Handout for owners regarding the clinical study on canine pyometra, and consent for participation

The Veterinary Teaching Hospital (VTH) of the University of Helsinki is conducting a study on the occurrence of surgical site infections and urinary tract infections in dogs diagnosed with uterine infection (pyometra) in need of surgical treatment. Approximately 200 dogs are needed for the study, and the study will be conducted during 2019-2022. Dogs, whose owner has given a written consent, will be accepted in the study.

Your dog may be suited for the study. We ask you to familiarize yourself with this handout carefully. If you agree with the study, please sign the two consent forms at the end of this handout. One of the forms will be given to you, and one of them will remain at the VTH.

Why is the study being conducted?

Pyometra is a common disease of female dogs, in which pus accumulates in the uterus. Left untreated, the disease is life threatening. The primary treatment is surgery, in which the infected uterus and ovaries are removed. The patients are given antibiotics during the surgery and often also postoperatively. The postoperative antibiotics are needed, if the infection has spread to the abdominal cavity (peritonitis). On the other hand, it is currently unknown if the patients without peritonitis benefit from antibiotic treatment at all.

Antibiotic treatment should be reserved for diseases in which their efficacy is proven. Bacterial resistance to antibiotics has increased rapidly. By avoiding unnecessary use of antibiotics the development of resistance can be controlled, the risk for adverse effects lowered, and the costs for the dogs' owners reduced.

Aims of the study

The study will clarify the occurrence of post-operative infections, the prevalence of urinary tract infections in patients with pyometra and the characteristics of the bacteria causing urinary tract and uterine infections (part A). In addition, the study will compare the occurrence of post-operative infections between patients receiving antibiotic treatment or placebo (part B).

What kind of dogs are suited for the study?

All dogs with pyometra being surgically treated are suited for **part A** of the study. From part A the dogs with an intact uterus and no illness or medication increasing the risk for infection are chosen for **part B**. The suitability for part B will be defined by owner survey, patient's clinical examination and blood samples. The suitability for part B is confirmed during surgery.

Participation in part B is possible, if the dog

- has an intact uterus and there are no signs of peritonitis
- is in good or moderate general condition
- weighs 3-93 kg and its breed is other than Dobermann Pinscher
- has no allergies or hypersensitivities to sulfa drugs
- has no primary disease that increases the risk for infection (such as diabetes mellitus, adrenal dysfunction, chronic severe liver or kidney disease, malignant neoplasia, urinary bladder tumor, immune deficiency)
- is not being treated with an immunosuppressant (such as prednisone/prednisolone >1 mg/kg/d, cyclosporine >5 mg/kg/d, azathioprine ≥2 mg/kg/d or cytostatic agent)

Risks involved with the study

Risks for patients with pyometra independent of the study: Approximately 6% (6/100) of patients develops a post-operative infection regardless of antibiotic treatment, most typically a mild surgical wound infection. Very rarely the animal develops a deep wound infection or peritoneal/uterine stump infection. Especially a peritoneal/uterine stump infection often requires surgery and hospitalization. A severe infection is more likely, if the uterus has ruptured. These patients are severely ill when presenting for surgery. Deaths associated with pyometra surgeries are extremely rare and are almost always associated with the severity of the patient's condition or primary illness. A small risk of anesthetic complications is also always associated with surgery. Severely ill patients will not be accepted for part B of the study, but they may participate in part A.

Risks potentially associated with the study: Half of the patients participating in part B will receive antibiotics post-operatively; the other half will receive a placebo. The assumption of the researchers is that the prevalence of infections will be the same in the group treated with antibiotics as the placebo group. The dogs suffering from a urinary tract infection in addition to pyometra who receive a placebo may have a slightly increased risk to develop a urinary tract infection within two weeks from the surgery, compared to the dogs receiving antibiotics.

Risks associated with antibiotics: According to national recommendations, all dogs undergoing pyometra surgery are primarily treated with sulfonamide-trimethoprim, if there are no contraindications (such as allergy or hypersensitivity). Other antibiotics may have to be used because of antibiotic resistance or the severity of the infection. Typical adverse effects of antibiotics are gastrointestinal disturbances (lack of appetite, vomiting, diarrhea) and hypersensitivity reactions. Rare adverse effects typical to sulfa drugs are polyarthritis and dry eye. Possible adverse effects include fever, a frequent need to urinate and development of urinary crystals. Hepatitis possibly associated with hypersensitivity to sulfa drugs has been reported very rarely. The emergence of adverse effects demanding cessation of treatment within the 5 day treatment period is very unlikely. If such effects should appear in dogs participating in part B, treatment with the study preparation will be discontinued if necessary, and treatment will be continued with another drug. In dogs participating only in part A, medications will be discontinued or changed as appropriate.

If the owner notices signs of surgical site infection or urinary tract infection within the follow-up period (up to 30 days or 15 days after surgery, respectively), they must immediately contact the VTH for assessment on the need of treatment. Infections are diagnosed and treated as is customary.

Carrying out the study

The owner of the animal fills out a form collecting preliminary information. A clinical examination will be conducted on the dog, and a blood sample will be taken to determine the general condition and suitability for surgery. A sample of urine will be taken by bladder puncture during the surgery (under general anesthesia) from all patients. The procedure is common and no additional pain or discomfort will be caused to the patient. A sample for bacterial culturing will be taken from the uterus after its removal. The dogs participating in only part A will receive standard prescriptions.

If the dog is also suitable for part B, it will be randomized after the surgery to either antibiotics (sulfadiazine-trimethoprim) or placebo group. The owner will receive a study preparation, containing one or the other, which will be dosed according to the package instructions for 5 days. The researchers or the dog's owner do not know which product the animal is getting, in other words they are blinded. In a state of emergency the blinding can be broken.

Observation at home: The owner will monitor the dog's general well-being as instructed, as well as possible signs of urinary tract or surgical site infections, and contact the VTH if the dog's condition worsens or afore-mentioned signs appear.

Urinary tract infections: The occurrence of post-operative urinary tract infections are monitored for up to 15 days after surgery in patients whose sample of urine obtained during surgery has bacterial growth.

Surgical site infections: The occurrence of surgical site infections are monitored for up to 30 days after surgery in all patients participating in the study.

Check-ups: All patients will have a **check-up 12 (+/- 3) days after surgery**, during which the owner is interviewed and the dog's surgical wound is examined. If the wound has been closed with non-absorbable sutures, the sutures will be removed. A sample of urine will be taken by bladder puncture from the dogs that had bacterial growth in their urine sampled during the surgery AND have not developed signs of urinary tract infection. The owners of the dogs participating in part B are asked to return the study preparation. **The final interview will be conducted 30 (+/- 4) days after the surgery by telephone or electronically.** The interview will survey the animal's health, recovery and healing of the surgical wound.

Costs

The following are free of charge for the owner:

- Measurement of the inflammatory marker CRP from the blood sample before surgery
- Follow-up appointment
- Urinary sampling and examination in the following cases:
    - Sample taken from all dogs during surgery
    - Sample taken to assess need for treatment in patients that had bacterial growth in the sample taken during surgery AND that develop signs of urinary tract infection within 15 days from the surgery.
    - One control sample after treatment of the urinary tract infection
- Postoperative treatment with the study preparation (placebo or antibiotics for 5 days) in dogs participating in part B
- Assessment of surgical site infection (up to 30 days from the surgery) and need for treatment, as well as the costs associated with the necessary appointments, procedures and cultures at the VTH in dogs participating in part B

The owner is responsible for the following costs:

- Usual examinations, samples, procedures, materials and care associated with diagnosing and treating pyometra
- Medications and materials necessary for post-operative care
- Costs associated with the patient's primary or other illness
- Costs associated with transporting the patient
- Costs from treatment outside the VTH
- Post-operative antibiotic treatment in dogs participating only in part A
- Medications and materials needed for treatment of surgical site infection
- All laboratory, appointment, procedure and treatment costs are billed according to normal convention after the owner opts out of the study

Right to discontinue the study

The owner of the animal has the right to opt out of the study at any point without the need to announce the reason. Opting out will not affect the treatment received or the patient relationship. All laboratory examinations, appointments, procedures and treatments are billed normally after discontinuation.

The will to discontinue in the study can be notified to the researchers verbally or in writing. The research group wishes for the reason to be announced, because it may affect the general reliability or continuation of the study. The information collected before opting out will be used as part of the research data, because it is necessary for the reliability and safety assessment of the study.

Permits for the study

The Viikki Campus Research Ethics Committee has stated that the study follows the principles of research ethics, and the study is ethically acceptable (5/2018). Prior notice has been given to Finnish Medicines Agency Fimea according to §88a of the Finnish Medicines Act (395/1987). The research and procedures will be conducted responsibly and ethically. No permit is needed from the Animal Experiment Board, because no additional procedures will be conducted on the animals, than what is necessary for diagnosing the disease.

Confidentiality and privacy protection

The patient records are logged in the VTH's electronic record-keeping software, and partially on paper forms stored in a locked area. We may ask for more information regarding your dog from the veterinarian previously in charge of the care, if they are necessary for the treatment of pyometra or this study. Only privileged individuals with confidentiality agreements handle the information. Saving and processing the records in the analysis software is anonymous, and the animals are identified only by a code. Personal information will not be recorded in the software. Information will be processed and the records kept according to current legislature, and the study will be conducted responsibly. No information will be handed to a third party.

Contact information

The responsible researchers for this study are Professor Outi Vapaavuori and Docent Merja Rantala, one of whom can be contacted during the entire study period. If you have any questions about the study, you may contact members of the research group on weekdays between 8 AM and 4 PM. The e-mail addresses are formatted firstname.lastname@helsinki.fi.

- Anna Ylhäinen, DVM, PhD student; 02941 57216
- Katariina Thomson, DVM, PhD
- Sari Mölsä, DVM, PhD, DiplECVS; 02941 57296
- Outi Vapaavuori, Professor of Small Animal Surgery, DiplECVS; 02941 57287
- Merja Rantala, Docent, Specialist in Infectious Animal Diseases

Outside the regular working hours in urgent questions regarding the animal's condition or care, please contact the VTH's emergency service. The emergency service operates weekdays from 4 PM to 8 AM, as well as on weekends and mid-week holidays. Telephone number for the emergency service is 0600-974 11. Cost of the phone call is €2.03/min + local network charge. Queueing is subject to a charge.

CONSENT OF THE OWNER OF THE DOG FOR PARTICIPATING IN THE PYOMETRA STUDY – OWNER'S COPY

I have been asked for permission to let my dog to participate in the study for canine pyometra. I have familiarized myself with the handout above, gotten enough information on the study as well as sufficient answers for my questions. I understand that participation is voluntary.

I know I have the right to discontinue my dog's participation in the study at any point, without having to inform the reason for discontinuation. Discontinuation will not affect the possible care for my dog or my relationship with the Veterinary Teaching Hospital. I am aware that any information gathered prior to discontinuation may be used as a part of the study.

I am responsible for all the charges caused by my dog's illness, except for the ones mentioned in this handout to be free of charge. I am aware that the general conditions for patient care at the Veterinary Teaching Hospital are applied to research patients as well.

I commit to coming to a follow-up appointment 12 (+/- 3) days after the surgery, and participating in an interview conducted by telephone or electronically 30 (+/- 4) days after the surgery. If my dog is accepted to part B of the study, I commit to dosing the study preparation according to the instructions and returning the leftover preparation in its original packaging during the follow-up appointment.

I will monitor my dog according to the instructions and contact the Veterinary Teaching Hospital if my dog has any signs of urinary tract or surgical site infection (instructions given at discharge) or if my dog's condition gives reason to worry. I agree that the veterinarian previously in charge for treating my dog may give out information regarding my dog, if the information is necessary for the study.

I hereby confirm with my signature that my dog may participate in the study described in this handout:

_____	_____	_____
Name of the dog	Birth date or age	Identification (patient number/microchip/tattoo)

_____ _____

Date Signature of the owner of the dog

_____

Name in block letters

NB! The owner must sign and date the form in one's own hand. A representative of the hospital may fill out the animal's information.

Consent received (representative of the hospital)

_____ _____

Date Signature of the receiver of the consent

_____

Name in block letters

Two copies of this form have been made, one of which forms will be given to the owner, and one of them will remain at the VTH.

OWNER'S COPY

CONSENT OF THE OWNER OF THE DOG FOR PARTICIPATING IN THE PYOMETRA STUDY – VTH'S COPY

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_____	_____	_____
Name of the dog	Birth date or age	Identification (patient number/microchip/tattoo)

_____ _____

Date Signature of the owner of the dog

_____

Name in block letters

NB! The owner must sign and date the form in one's own hand. A representative of the hospital may fill out the animal's information.

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Date Signature of the receiver of the consent

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Name in block letters

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VTH'S COPY