained under general anaesthesia in transverse, dorsal, and sagittal planes of orientation before and after the intravenous administration of 0.1 mmol/kg gadolinium (Magnevist®, Schering, Germany). On T1-weighted (T1-W) images (TR: 850 ms, TE: 26 ms) an isointense ill-defined space-occupying round lesion was visualised in the diencephalon, compressing the surrounding brain parenchyma and lateral ventricles. On T2-weighted (T2-W) images (TR: 3110 ms, TE: 80 ms) the lesion had uniform high signal intensity, demarcated margins and appeared to compress the hypothalamus. After intravenous administration of contrast medium there was moderate homogeneous enhancement (Fig. 1, Fig. 2). In particular, sagittal post-contrast T1-W images showed that the lesion was dorsally displacing the rostral portion of the mesencephalon (Fig. 2). Differential diagnoses for the lesion included glioma, meningioma, IGCT, pituitary tumour and craniopharyngioma. Before planning any treatments, diagnostic needle biopsy of the mass was offered but the owner elected for euthanasia of the dog. Post-mortem examination was confined to the brain that was fixed in 10 per cent formalin and submitted for histopathological evaluation. The fixed brain ventral surface had an irregular rough pale area (20x15 mm diameter) dorsal to the pituitary gland. Cut surfaces revealed an overlying suprasellar hypothalamic firm pale area (20 mm diameter) that was poorly demarcated from

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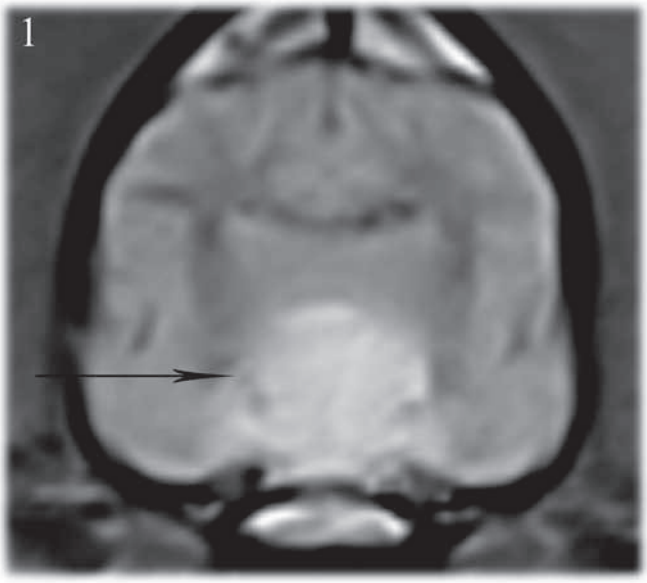
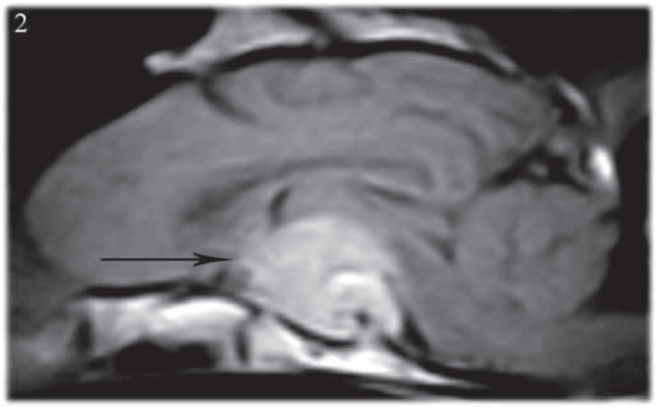
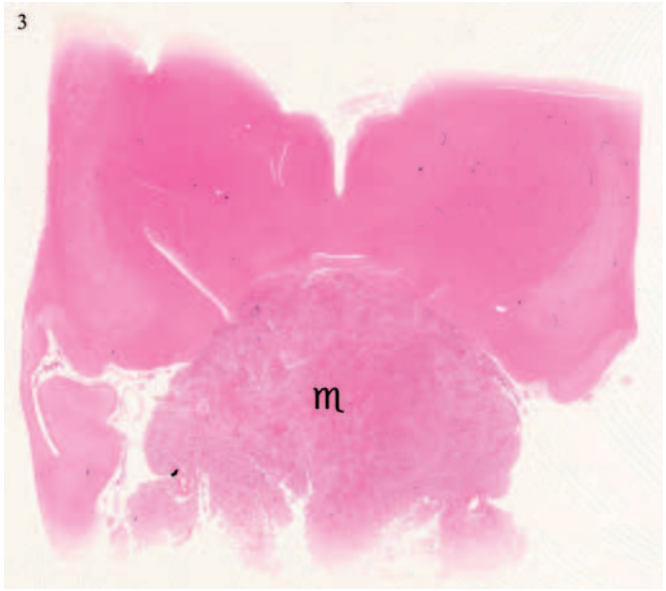




Transverse (Fig 1) and sagittal (Fig2) post-contrast T1-weighted MR images of the brain at the level of the interthalamic adhesion. The lesion shows homogeneous contrast enhancement, a round shape and demarcated margins. In addition, note how the lesion is dorsally displacing the rostral portion of the mesencephalon.

the adjacent compressed neuropil. The cerebrum, cerebellum, brain stem and ventricles were otherwise unremarkable. The hypothalamic mass (Fig. 3) consisted histologically of abnormal tissue with three intermingled areas: 1) organoid clusters of pleomorphic germ cells (Fig. 4); 2) multilocular cysts lined by columnar epithelial cells (Fig. 5). Cysts and surrounding neuropil contained cell debris, stands of basophilic mucinous material and cholesterol clefts (Fig. 6); 3) Foci of lymphocytes and macrophages with foamy pale cytoplasm. Also present were foci of acidophilic pituitary epithelial cells (Fig. 7). Compressed neuropil around the suprasellar mass contained reactive gemistocytes. Immunohistochemical staining was carried out using commercial antibodies linked to horseradish peroxidase (HRP) (DAKO Corporation, Glostrup, Denmark) as follows: alpha-fetoprotein (AFP)-polyclonal rabbit antihuman; human chorionic gonadotrophin (HCG)-polyclonal rabbit antihuman; epithelial cytokeratin 5/6-monoclonal mouse antihuman cytokeratin; CD30-monoclonal mouse antihuman germ cell (embryonal carcinoma) marker. Immunostaining with antibodies linked to horseradish peroxidase gave a strongly positive reaction for AFP (Fig. 8) and a less strong focal reaction for HCG in the suprasellar pleomorphic cells (Fig. 9). There was positive immunostaining of these cells with antibody (CD30) against embryonal carcinoma. Cells lining cysts were positively immunostained for epithelial cytokeratin 5/6 (Fig. 10). On the basis of the anatomic site, histological appearance and positive immunostaining for AFP and HCG the lesion was considered to consist of germ cells, pituitary acidophils and epithelial cysts with secondary degenerative changes.

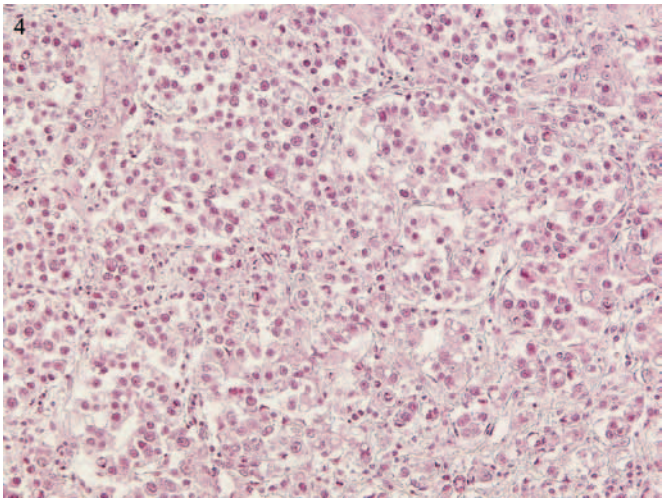
Fig. 3: Section of a suprasellar mass (m) in a 30 months old Airedale Terrier. There is compression of the overlying hypothalamus. Haematoxylin & Eosin X6



Discussion

Germ cell tumours are a group of primitive gonadal neoplasms but they may also occur in extra-gonadal sites [1, 2]. In man and in dogs, primary central nervous system germ cell tumours are rare [3-7, 9, 10, 12]. In man IGCT occur predominantly in

Fig. 4: Organoid clusters of pleomorphic germ cells in a suprasellar mass. Haematoxylin & Eosin X80



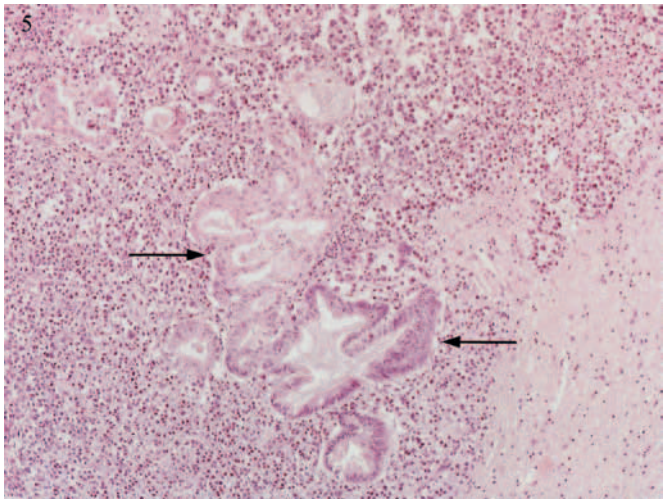


Fig. 5: Suprasellar mass showing multilobular cysts (arrows) with surrounding germ cells. Haematoxylin & Eosin X100

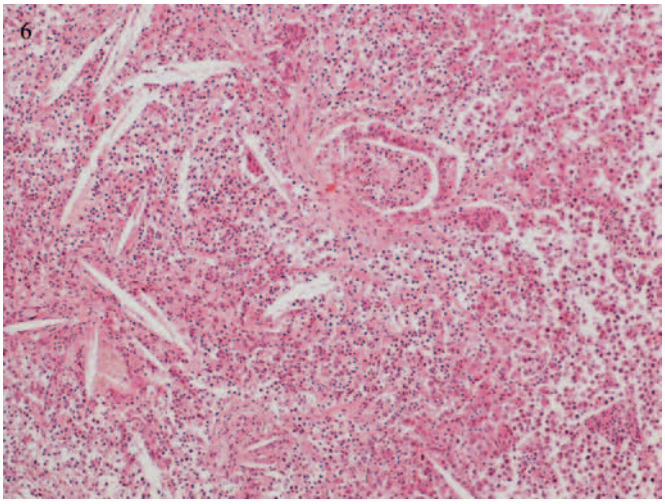


Fig. 6: Suprasellar mass showing degenerate germ cells and cholesterol clefts around an epithelial cyst. Haematoxylin & Eosin X100

children and adolescents [5, 9]. Affected dogs are usually 2 to 5 years of age and it seems that IGCT may be over-represented in Doberman Pinschers, although this tumour has also been reported in other breeds [3, 4, 6, 7, 12]. This is the first report of an IGCT in an Airedale Terrier.

The polymorphic histological nature of the suprasellar mass in this report was interpreted as consisting of 3 separate intermingled components: primitive germ cells; epithelial cysts resembling craniopharyngioma; pituitary acidophils. Post mortem examination was limited to the brain and histological examination of the pituitary was not undertaken but the presumption is that the lesion originated there. Case reports of primary intracranial tumours at this anatomic site and with this histological appearance have been published as craniopharyngioma in dogs, but are now classified as germ cell tumours on the basis of these criteria: 1) anatomic location, 2) the presence within the tumours of several distinct cell types, 3) positive staining for AFP [3, 4].

Human patients with this tumour may have clinical signs of headache and visual disturbances that may be related to raised intracranial pressure and optic chiasmal compression. In addition, because these neoplasms are usually located in the suprasellar region of the brain, tumour growth may cause endocrine dysfunctions such as diabetes insipidus, amenorrhoea, growth retardation, and precocious puberty [8, 11]. Clinically, our patient had depressed mental status and anisocoria with constant dilatation of the right pupil. These neurological findings supported involvement of the brain and the parasympathetic portion of the right oculomotor nerve. Lesions of this nerve may cause a dilated pupil that is unresponsive to light because of loss of the parasympathetic preganglionic neurons that innervate

Fig. 7: A cluster of eosinophilic pituitary epithelial cells (arrows) in a suprasellar germ cell tumour. Haematoxylin

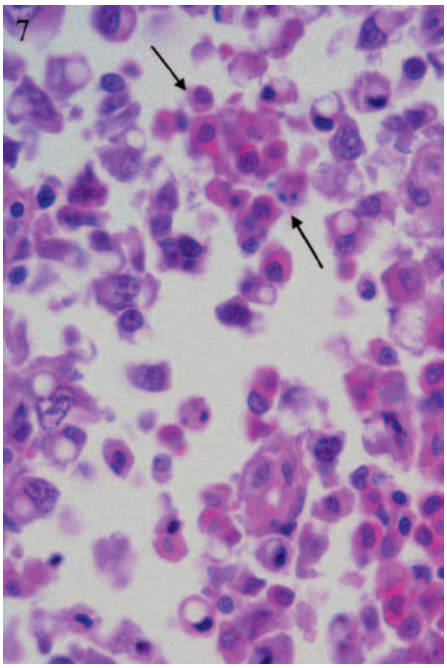
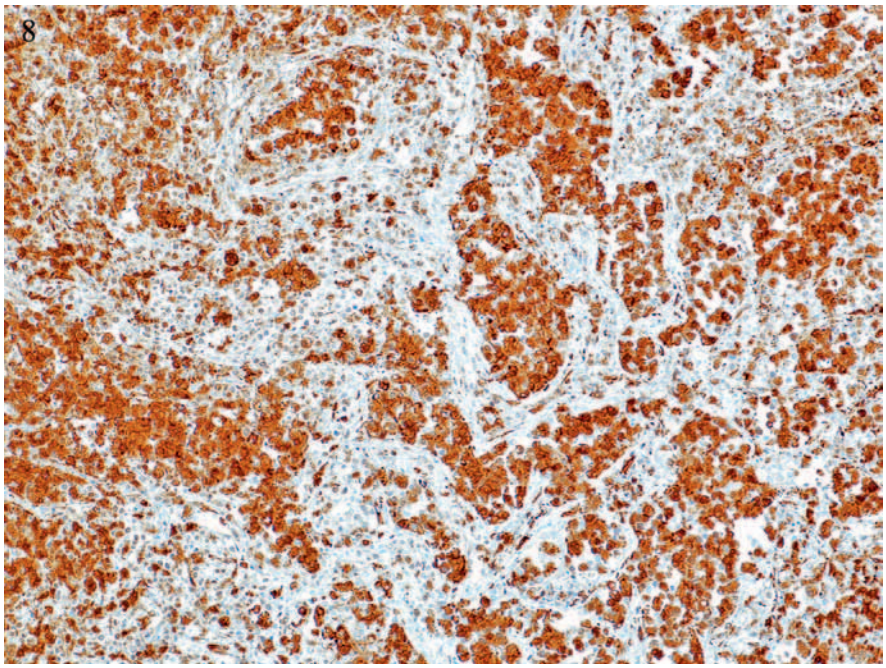


Fig. 8: Suprasellar germ cell tumour with strong multifocal AFP staining. HRP-AFP/Haematoxylin & Eosin X100



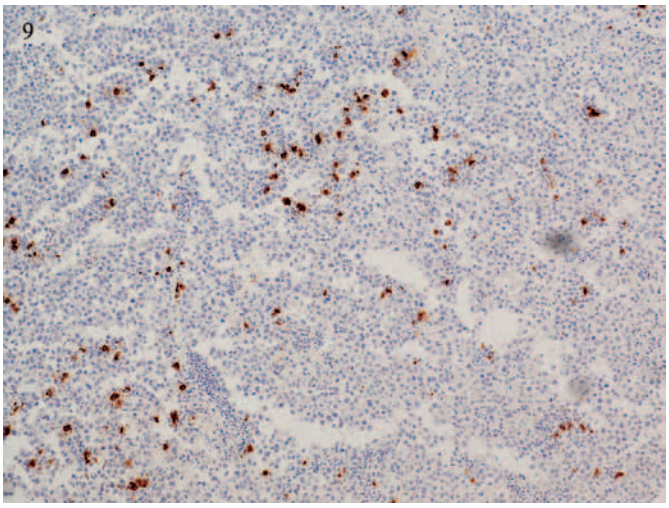


Fig. 9: Suprasellar germ cell tumour with focal HCG staining. HRP-AFP/Haematoxylin & Eosin X100

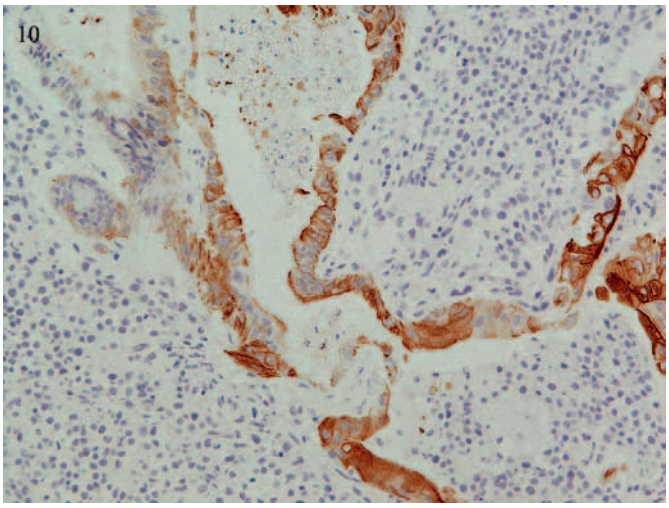


Fig. 10: Suprasellar germ cell tumour showing cytokeratin positive cyst epithelial cells and surrounding germ cells. HRP-cytokeratin/ Haematoxylin & Eosin X200

the iris constrictor muscle [12]. In this particular case it is likely that the suprasellar mass was compressing the right oculomotor nerve and the diencephalon with secondary involvement of the ascending reticular activating system, a network of neurons responsible for maintaining the state of wakefulness [12]. Because IGCT can extend from the olfactory peduncles to the pons and pyriform lobes, other neurological deficits caused by enveloping of other cranial nerves and compression of the surrounding brain parenchyma may be expected and can include head pressing, circling, blindness, partial or total ophthalmoplegia externa and bradycardia [3, 7, 12]. Rarely, in dogs IGCT have been associated with pituitary dysfunction [3]. In the case under study, the reduced L-Thyroxine and low-normal basal cortisol and thyroid-stimulating hormone was thought to reflect incipient panhypopituitarism. It is possible that these neoplasms may behave differently: in some cases sufficient pituitary tissue may persist to maintain adequate pituitary function, [3, 4] whereas in other cases tumour may invade and destroy the pituitary impairing normal physiologic function of the gland. In human patients computed tomography or MRI, with and without intravenous administration of contrast medium, may be employed to establish the presumptive diagnosis of IGCT. However, MRI is preferred under most circumstances, providing superior resolution and multiplanar imaging capabilities, and avoiding the "spray" artefact from the petrous ridge that may obscure computed tomography images of the base of the brain [8]. Moreover, in man MRI has been reported as the investigation of choice to presumptively diagnose IGCT and to plan the surgical approach [13]. In this particular case MRI was very helpful to precisely locate the anatomical site of the suprasellar mass and to delineate the extent of the tumour and its involvement with the surrounding brain. The tumour was localised in the diencephalon and this finding is in accordance with previous studies in dogs as well as in people where IGCT are often visualised in the suprasellar region [8, 12, 13] although they have also been identified in the pineal region [2] and in the midbrain [14]. MRI features of IGCT have been reported in dogs where a homogeneous moderately enhancing mass was detected on T1-W post-contrast images corresponding to the suprasellar region [12]. However, there was no mention of the signal intensity in the other MRI sequences. In accordance with human literature, the tumour in our patient appeared isointense relative to the adjacent brain on T1-W images, hyperintense on T2-W images and had moderate homogeneous enhancement after intravenous administration of the contrast medium [13]. Several lesions including meningioma, pituitary tumour, glioma and craniopharyngioma may mimic IGCT. All these brain lesions may appear iso- to hypointense on T1-W images, hyperintense on T2-W images and they usually show enhancement on postcontrast T1-W images. In addition, they may be associated with mass effect and they can be localised in the suprasellar region [15-21]. However, meningioma and glioma were considered to be less likely because these primary brain tumours are rarely located in the diencephalon and would be uncommon in a dog of this relative youth [18, 20, 21]. Pituitary tumours may impinge on the ventral aspect of the forebrain at the level of the diencephalon and may be adenomas or adenocarcinomas. These secondary brain tumours might be suspected as they usually appear as fairly sharply marginated masses that can displace and/ or invade the overlying brain [17-19, 22, 23] but they would be unusual in a dog of this young age [22, 23]. At present there are no data on the MRI findings of craniopharyngioma in dogs. In one study craniopharyngioma was suspected in a dog on the basis of clinical findings and computed tomography images [24]. MRI features of craniopharyngioma have been reported in a cat: an ovoid mass invaded the hypothalamus and optic chiasm but there was no mention of the magnetic resonance signal intensity features [25]. In man craniopharyngioma tends to have a suprasellar location and the most common MRI pattern of this tumour is that of iso- to hypointensity on T1-W images and high signal intensity of variable homogeneity on T2-W images. The tumour usually shows enhancement on T1-W postcontrast images [15, 16]. On the basis of MRI findings in this report we were unable to definitively diagnose the exact nature of the lesion. Ante-mortem diagnosis by surgical biopsy was declined by the owner. In man stereotactic surgery (a surgical intervention which makes use of a three-dimensional coordinates system to locate small targets inside the body and to perform on them biopsies or other procedures) is the preferred surgical approach both for diagnostic and therapeutic reasons, because

of the low associated morbidity [26]. In dogs, transsphenoidal hypophysectomy may be used to achieve a final histopathological diagnosis of pituitary masses and is expected to have the best outcome when used in case of nonenlarged or moderately enlarged pituitaries [27]. In man gross resection of IGCT is not recommended in view of the potential morbidity associated with this procedure [13] and these suprasellar tumours are treated with craniospinal irradiation and chemotherapy. However, even with aggressive therapy, the 5-year survival is less than 50% [28, 29]. At present, there are no data on treatment and outcome of IGCT in dogs. One recent study of 46 dogs with pituitary masses showed that dogs that underwent radiotherapy had significantly longer survival times than untreated dogs: but pre- and post-mortem histological evaluation of the pituitary lesions was not carried out [30]. It may be that conventional radiotherapy could be effective for controlling and inhibiting IGCT growth in dogs but further studies would be required to assess the benefits and risks of this medical approach. In conclusion we report the first case of IGCT in a young male Airedale Terrier. The lesion was detected by MRI and confirmed histologically. On the basis of MRI findings alone we were unable to definitively diagnose the exact nature of the lesion and histopathological evaluation was necessary for morphologic diagnosis of the complex nature of the suprasellar mass.

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REPRINT PAPER (F)

Three cases of canine lichenoid dermatitis of bacterial origin

D.N. Carlotti [(1)], *F. Gardini*[(2)], *P.A. Germain*[(3)]

SUMMARY

Three cases of canine pyoderma associated with a lichenoid reaction are presented. These three dogs were dolichocephalic and were used regularly for hunting. Lesions observed in the three cases were similar and had the same localisations: clusters of papular and nummular plaques and plaques frequently covered by thick crusts, on the ear pinnae, face and limbs. Skin biopsies revealed a dense band-like infiltrate of lymphocytes, plasma cells and histiocytes associated with epidermal basal cell lesions, and subcorneal and/or follicular pustules. The response to antibiotic therapy was excellent and rapid, the lesion disappearing in 3 weeks. This presentation of pyoderma is rare. Lichenoid dermatitis is probably due to a particular reaction pattern.

Key words: Dermatology – Dog – Pyoderma – Lichenoid reaction.

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Prat Méd Chir Anim Comp *(2006) **41** : 79-83

Introduction

Pyoderma is a very common canine disease. Pustular lesions are frequently a symptom of this disease but a wide diversity of symptoms have been observed [1,2].

Lichenoid dermatites are rare diseases whose origin is often unknown in dogs. The clinical characteristics are papular lesions which can coalesce and form plaques [3].

In this article, we present three retrospective cases of pyoderma with a lichenoid aspect from a clinical and histopathologic point of view. In addition they show epidemiological similarities.

These three animals were brought for consultation in 1985, 1987 and 2003 respectively.

Case Number 1

A 3 year old neutered female Pointer was brought in for consultation with chronically evolving scabby lesions on the ventral aspect of the ear pinnae. The dog lived freely in the countryside and was regularly used for hunting.

The lesions had appeared six months previously. A systemic antifungal treatment (griseofulvin) and local treatment (enilconazole, Imaveral®) had been administered, without result. A fungal culture did not show the presence of dermatophyte. The use of benzoyl peroxide (Peroxydex®) led to a partial improvement of the lesions.

A clinical examination of the dog did not show any anomalies other than cutaneous .

Several clusters of scaly papular and nummular plaques and plaques, sometimes coalescent, were present on the ear pinnae and limbs (figures 1 and 2). Some of the lesions were ulcerated and covered with crusts.

A new fungal culture and several skin biopsies were performed. No fungal colony developed. The histopathologic examination had showed the presence of sero-cellular crusts, an important follicular orthokeratotic hyperkeratosis, and a dense band-like infiltrate of lymphocytes and plasma cells. We reached the conclusion that it was a superficial pyoderma of bacterial origin.

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* Presented by AFVAC (France)

Antibiotic treatment with oxacillin (Bristopen®, 500 mg PO, BID) was prescribed together with benzoyl peroxide shampoos. The dog made a complete and rapid recovery and a check-up 3 weeks later showed no further skin lesions. Two relapses occurred 2 months and 2 years respectively after the first episode and responded to the same treatment. There was a clear relationship between these relapses and use of the dog for hunting.

Case Number 2

A 2½ year old neutered male German pointer was brought for consultation with recurrent and generalised scabby lesions.

The dog lived in a house and had access to a garden. He was regularly used for hunting. The lesions had appeared 3 months earlier, shortly after the dog was used for hunting. The lesions, at first localised and consisting of crusty papules, had been treated orally with amoxicillin and hydrocortisone. The lesions totally disappeared but a relapse was observed one month later.

A clinical examination of the dog showed only the cutaneous anomalies.

Clusters of papular and nummular plaques, frequently covered by scales and thick crusts, were observed on the ear pinnae and limbs (figure 3). Some hyperpigmented macules surrounded by epidermic collarettes were also observed on the abdomen.

Skin scrapings, a trichogram and a fungal culture all gave negative results.

A cytological examination obtained by skin smear revealed numerous neutrophils, macrophages and *Cocci*, frequently phagocytosed by the polymorphs.

The bacteriological examination identified a strain of *Staphylococcus intermedius* susceptible to different antibiotics (penicillins, cephalosporins, aminoglycosides, macrolides, sulfonamides).

The histopathological examination revealed numerous serocellular crusts with colonies of *Cocci*, an important follicular orthokeratotic hyperkeratosis, and signs of basal cells degeneration associated with some apoptotic cells. A dense and diffuse infiltrate that included lymphocytes, plasma cells and histiocytes was observed in the superficial and periannexial dermis (figure n°4). In some areas, neutrophils and signs of suppurative folliculitis and furunculosis, with free keratin in the pyogranulomatous infiltrate, were observed. We concluded this confirmed a superficial and deep pyoderma of bacterial origin.

A systemic antibiotic treatment with amoxicillin potentiated clavulanic acid (Synulox®, 500 mg PO, BID) was started. A marked improvement of the lesions was observed within 10 days. The treatment was continued for an additional 25 days and at the check-up the lesions had completely disappeared. The case was not seen again and follow up was not possible.

Case Number 3

A 4 year old male Pointer was brought in for consultation for a multifocal crusting dermatosis.

The dog lived in a house and had access to a garden. He was regularly used for hunting. The lesions had appeared 1 month before the consultation. Local treatment using Panolog® (nystatin, neomycin, triamcinolone) had not resulted in an improvement.

A clinical examination of the dog showed only the cutaneous anomalies.

Numerous nummular erythematous papules and plaques of varying sizes, frequently eroded and covered by a thick crust, were observed on the ear pinnae, the head and the front legs (figure 5).

Skin scrapings, a trichogram and a fungal culture all gave negative results.

A cytological examination obtained by skin smear revealed numerous neutrophils, macrophages and *Cocci*, frequently phagocytised by the polymorphs.

The bacteriological examination enabled the identification of a strain of *Staphylococcus intermedius* susceptible to different antibiotics (penicillins, cephalosporins, aminoglycosides, macrolides, sulfonamides, quinolones).

The histopathological examination revealed several subcorneal pustules in the process of drying up, some signs of hydropic degeneration and apoptosis in the basal layer of the epidermis (figure 6) and a marked pigmentary incontinence. A dense and diffused infiltrate of lymphocytes, plasma cells and histiocytes was observed in the superficial dermis and some areas of suppurated folliculitis were noted (figure 7). We concluded that this was a superficial pyoderma of bacterial origin.

Systemic antibiotic treatment using cefalexin (Rilexine®, 600 mg PO, BID) was started. A marked improvement in the lesions was observed after 15 days (figure 8). The treatment was continued for 15 more days and resulted in the complete disappearance of the skin lesions. No relapse had been reported during the following year.

Discussion

These three cases presented several similarities (table 1). In all three cases, the dogs were dolichocephalic and used regularly for hunting. The lesions observed and their localization were the same, papular and nummular plaques and plaques covered with thick crusts on the ear pinnae and limbs. The histopathological examination showed a dense band-like sub-epidermal infiltrate, mainly composed of lymphocytes and plasma cells, associated with epidermal basal cell lesions. Subcorneal and follicular pustules were often present. The response to antibiotic therapy was excellent and rapid.

Table 1: Summary of the three cases

Breed	2 Pointers and a German Pointer
Sex	2 males (1 neutered) and 1 female (neutered)
Age	**Young adults** (approximately 3 years)
Way of life	**Hunting**
Reason for consultation	**Crusting** dermatitis
Dermatological examination	**Several nummular erythematous papules** and **plaques**, frequently covered by **crusts**, on the **ear pinnae** and **limbs**
Cytological examination	Neutrophils, phagocytosis of Cocci (2/3)
Histopathological examination	**Hydropic degeneration and apoptosis in the basal layer of the epidermis** (2/3) **Lymphoplasmocytic subepidemal band-like infiltrate** (3/3) **Suppurated folliculitis** (2/3) Perifolliculitis (1/3)
Treatment	**ß-lactamine antibiotics** 20 – 30 days
Follow-up	**Recovery in 2-3 weeks** (In 1 case: 2 relapses at 2 months and 2 years)

The term "lichenoid" means "of lichen-like appearance". In human dermatology, lichenoid dermatitoses are inflammatory diseases characterised, clinically by papular lesions resembling botanical lichen and histopathologicaly by a band-like infiltrate of mononuclear cells in the superficial dermis, associated with lesions in the lower layers of the epidermis, which suggest a cell-mediated autoimmune reaction against the epidermis [4]. The skin conditions which match this definition are : idiopathic lichen planus , lichenoid drug reactions, lichenoid contact dermatitis, lichen striatus, solitary lichenoid keratosis, graft versus host disease, lupus erythematosus, lichen nitidus and prurigo pigmentosa [4].

In veterinary dermatology there is a certain amount of confusion surrounding this term. Some entities present both the clinical and histopathological sides of a lichenoid dermatitis in the true sense: lichenoid keratosis, psoriasiform lichenoid dermatitis and idiopathic lichenoid dermatitis[1]. But several histopatologist authors have used the term "lichenoid" to define a band-like mononuclear infiltrate in the superficial dermis associated with epidermal basal cell lesions, independent of the clinical aspect [5]. For some of them, damage to the lower layers of the epidermis (known as interface dermatitis) is not an essential criterion [6]. In this case, it can be considered that many dermatitoses reveal a "lichenoid" reaction on histopathological examination. A "lichenoid" infiltrate, that is to say in a sub-epidermal band, is effectively present in numerous conditions such as mucocutaneous pyoderma, cutaneous lupus erythematosus, systemic lupus erythematosus, pemphigus erythematosus, uveo-cutaneous syndrome, vitiligo, erythema multiforme, actinic keratosis, mycosis fungoides [6].

In terms of clinical nosology it would be logical to restrict the use of the term "lichenoid" to dermatitis which show signs both on a clinical and histopathological level. In the same way, on the histopathological level it would be preferable to use the term "lichenoid" for a sub-epidermal infiltrate, whether it has interfacial dermatitis or not.

The symptoms of lichenoid dermatitis are scaly and flat papules and plaques usually localised on the external face of the ear pinnae, on the ventral region of the thorax and the abdomen. Other locations are less frequently described [3, 7, 8]. In our three cases, these flat papules and plaques, sometimes covered by thick crusts, were found on the ear pinnae (and in one case, on the head) and the limbs.

In these three cases the term lichenoid dermatoses can be used.

Lichenoid dermatoses are rare diseases whose cause is unknown. In human dermatology the hypothesis currently regarded as the most plausible by certain authors is of an auto-immune cause, possibly triggered and localised by a viral infection (hepatitis C virus) [4,9]. In dogs, an immunological mechanism is also considered likely [10]. In certain cases, genetic determinism and the intervention of infectious or traumatic factors are also evoked. These diseases are described in the Doberman but also in other breeds [3, 7, 8, 11, 12]. Our three cases concern 2 Pointers and 1 German Pointer all of about 3 years old, used regularly for hunting. It could be imagined that regular use for hunting increases the risk of trauma and bacterial infections on the face, the ear pinnae and the forelimbs. The head conformation (dolichocephalic breeds) could be another factor which leads to auricular trauma during hunting sessions.

The lichenoid dermatitis diagnosis is based upon the case history, the type and localisation of the lesions, and the histopathological examination. In our cases, in view of the clinical aspect, we have suggested two main groups of dermatoses for the differential diagnosis: pseudoneoplasms (bacterial, fungal, parasitic or sterile) and neoplasms [13].

The supportive investigations to be carried out are skin scrapings, cytological and bacteriological examinations using exudates, and fungal cultures. Histopathological examination is essential for a definitive diagnosis: it shows in the epidermis a more or less regular hyperkeratosis and acanthosis and signs of hydropic degeneration of the basal layer cells, as well as some apoptotic keratinocytes. In the superficial dermis, a dense infiltrate is

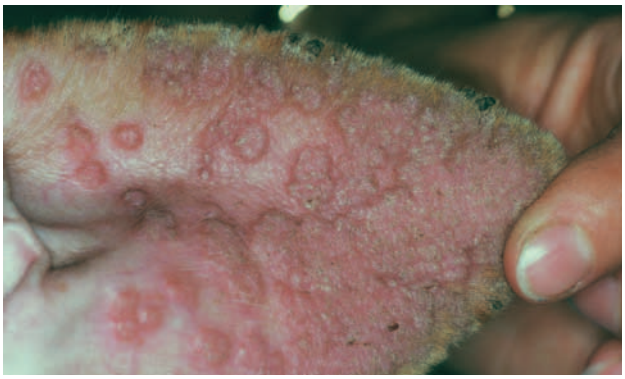

Figure 1:
Lightly scaly and erythematous papules and plaques frequently confluent on the internal aspect of ear pinnae (Case Number 1).

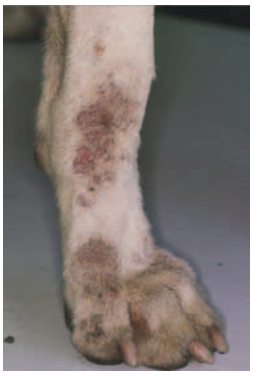

Figure 2:
Erythematous plaques on a forelimb (Case Number 1).

Figure 3:
Multiple localised scaly papules with crusts on the face and ear pinnae (Case Number 2).

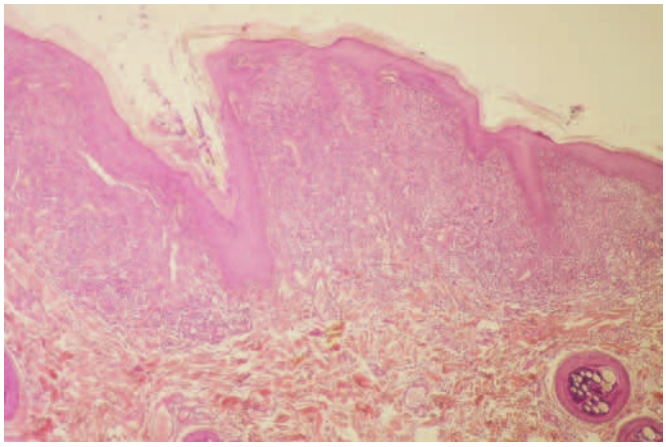

Figure 4:
Histopathological examination of a lesion (from Case Number 2) (HES, x 40): sub-epidermal dense band-like infiltrate

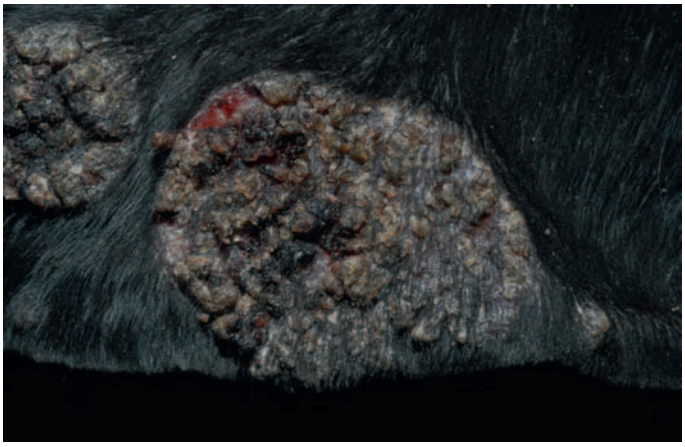

Figure 5:
Close-up of lesions on ear pinnae: plaques covered with a thick crust can be observed (Case Number 3).

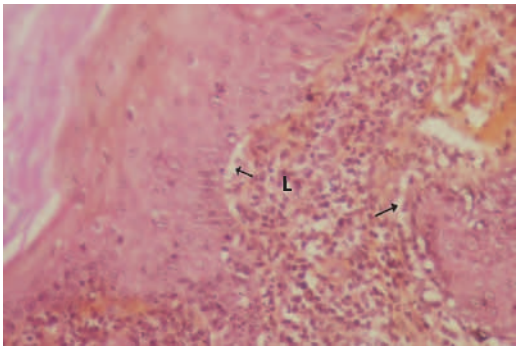

Figure 6:
Histopathological examination of a lesion (from Case Number 3) (HES, x 250): interface dermatitis characterised by a mainly lymphocytic (L) infiltrate associated with an hydropic degeneration of cells of the basal layer of the epidermis (small arrows).

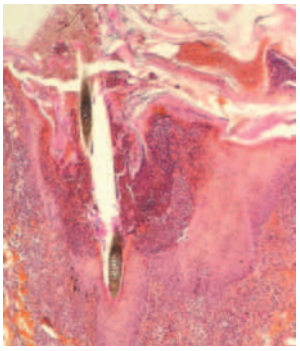

Figure 7:
Histopathological examination of a lesion (from Case Number 3) (HES, x 40) : suppurative folliculitis associated with a dense periannexial infiltrate.

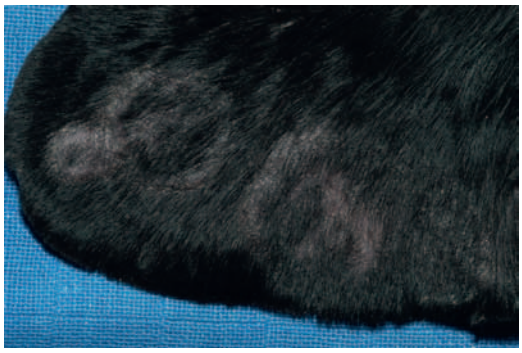

Figure 8:
Close up of the lesion illustrated in figure 5 after 15 days of antibiotic treatment (cefalexin): a marked improvement in the lesions can be seen. Some areas of alopecia remain.

visible, composed mainly of lymphocytes and plasma cells and a marked pigmentary incontinence [5, 6]. This histopathological feature is dominant in our three cases. Modifications in the basal layer with images of apoptosis and hydropic degeneration were observed in two cases (for the first case – in 1985 – we were unable to re-evaluate the histopathological examination). In the affected areas, serocellular crusts with colonies of *Cocci*, sub-corneal pustules and follicular pustules are often visible. It is therefore possible to conclude to a superficial pyoderma, presumably of bacterial origin, associated with a secondary "lichenoid" reaction which accounts for the unusual clinical aspect of the lesions.

There is no specific treatment for lichenoid dermatitis. The evolution can alternate between phases of improvement and worsening. An antibiotic therapy using cefalexin has resulted in an improvement in the lesions in some cases [3,7]. Surgical removal of the lesions has provided a cure in other cases [12].

In our cases, a systemic antibiotic treatment has led to a complete and rapid recovery in 2 – 3 weeks, which is in favour of a bacterial origin.

Conclusion

Lichenoid dermatoses are rare and still poorly understood. A good response to antibiotic treatments, in certain cases, would suggest the involvement of infectious factors in their pathogenesis. They are increasingly considered as a reaction in the skin tissue to various antigenic stimulations [7, 10].

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* Note: A second Edition of this book is now available. Gross TL, Ihrke PJ, Walder EJ *et al.* Skin diseases of the dog and cat: Clinical and Histopathological Diagnosis 2005. Oxford: Blackwell Science.

REPRINT PAPER (CH)

Cardiogenic and non-cardiogenic pulmonary oedema – pathomechanisms and causes

T.M. Glaus[(1)#], *S. Schellenberg*[(2)], *J. Lang*[(3)]

SUMMARY

The development of pulmonary oedema is subdivided into cases of cardiogenic and non-cardiogenic origin. Cardiogenic oedema pathogenically is caused by elevated hydrostatic pressure in the pulmonary capillaries due to left sided congestive heart failure. Non-cardiogenic pulmonary oedema is categorised depending on the underlying pathogenesis in low alveolar pressure, elevated permeability or neurogenic oedema. Some important examples of causes are upper airway obstruction as in laryngeal paralysis or strangulation for low alveolar pressure, leptospirosis and ARDS for elevated permeability, and epilepsy, brain trauma or electrocution for neurogenic oedema. The differentiation between cardiogenic versus non-cardiogenic genesis is not always straightforward, but most relevant, because treatment markedly differs between the two. Of further importance is the identification of the specific underlying cause in non-cardiogenic oedema, not only for therapeutic but particularly for prognostic reasons. Depending on the cause the prognosis ranges from very poor to good chances of complete recovery.

Keywords: alveolar pressure, re-expansion, airway obstruction, ARDS, neurogenic

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Introduction

The physiological movement of fluid through a vascular membrane into the surrounding tissue depends on 3 factors: membrane permeability, oncotic pressure gradient and hydrostatic pressure gradient. An additional factor, lymphatic drainage, counteracts extravascular fluid accumulation. Oedema develops if one of these 4 factors is disturbed to a degree that cannot be compensated. For pulmonary oedema to develop, essentially an increased intravascular hydrostatic pressure or a disturbed vascular permeability is always responsible [1]. For clinical purposes, pulmonary oedema is divided based on pathophysiology into cardiogenic and non-cardiogenic oedema. The exact differentiation and diagnosis is made based on a combination of clinical and radiological findings and considerations.

Whereas in human medicine a vast amount of literature on non-cardiogenic pulmonary oedema is available [e.g. reviews, 2-6], in dogs and cats only a few case reports [7-10] and original articles have been published [11-17]. This article will review the pathophysiological mechanisms, known causes, variable prognosis and briefly, therapy of pulmonary oedema.

Pathogenesis and causes of cardiogenic pulmonary oedema

Cardiogenic pulmonary oedema develops secondary to a rise of hydrostatic pressure in the pulmonary capillaries (normal <12 mmHg). When the rise in pressure is gradual, pressure may exceed 20 mmHg before pulmonary oedema develops, because the capacity of lymphatic drainage can be increased [18]. Left-sided congestive heart failure as a result of an identifiable

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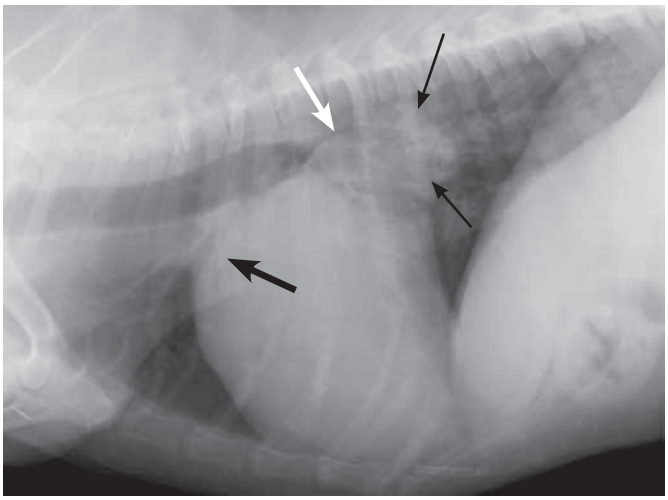


Fig. 1: Radiographs of a 11-year old Dachshund with cough due to advanced degenerative mitral valve disease.
There is radiological evidence of left-sided cardiomegaly (dorsal displacement of trachea) and severe left atrial dilation (small arrows) causing dorsal displacement and compression of the left stem bronchus (white arrow). The pulmonary veins are enlarged (large arrow) and the caudo-dorsal lung field is mildly opaque, to be interpreted as early stage cardiogenic oedema. From a clinical standpoint the diagnosis is plausible if a loud typical murmur of mitral insufficiency is auscultable.

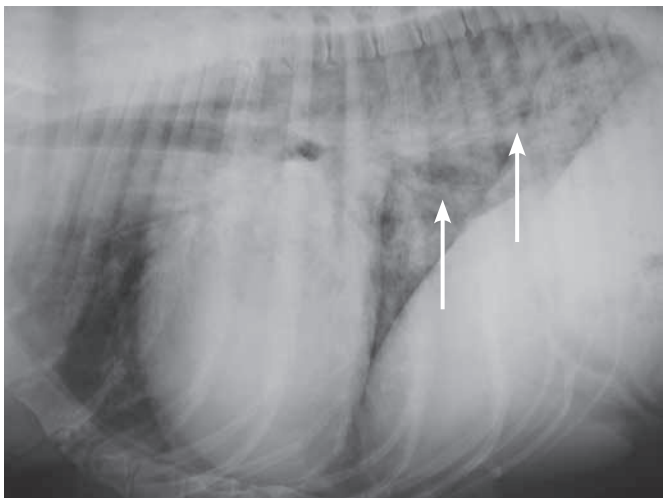
underlying cardiac disease must be present for cardiogenic pulmonary oedema to develop. The most important acquired diseases are advanced degenerative mitral valve disease and dilated cardiomyopathy. The single most important congenital disease is patent ductus arteriosus. Rarely pulmonary oedema may also develop in cases of ventricular septal defect (VSD) and subaortic stenosis (SAS). Most VSDs are restrictive (resistive), and only rarely lead to congestive heart failure [19]. In severe

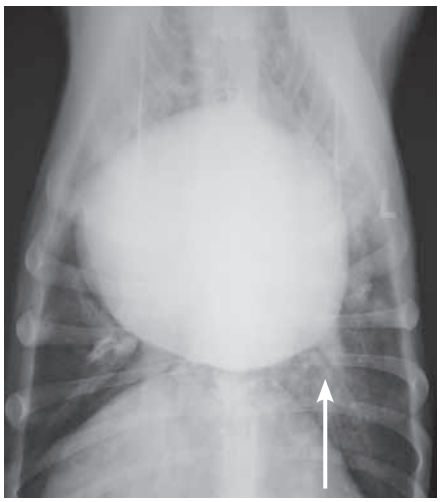
Causes according to pathophysiology *	Time interval
Low alveolar pressure, postobstructive oedema	**0-2 hours**
Laryngospasm, e.g. post extubation	
Laryngeal paralysis	
Strangulation	
Tracheal collapse	
Tracheoscopy	
Low alveolar pressure, re-expansion oedema	**0-24 hours**
Post-expansion oedema after thoracocentesis and fast removal of pleural effusion or pneumothorax	
Post surgical correction of (chronic) diaphragmatic hernia	
Post pneumonectomy	
Neurogenic	**Minutes to hours**
Electrocution	
Seizure, during postictal phase	
Skull / brain trauma,	
Cerebral haemorrhage	
Meningoencephalitis	
Hunting dogs	
Cerebral oedema secondary to hyponatraemia in endurance athletes	
Abnormal permeability / vasculitis	**Hours to days**
ARDS	
Leptospirosis	
Others	**Hours to days**
High altitude pulmonary oedema (HAPE)	

*These causes should be considered in small animals, even if not all of these have been published in the scientific literature.

Table 1: Causes of non-cardiogenic pulmonary oedema and time interval from insult to its development

Fig. 2: Radiographs of a 6-year old male Doberman with coughing and gagging.
The caudodorsal lung areas show marked opacification (arrows); there is severe left atrial dilation and cardiomegaly, particularly prominent on the DV- projection. Cardiac changes and localisation of increased pulmonary densities make cardiogenic oedema probable. The echocardiographically documented underlying disease of dilated cardiomyopathy provides a plausible cause of cardiogenic oedema.





SAS congestive failure is an equally rare incident; affected dogs may die suddenly [20].
Radiologically, congestion is manifested by dilated pulmonary veins and cardiogenic oedema that initially is characterised by an increased interstitial lung pattern progressing to an alveolar pattern. Typically, the oedema starts in the perihilar area progressing to the caudo-dorsal lung fields (Fig. 1 & 2). In addition, there should generally be clear radiological signs of left sided cardiac disease with distinct left atrial dilation as well as clear clinical signs of an underlying cardiac disease that concurs with the radiograph findings [21].

Pathogenesis and causes of non-cardiogenic pulmonary oedema

Various mechanisms are responsible for non-cardiogenic oedema to develop; i.e. low alveolar pressure, increased vascular permeability, increased hydrostatic pressure and a combination of these. The various causes, according to pathophysiology are summarized in Table 1. The risk of developing non-cardiogenic pulmonary oedema seems to be higher in younger animals [16]. Low alveolar pressure develops after fast removal of pleural effusion, pneumothorax, or lung lobe torsion, called re-expansion oedema. Mortality of this rare complication in humans is described as 20% [22]. In veterinary medicine, 2 feline cases have been described in which both died [8,9]. Low alveolar pressure also results from upper airway obstruction, called postobstructive oedema; e.g. in brachycephalic syndrome, laryngeal paralysis, tracheal collapse, strangulation (Fig. 3), and iatrogenic causes during intubation and bronchoscopy (Fig. 4) [3,14,15,23]. The non-cardiogenic oedema in some hunting dogs may partially be caused by obstruction, specifically laryngeal oedema associated with prolonged and constant barking. More likely in these dogs it is neurogenic oedema associated with a very high catecholamine level (see below) [17]. Postobstructive pulmonary oedema in dogs and cats is probably much more common than diagnosed. Many cases may be misdiagnosed as cardiogenic oedema, because dyspnoea and oedema are associated with exercise or a stress situation, e.g. in laryngeal paralysis or oedema associated with anaesthesia, or because affected animals may have two concomitant diseases, e.g. tracheal collapse and degenerative mitral valve disease [24].
A further important cause of non-cardiogenic oedema is neurogenic oedema. Pathophysiologically, excessive sympatho-adrenergic activation in the medulla oblongata plays the central role. This results in pulmonary venous constriction shifting blood from the systemic to the pulmonic circulation, increase in pulmonary hydrostatic pressure and finally oedema [25]. Causes described in dogs are brain trauma, epileptic seizures and electrocution [11,13,15]. Pulmonary oedema occurs in hunting dogs during or after the hunt and is thought to be a neurogenic oedema caused by excessive catecholamine secretion [17]. A

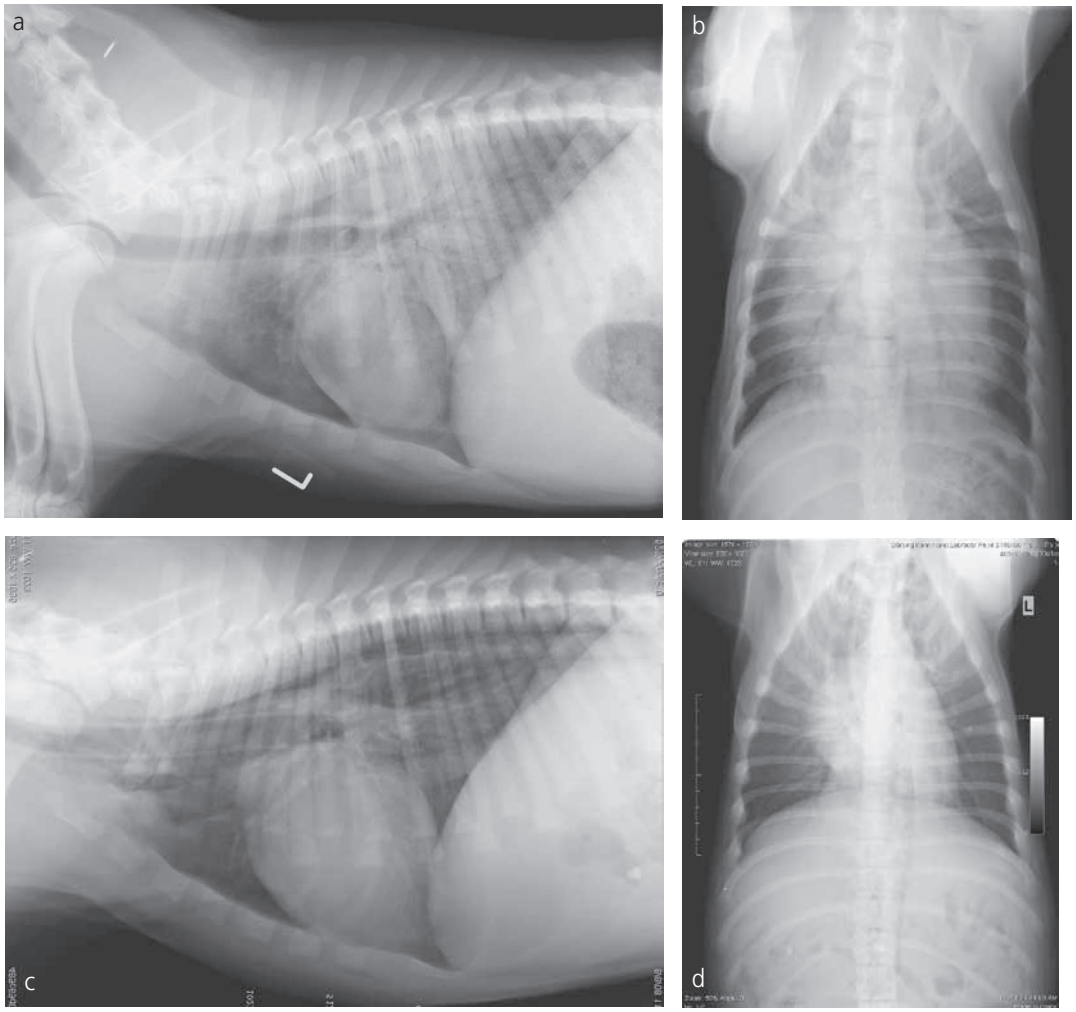


Fig. 3: Radiographs of a 7-month old Labrador with severe dyspnoea after strangulation. The dog was tied to a leash and unobserved for a short moment, and subsequently developed severe dyspnoea. The radiological correlate is a diffuse alveolar pulmonary opacification, most prominent in the caudo-dorsal lung field (3a & b).The heart appears hypovolaemic. Treatment with artificial respiration (PEEP) over 36 hours resulted in gradual stabilisation of the critical state. Radiographs obtained 48 hours after admission show marked regression of the oedema; however, as a consequence of PEEP an extensive pneumomediastinum can be recognized (3c & d).

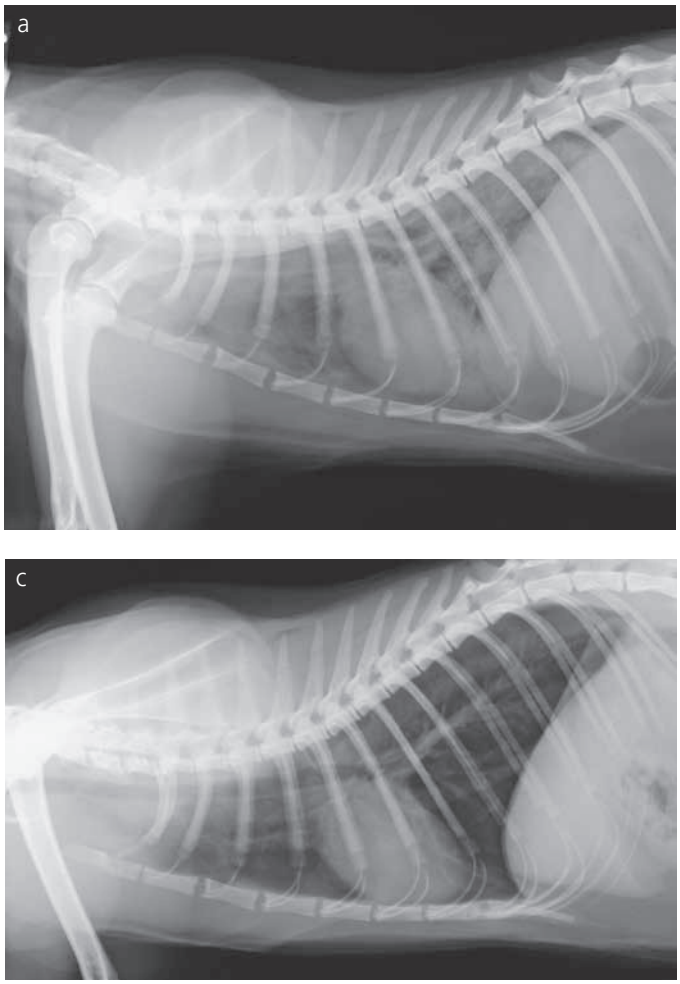


Fig. 4: Radiographs of a 3-year old cat with non-cardiogenic oedema occurring during bronchoscopy. During a bronchoscopic exam, a dramatic drop in oxygen saturation was observed on the pulse oximeter, and loud crackles were auscultable. The radiological correlate was a severe generalized alveolar pulmonary opacity, pronounced in the caudo-dorsal lung fields (4a & b). An echocardiographically normal heart excluded a cardiogenic cause. After 48 hours of absolute rest in an oxygen cage there was nearly complete resolution of the pulmonary changes (4c & d). The suspected pathogenesis was airway obstruction by the endoscope.

particular pathogenesis of neurogenic pulmonary oedema is the one in endurance athletes caused by cerebral oedema elicited by hyponatraemia [6]. Prognosis for complete recovery in neurogenic oedema is good with adequate supportive care.

Acute (formerly adult) respiratory distress syndrome, ARDS [2] is an important factor in the development of non-cardiogenic oedema. The underlying cause is severe and diffuse damage of the lung parenchyma resulting in endothelial and epithelial disturbance of permeability and exit of protein rich fluid. Complicating factors are coagulation disturbances, perfusion disturbances and loss of surfactant. ARDS may be a complication of primary lung damage, e.g. after inhalation of toxic gas (smoke intoxication), aspiration of gastric content, inhalation of hyperbaric oxygen (oxygen intoxication) or pneumonia. ARDS may also be a complication of a severe systemic disease like sepsis, extensive burns and acute pancreatitis. The prognosis even with intensive supportive care is poor [16]. Pulmonary oedema similar to ARDS can be elicited by multiple blood transfusions; even though this complication is life threatening, the prognosis is much better than in ARDS [2,5]. A further important cause of protein-rich pulmonary oedema is vasculitis and disturbed vascular permeability well recognised in dogs with leptospirosis [26]. This may be complicated by prognostically important pulmonary haemorrhages that may not be differentiated radiologically from oedema [27].

Finally, high altitude above around 3000 m may cause non-cardiogenic pulmonary oedema in susceptible individuals [28].

Pulmonary oedema and low oncotic pressure

Oncotic pressure, primarily dependent on plasma albumin concentration, is one of the important factors in keeping fluid inside the vasculature but it does not play an important role in the lungs. The pulmonary interstitial space normally has a higher albumin concentration than other interstitial tissue and a small oncotic gradient, because the permeability of pulmonary capillaries is higher than in other capillaries. When plasma albumin drops, the interstitial albumin concentration drops as well, therefore not markedly affecting the oncotic gradient. Thus, it is unusual to find pulmonary oedema when hypoalbuminaemia is the only abnormality [1].

Therapeutic principles for treating pulmonary oedema

In cardiogenic pulmonary oedema the central therapeutic focus is to decrease preload by aggressive diuresis using loop diuretics. In contrast, the various mechanisms of non-cardiogenic oedema are not affected by diuresis. Furthermore, in some diseases, fluid therapy is indicated rather than diuresis to supportively treat the underlying disease, e.g. in sepsis, pancreatitis and leptospirosis. However, in these cases, infusion therapy must be defensive/cautious. The primary supportive measure is optimised oxygenation. Depending on the cause and severity

of the oedema, keeping an animal quiet in an oxygen-rich environment may suffice, or artificial respiration using positive end exspiratory pressure (PEEP) may be needed [4]. The use of glucocorticoids is controversial. In a recent human study, low dose and early application of methylprednisolone had a positive effect on the course in ARDS [29]. Furthermore, extrapolated from human medicine, steroids seem useful in the pulmonary oedema in leptospirosis [30].

In summary, cardiogenic and non-cardiogenic causes may lead to the development of pulmonary oedema. The exact identification of the underlying cause is of paramount importance for therapy and prognosis. More and more so-called hopeless cases may be cured with progressive specialisation in intensive care medicine and with the dedication of veterinarians and animal owners allowing time consuming and costly treatments.

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How to create responsive clients

Caroline Jevring-Back,

Published by Saunders Elsevier, (http://intl.elsevierhealth.com.vet) (April 2010) E-Book Further details: http://saunderssolutions4vets.com/ ISBN-9780702040542 € 42 99 £ 35

How to create responsive clients is an "online" based educational programme for vets and practice managers who wish to learn more about client communication skills. This programme can also easily be used by nurses and receptionists. The format of this "e-book" is quite interesting as it mixes text, images, animations and sound. It reminds me very much some of the CD Roms and DVDs that were proposed in the 90s when LifeLearn wanted to launch their "Veterinary Staff Training Series".

The interactive component is clear, pleasant, and makes the learning experience educational and fun. The content is "scientifically sound" and of a good standard. Vets will acquire a solid basic understanding of client education features, including client compliance (a popular topic in the last few years). The author insists on the central role played by the client, which is crucial. Clients are indeed the "life-blood" of our business and are NOT "an incidental encounter vets have to (unfortunately) experience a few times through their working day"

The programme nicely mixes theory and case studies and makes the application of the lesson immediately relevant. It reinforces the impact of the messages. Examples are mostly interesting and pertinent. Some examples and quite "extreme" and could unfortunately make readers think they are "way out", thus losing their credibility as they listen to some poor answers and behaviour. However, one should not be put off by this initial impression, as things get better. It is probably a good learning experience for most of us to see and listen to "the very bad" and then to "the excellent" as the difference is striking and the point is well made.

Assessments are also inserted at each step of the module, helping the reader "check" his or her learning curve and fully understand the course. The narrative component is excellent and professionally produced: the speech is clear and well paced. The "post-its" that are placed on the screen are a good idea and an effective way to emphasize some key points throughout the segment. When the wrong answer is given, a correct answer is then provided and explained in detail. For case study N°3 it was NOT striking to me that that dog was overweight (but maybe it is because I own a fat Labrador!). Still, I would have picked an obviously obese example in such case.

Conclusion and Summary

How to create responsive clients is an interesting and good programme in many respects. The module will certainly contribute effectively by helping staff to better use open and closed questions and also understand what compliance is all about. Readers will learn to adopt "active listening techniques" as well as "checking" with clients to make sure they have captured your message. I recommend this excellent basic programme to introduce your staff to client communication skills.

Philippe Moreau, DVM, MS, DECVIM, DECVN (F)

Textbook of Veterinary Internal Medicine Expert Consult, 7th Edition

Edited by Stephen J. Ettinger, DVM, DACVIM and Edward C. Feldman, DVM, DACVIM

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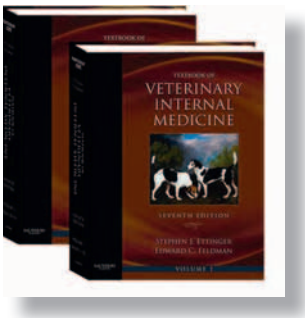

When I received and opened this edition I was pleasantly surprised by the colourful appearance, making manoeuvring through this book more exciting and fun then in the earlier editions.

In the introduction the reader gets as usual the list of outstanding contributors, most of them from the USA and Canada, but also quite a lot from Europe and Australia.

The first section is somewhat new and contains the latest information on genomics. After this comes the second more well known section containing some really good illustrated algorithms and up to date differential diagnostic lists which are very practical when working up a patient's problem list. Leading on from these two chapters there is an extremely well documented section on different techniques used in the different fields of internal medicine. Following these introductory sections the reader will find chapters focusing on specific disease entities, all well updated.

Those used to reading this textbook will be surprised by the many changes compared with the first six editions. Some changes may surprise readers unable to find certain information in its usual place- for example the section on haematology and immunology which is now in the first book.

I agree with the Editors, it was really good to remove some older subject matter making this edition a really good textbook keeping up with the explosive changes we meet every day in internal medicine.

The layout of this edition is made extremely user friendly through the use of colour, the enormous amount of very practical algorithms, tables and boxes, and the wide range of clear and relevant photographs.

If I had to be really picky, I have some issues with some aspects of the headings, especially in the second volume. They can be somewhat confusing: subtitles are sometimes larger than main headings (e.g. diagnosis, treatment). I personally prefer the main headings to be larger to have a better overview of the plain text.

As the editors point out, this seventh edition has become quite "electronic" making this textbook an ideal teaching resource. I really wish this had been available when I was studying!

References have been omitted in an attempt to be "green" (i.e., to save trees by not wasting paper). I understand the editors view completely although I personally like to have the references in the book.

Thus there is much in this edition making it not only extremely valuable for vets with a special interest in internal medicine but also for anyone in general practice and for veterinary students learning their way in internal medicine.

A must-have book with an enormous amount of recent information put together by a lot of well known contributors, in an extremely pleasant way to use and read.

Dr Greet Junius (B)

BSAVA Manual of Canine and Feline Reproduction and Neonatology, 2nd edition

Edited by Gary England and Angelika von Heimendahl

Published by BSAVA 2010 Distributed by Wiley-Blackwell 240 pages Paperback
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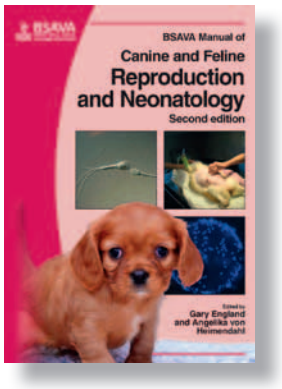
BSAVA members should order from www.bsava.com for member prices



Well known authors from France, Italy, Norway, Spain, Sweden, Turkey, the UK and the USA have contributed to this enlarged 2nd edition. It comprehensively covers the following topics.

- endocrinology and physiology of female and male reproduction,
- prevention of breeding in both the female and male,
- the clinical approach to the infertile bitch, queen and infertile male,
- artificial insemination in dogs,
- pregnancy diagnosis, normal and abnormal pregnancy and parturition in the bitch and queen,
- the clinical approach to unwanted mating and pregnancy termination,
- management and critical care of the neonate,
- the clinical approach to neonatal conditions.
- The last chapter covers the clinical approach to common conditions such as mammary gland disease, conditions of the non-pregnant and neutered bitch and queen, to conditions of the male and the clinical relevance of biotechnology advances.

This book is filled with many pictures and schematic diagrams and gives the reader a very good overview and a wealth of information covering all aspects of the approach and treatment of reproductive disorders of dogs and cats. It can be warmly recommended to veterinarians, veterinary nurses and students.

Dr. Hans-Klaus Dreier, (A)

Calendar of main European National Meetings and other continuing education opportunities

WSAVA & FECAVA Congresses (Red)
Principal annual meetings (blue)

A list of the addresses and telephone numbers of the Secretariat or person holding information is attached.

2011				
2 October	LSAPS	Riga	Practical issues in nephrology and urology	Russian
7 October	BSAVA	Dunkeld	Practical issues in diagnosis and treatment of canine and feline kidney diseases	English
8-9 October	VÖK	Kufstein	Neurology, Ophthalmology, Gastroenterology Seminar	German
8-9 October	CSAVA	Hradec Kralove	19th Annual Congress SA Endocrinology	Czech, English
8-9 October	AIVPA	Bentivoglio (BO)	National Congress INNOVATIONS IN VETERINARY MEDICINE 50 YEARS OF AIVPA: what has changed in the veterinary clinic?	Italian, English
10 October	BSAVA	Southampton	Practical issues in diagnosis and treatment of canine and feline kidney diseases	English
12 October	BSAVA	Cardiff	Practical issues in diagnosis and treatment of canine and feline kidney diseases	English
13 October	BSAVA	Gatwick	First aid in ophthalmology - A first line approach to ocular emergencies	English
15-16 October	HVMS	Athens	Reptile medicine and tick-borne diseases of the dog and cat	English, Greek
15-16 October	VÖK	Ried/Traunkreis	Urogenital tract Surgery Seminar	German
15-16 October	SkSAVA	Nitra	Annual congress - Nova Veterinaria 2011	English, Czech, Slovak
19 October	BSAVA	Gatwick	That's not a hamster, small furries with a difference	English
19 October	VICAS	Dublin	CE Surgery Module 1	English
20 October	BSAVA	Swindon	People! Can't live with them, can't live without them - A customer servcie workshop	English
20-22 October	ESVOT	Lyon(F)	ESVOT Courses 2011	English
21-23 October	SASAP	Belgrade	Annual Symposium / Neurology, Surgery, Anaesthesia, Orthopedics, Imaging	English/Serbian
22 October	BSAVA	St Helens	Advanced Abdominal Ultrasound - scanning the hidden depths	English
22-23 October	FAVP	Helsinki	Anaesthesia Seminar	Finnish
24-28 October	ESAVS	Madrid (E)	Cardiology IV - Advanced Echocardiography	English
25 October	BSAVA	Gloucester	CE A practical guide to oncology: No more lumps in your throat: Part II	English
26 October	VICAS	Sligo	CE Emergency Medicine	English
27 October	BSAVA	Manchester	CE Haematology	English
5-6 November	VÖK	Steyr	Ultrasound - Basic-Seminar	German
6 November	LSAPS	Riga	WSAVA CE Dermatology	English
9 November	VICAS	Limerick	CE Emergency Medicine	English
9 November	BSAVA	Beaconsfield	The Essentials of Rabbit Medicine in One Day!	English
10-11November	SSAVA	Uppsala	Haematology – haemostasis and inflammation	Swedish ,English TBC
11 November	BSAVA	Kegworth	The Essentials of Rabbit Medicine in One Day!	English
12-13 November	VÖK	Wels	Neurology Seminar & Workshop	German
14 November	BSAVA	Wetherby	The Essentials of Rabbit Medicine in One Day!	English
15 November	BSAVA	Kettering	The challenges of old age: optimizing veterinary care of the geriatric cat	English
14-25 November	ESAVS	Utrecht (NL)	Internal Medicine I	English
16 November	BSAVA	Chatham	The Essentials of Rabbit Medicine in One Day!	English
17 November	BSAVA	Gatwick	A stitch in time - all you need to know about small animal ophthalmic surgery	English
19 November	VÖK	Krems	X-Ray-Seminar	German
22 November	BSAVA	Gloucester	Medical neurology of the dog and cat: how to make sense of the wobbly, weak or collapsing patient	English
23 November	VICAS	Sligo	CE Surgery Module 1	English
24 November	BSAVA	Manchester	CE Clinical Nutrition: Let food be your first medicine	English
24 November	ISFM	London	London Vet Show Seminar 'Developing a cat friendly clinic and business'	English
26 November	VÖK/VUW	Vienna	Otitis-Workshop	German
29 November	BSAVA	Gloucester	Practical haematology: how the microscope can help you make a diagnosis	English
30 Nov - 2 Dec	FAVP/SELL	Helsinki	Annual Congress	Finnish, English
1 December	BSAVA	Gatwick	Feline stress: the basis of elimination, spaying and inter-cat conflict problems	English
2 - 4 December	AFVAC	Lyon	Annual Congress	French
3-4 December	SkSAVA	Smolenice	Small animal stomatology	English, Czech, Slovak

6 December	VICAS	Dublin	CE Ultrasound - Intermediate/Development Level	English
6 December	BSAVA	Kettering	Old dogs and new tricks: Canine Geriatrics	English
8 December	BSAVA North East Region	Wetherby	Haematology	English
8 December	BSAVA	Gatwick	The eyes have it - ocular manifestations of systemic disease	English
9-14 December	ESAVS	Davos (CH)	Excellence in Veterinary Therapy: Internal Medicine & Emergency Care	English
2012				
27-29 January	VICAS	Kilkenny	Annual Winter Conference	English
29 February-01 March	ISFM	Hong Kong	International Feline Symposia 'Feline Diagnostic - Clinical pathology and diagnostic imaging'	English
24-25 March	AVEPA	Cordoba	Veterinary Specialities Congress	Spanish
5-8 April	HVMS		Annual Congress	Greek, English
12-15 April	FECAVA / WSAVA /BSAVA	Birmingham	FECAVA European and WSAVA Congress hosted by BSAVA	English and others
26-28 April	NACAM	Amsterdam	Voorjaarsdagen	Dutch, English
24-26 May	ECVD	Lisbon (P)	21st European Congress of Veterinary Dentistry	English
8-9 June	ESVD	Mallorca, Spain	Workshop Feline dermatology	English
13-16 June	SVK/ASMPA with Swiss Veterinary Association	Interlaken	Annual Congress	German, French, English in case of English lectures
13-17 June	ISFM (H)	Budapest	Annual European Feline Congress	English
24-28 July	ECVD ESVD WAVD	Vancouver, Canada	7th World Congress of Veterinary Dermatology	English Others???
26-29 July	ISCFR-EVSSAR Symposium	Whistler, Canada	International Symposium on canine and feline reproduction	English
12-15 September	ESVOT	Bologna (I)	Annual ESVOT Congress	English
14-15 September	ESVN	???	Annual Congress	English
17-21 September	EVSSAR	Milan(I)	3rd Small Animal Reproduction Course	Italian
19-20 September	ESVD	Valencia(E)	26thAnnual Congress	English
21-23 September	VÖK	Salzburg	Annual Congress	???
18-21 October	AVEPA	Barcelona	47th AVEPA- 6th SEVC Annual congress	Spanish, English, Polish, Italian, Russian, Portuguese
30 Nov-2nd Dec	AFVAC	Paris - La Defense	Annual Congress	French
27-29 December	VICAS	Kilkenny	Annual Winter Conference	English

Advance notice				
2013	Voorjaarsdagen 25-27 April			
4-8 June	SVK/ASMPA with Swiss Veterinary Association	Berne	Annual Congress	German, French, English in case of English lectures

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(Full Association names are given at the front of the Journal)

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