



Antimicrobials administration, treatment outcome and bacterial susceptibility in canine pyometra cases subjected to ovariohysterectomy

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ABSTRACT

Pyometra is a bacterial uterine infection that frequently affects intact older bitches. The treatment of choice is ovariohysterectomy, often associated with perioperative antimicrobial therapy. The aim of this retrospective investigation was to evaluate the antibiotic choice at different administration times (pre-surgery, at surgery/during hospitalization, and post-surgery) against complications and outcomes, considering the susceptibility profile of bacteria.

The medical records of 51 bitches referred to the Veterinary Teaching Hospital of the University of Turin (January 2021–November 2023) and subjected to ovariohysterectomy and bacteriological examination (bacterial culture and susceptibility tests) of the uterine exudate, were analysed. All animals had a positive outcome without surgical site infections, with a longer hospitalization time in case of peritonitis or sepsis; antimicrobials were administered for an average of 7 days. Comparing the susceptibility of the isolated bacteria towards the antimicrobials administered before, during and after surgery, complete efficacy was observed in 42 %, 46 % and 50 % of cases, respectively. In addition, 5/16 peritonitis cases were treated with an *in vitro* ineffective antimicrobial, and 30 % of the bitches never received a fully effective antibiotic, according to susceptibility tests using the minimum inhibitory concentration method (MIC). Cephalosporins resulted the best option for *Escherichia coli*, the most frequently isolated bacterium. Our study confirms that pyometra has a good prognosis following ovariohysterectomy and antibiotic administration. Monitoring the clinical evolution without changing the antibiotic according to bacterial susceptibility could represent the right choice in uncomplicated cases. Evaluation of outcomes without postoperative antibacterial treatment or with a shorter course would be another topic worth investigating, with the aim to judiciously reduce the use of antibiotics.

Introduction

Pyometra is a commonly seen bacterial infection of the canine uterus, occurring during diestrus in a significant percentage (20–25 %) of middle-aged to elderly intact animals (Egenvall et al., 2001; Hagman, 2023). The predisposition of dogs to pyometra is due to the effects of prolonged exposure of the canine endometrium to progesterone during the 60–90 days of diestrus (Hoffmann et al., 2004), resulting in endometrial proliferation, uterine glandular secretion, decreased myometrial tone and a reduced local immune response (Smith, 2006). These effects are cumulative, sometimes also leading to cystic endometrial hyperplasia, which is a common histopathologic finding (De Bosschere et al., 2001).

Pyometra is an ascending bacterial infection, involving

microorganisms from the host's vaginal or intestinal flora (Sandholm et al., 1975). The most frequently isolated bacterium from uterine exudates is *Escherichia coli* (*E. coli*) but the strains associated with canine pyometra resulted different from commensal intestinal *E. coli* or strains that cause gastrointestinal disorders, having specialized virulence factors that promote colonization of extraintestinal sites (Xavier et al., 2024). A similarity to *E. coli* strains associated with urinary tract infections has been reported (Chen et al., 2003), suggesting that subclinical urinary tract infections can represent a bacterial source (Smith, 2006). Other bacteria may also be involved in pyometra, such as *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., *Proteus* spp., *Klebsiella* spp., in pure or mixed culture (Huber et al., 2022; Hagman, 2023).

Ovariohysterectomy (OVH) is the most effective treatment of canine

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pyometra because the infected organ is removed and recurrence is prevented (Hagman, 2023). Antimicrobials are usually administered perioperatively, although there is no general consensus about time of administration and treatment duration, ranging from no antibiotic use as suggested by the Swedish antibiotic treatment guidelines for animals not showing depressed general demeanor (Turkki et al., 2023) to usual post-operative antibiotic course (Lavin and Maki, 2023). Also, recent studies are lacking regarding antimicrobial agent choice (Lavin and Maki, 2023; Ylhäinen et al., 2023).

The Veterinary Teaching Hospital (VTH) of the University of Turin (Italy) is a referral clinic also for pyometra patients; currently, antibiotics are administered pre (at diagnosis), intra and post-operatively, possibly adjusting the antimicrobial choice upon culture results.

The objective of this retrospective investigation is to evaluate the antibiotic choice at different administration times (pre-surgery, at surgery/during hospitalization, and post-surgery) against complications and outcomes, taking into account the susceptibility profile of bacteria.

Materials and methods

Animals

Fifty-one bitches affected by spontaneous pyometra were the object of this retrospective study. The bitches were referred to the VTH of the University of Turin during the period January 2021–November 2023, and the inclusion criteria were: in addition to being a patient with pyometra, having been subjected to OVH and having a bacteriological examination of the uterine content in their clinical records.

Written consent is always obtained from the owners for the use of the medical record for scientific purposes.

Clinical data

The following data were acquired from the clinical records:

breed, age, weight, type of pyometra (open/closed cervix), leukogram, presence of peritonitis at the time of surgery, antimicrobial treatment, days of hospitalization, complications, and clinical outcome.

All surgeries were performed on stable (when heart rate, blood pressure, blood oxygen, acid-base balance are within normal limits; the animal is conscious, not depressed and without strong signs of distress) or stabilised animals, following standard internal surgical procedures. Before celiorrhaphy, the abdominal cavity was lavaged and, in case of peritonitis, the operation was repeated until the aspirated fluid was clean.

All patients were hospitalized for at least one night after surgery.

Complications that occurred within 10 days of surgery were defined as surgical site infection (SSI) or haemorrhage. SSI are categorized as superficial, deep or organ/space infections (i.e. peritonitis and cervical stump infections) (Turkki et al., 2023).

Samples for bacteriological examination of the uterine content were collected immediately after surgery, using a sterile swab (ESwab, 480CE, Copan Italia Spa, Brescia, Italia) through a small incision of the uterine wall, done with a sterile blade. Bacterial culture (aerobic and anaerobic) and susceptibility tests (Minimum inhibitory concentration method -MIC) were performed at the Istituto Zooprofilattico Sperimentale delle Venezie (PD, Italy), according to standard laboratory techniques, within 48 h of collection (Rota et al., 2021). The following groups of antimicrobials were considered and, for each group, the most representative antibacterial agents or the prototype agent were tested. Two specific panels of antimicrobials were used for Gram positive and Gram negative bacteria, respectively.

- Gram positive bacteria: Penicillins/Beta lactam/Beta lactamase inhibitor combinations (penicillin, ampicillin, amoxicillin-clavulanic acid, oxacillin), Cephems (1st generation cephalosporin: cephalexin, cephazolin; 3rd generation cephalosporin: cefpodoxime),

Tetracyclines (tetracycline, doxycycline), Aminoglycosides (clindamycin, gentamycin, erythromycin, kanamycin), Phenicol (florphenicol), Fluoroquinolones (prototype: enrofloxacin), Folate pathway inhibitors (trimethoprim sulfamethoxazole).

- Gram negative bacteria: Beta lactam/Beta lactamase inhibitor combinations (ampicillin, amoxicillin-clavulanic acid), Cephems (1st generation cephalosporin: cephalexin, cephazolin; 3rd generation cephalosporin: cefpodoxime, cefovecin), Tetracyclines (tetracycline, doxycycline), Aminoglycosides (gentamycin, erythromycin, kanamycin, amikacin), Fluoroquinolones (prototype: enrofloxacin), Folate pathway inhibitors (trimethoprim sulfamethoxazole).

Analysis of data

Count variables related to the patients' characteristics and clinical data were expressed as n and %, while numerical variables with normal distribution were expressed as mean±standard deviation. Non-normally distributed data were reported as median and range.

Normality was assessed using the Shapiro-Wilk test.

Correlations between the haematological parameters and between these and the number of hospitalization days were evaluated using Spearman's rank correlation test.

The effects of the following parameters: open/closed pyometra, presence of abdominal fluid/peritonitis on the duration of hospitalisation were analysed by means of Mann-Whitney U test.

Differences between animals treated with effective/ineffective or no antibiotics were evaluated using Fisher's exact test; animals were grouped according to outcome (live or death), complications (presence or absence of SSIs) and number of days of hospitalisation (≤ 1 day or > 1 day).

Significance was set at $P < 0.05$ for all analyses.

Results

The average age of the 51 patients was 8.8 ± 3.1 years (mean ± standard deviation), 33.3 % were mixed breed and 66.7 % were different breeds (Labrador Retriever was the most represented one with 5 animals). Thirty cases (58.8 %) were recorded as open form of pyometra and 21 (41.2 %) as closed.

All the animals were within 2 months following estrous signs.

In 16 cases, signs of peritonitis and/or abdominal fluid were detected at surgery or during ultrasonographic examinations routinely performed to assess the condition of the reproductive tract.

The outcome was positive in all the 51 animals and no SSIs were reported during the observation period. The only mayor complication was a patient that developed post operative haemorrhage (related to surgical technique issues), that required surgical revision, with a positive outcome.

Hospitalization lasted 1–8 days (median=1); no differences were observed between open or closed forms of pyometra while bitches with signs of peritonitis had a longer hospital stay than animals without abdominal involvement ($P=0.038$). A positive correlation was found between leukocyte and neutrophil count ($r=0.66$, $P<0.0001$), while a negative relationship was observed between leukocyte count and blood glucose level ($r=-0.44$, $P=0.038$). No correlations were observed between the number of hospitalised days and the haematological parameters evaluated (leukocyte and neutrophil count, glycaemia) (Table 1).

Bacteria isolation

The bacteriological examination was negative in only one case. In the vast majority of patients ($n=45$; 88.2 %), a single species was isolated, while mixed cultures were obtained in 5 animals (9.8 %), giving a total of 56 isolates.

The bacterial species and frequency of isolation are shown in Fig. 1.

Table 1

Haematological parameters (leukocyte and neutrophil count, glycaemia) and days of hospitalization in bitches with and without peritonitis.

	Bitches with peritonitis (n=16)		Bitches without peritonitis (n=35)	
	Median	Range	Median	Range
Leucocytes (x10 ³ cells/ μ L; median, range)	17.80	2.29–103.18	17.54	5.19–82.67
Neutrophils (x10 ³ cells/ μ L; median, range)	12.45	0.47–75.84	9.30	0.15–66.10
Glycaemia (mg/dL; mean, sd)	74.43	25.41	92.49	21.03
Days of hospitalization (days; median, range)	2	1–8	1	0–5

Escherichia coli was by far the most represented species (n=37), accounting for 66.1 % of isolates, including haemolytic (62.2 % of *E. coli* isolates) and mucous (18.9 % of *E. coli* isolates) strains. *Enterococcus* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Staphylococcus pseudintermedius* and *Streptococcus canis* were isolated between 2 and 3 times.

The susceptibility profile of the *E. coli* strains showed a fairly high percentage of resistance to amoxicillin-clavulanic acid (72.7 % were

resistant and 9.1 % showed intermediate susceptibility), while 14.6 % and 31.7 % were resistant and intermediate resistant to cephalosporins, respectively, and 6.8 % were resistant to a fluoroquinolone.

Antibiotic administration

At admission and in the days prior to surgery, 32 patients (62.8 %) had received no antibiotics, while 18 animals (35.3 %) had received cephalosporins or amoxicillin-clavulanic acid for 12–96 hours. A single bitch had been treated with a combination of cephalosporins and a fluoroquinolone (marbofloxacin) 24 hours prior to ovariohysterectomy. The times and doses are shown in Fig. 2.

Cephalosporins (20 mg/kg i.v. q12h) (TEVA Italia s.r.l.) were administered intravenously at surgery and during hospitalization, and marbofloxacin (2 mg/kg SC q24h) (Marbocyl FD 1 %, Vetoquinol) was associated in unstable cases showing abdominal fluid or peritonitis.

On discharge from hospital, all bitches received a 5-day course of antibiotics. Twenty-nine bitches (56.9 %) received amoxicillin-clavulanic acid, ten (19.6 %) a Fluoroquinolone (marbofloxacin), in one case a 1st generation cephalosporin was administered (cefalexin)

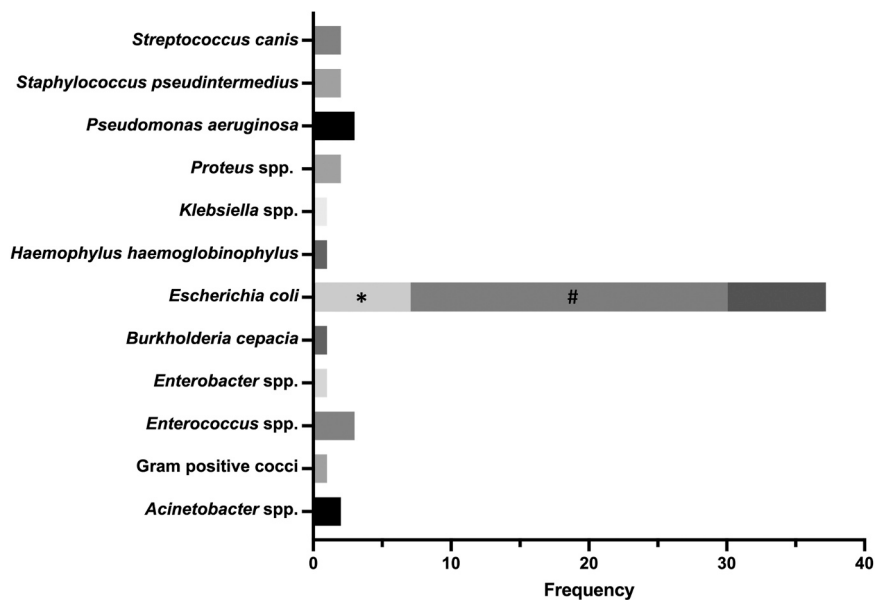


Fig. 1. Bacteria species and frequency of isolation (number of isolates=56). Haemolytic (#) and mucous (*) *Escherichia coli* strains accounted respectively for 62.2 % and 18.9 % of *E. coli* isolates.

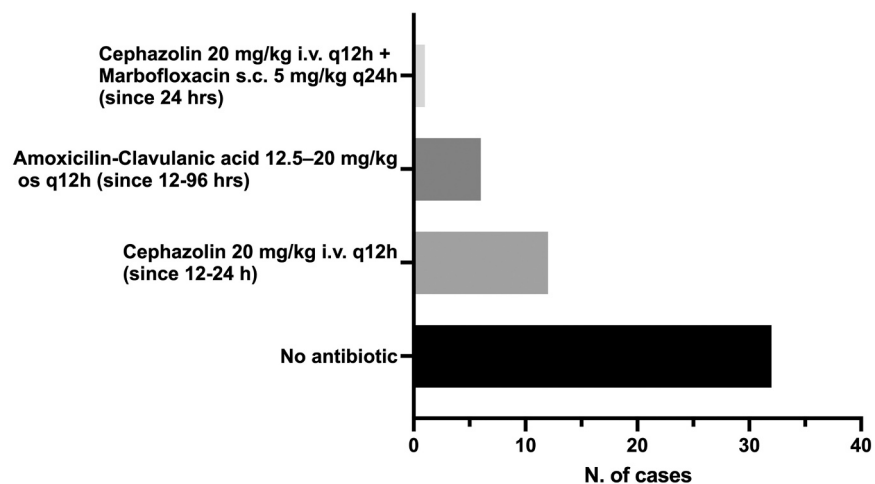


Fig. 2. Number of bitches treated or not with antibiotics in the days before ovariohysterectomy, and treatment schedule with the different antimicrobial agents.

and in another case a IIIrd generation cephalosporin was used (ceftriaxone), which was in combination with marbofloxacin in other two cases. Overall, an association of antibiotics was used in 10 cases (19.6 %), (Fig. 3). The average duration of the course of antibiotics was 7 days, at least intraoperatively, during hospitalization and after discharge from the hospital.

The clinical records showed that the antibiotic was never changed according to the bacteriological exam results.

Fig. 4 shows when (pre-surgery, at surgery/during hospitalization or post-surgery) the selected antimicrobial agent was deemed effective against the isolated bacteria, according to the susceptibility results, and when it was not. In the presence of multiple bacterial strains, i.e. *E. coli* and haemolytic *E. coli*, the more resistant one was considered, as more clinically relevant.

All *E. coli* strains resulted susceptible to the IIIrd generation cephalosporin cefpodoxime; ceftriaxone is the IIIrd generation cephalosporin used at the VTH, a parenteral formulation with a similar spectrum of antibacterial activity (Balfour and Benfield, 1996).

Six of the 19 bitches treated prior to surgery received an antibiotic to which the bacteria were resistant (31.6 %), and in 5 cases (26.3 %) the bacteria had intermediate susceptibility, meaning that overall, more than 50 % of therapies may have not been fully effective.

At surgery and during hospitalization, cephalosporin resulted fully effective, according to bacteria susceptibility, in almost half of the cases ($n=23$, 46.0 %), while the bacteria showed intermediate susceptibility in 13 cases (26.0 %) and were resistant in 14 cases (28.0 %).

After OVH, 22 of the 50 bitches with a positive uterine culture (44.0 %) were treated with an 'ineffective' antibiotic, 3 (6.0 %) received a potentially only partly effective antibiotic and only in half of the cases (25; 50.0 %), the antimicrobial agent resulted to be the correct choice according to the susceptibility of the microorganism isolated in the uterus. Furthermore, 5 of the 16 cases of peritonitis had been treated with the 'wrong' antimicrobial, i.e. with an antibacterial agent to which the isolated bacteria were not susceptible (Fig. 4).

In 15 cases (30 %), the bitches never received an antibiotic to which the isolated bacteria were fully susceptible. When signs of peritonitis had been recorded, no statistically significant differences were found in terms of days of hospitalization if the bitches were not treated or received an ineffective antimicrobial agent before surgery. Similarly, no

differences were observed when the antibiotics administered during surgery were taken into account.

Considering all cases together (bitches with and without peritonitis), no statistically significant differences were found in the length of hospitalization when antibiotics were administered or not before or during surgery and when bacteria were susceptible or not.

Discussion

The course and timing of antibiotic administration in pyometra is debated (Turkki et al., 2023), with the aim of limiting the use of antibacterials to clinically unstable or complicated cases, and ovariectomy is considered curative per se in stable cases (Hagman, 2023). However, when clinically stable bitches do not receive antibiotics perioperatively (i.e. before and during surgery), there is a higher risk of postoperative complications and even death (Turkki et al., 2023).

Postoperative mortality was not present in our investigation, neither were SSIs. In clean surgeries, the aim of perioperative antimicrobial prophylaxis is to minimize the risk of residual infectious bacterial inoculum in the surgical site (Boothe and Boothe, 2015), which is related to the procedural environmental condition. However, OVH for pyometra is not a clean surgery, as abdominal contamination by oviduct/ovarian bursae content or vaginal/cervical stump may occur. In addition, pyometra is a bacterial disease that carries the risk of sepsis and toxemia as well as compromised host defenses: antibacterial agents are part of the treatment, and are not only used with prophylactic goals.

All the bitches in our study received antimicrobials for an average of 7 days, at least intraoperatively, during hospitalization and after discharge from the hospital.

Our results show that they recovered despite the discrepancy between the susceptibility of the bacteria and the antibiotic used, even when peritonitis was present, and that even with the 'incorrect' antibiotic, i.e. when an antibacterial agent to which the isolated bacteria were not susceptible was administered, no postoperative infection developed.

These results could suggest that *in vitro* susceptibility may differ from *in vivo* susceptibility because the host defenses can play an active role. Furthermore, superficial or deep incisional wound infections may originate from bacteria that are different from the pyometra agents and may

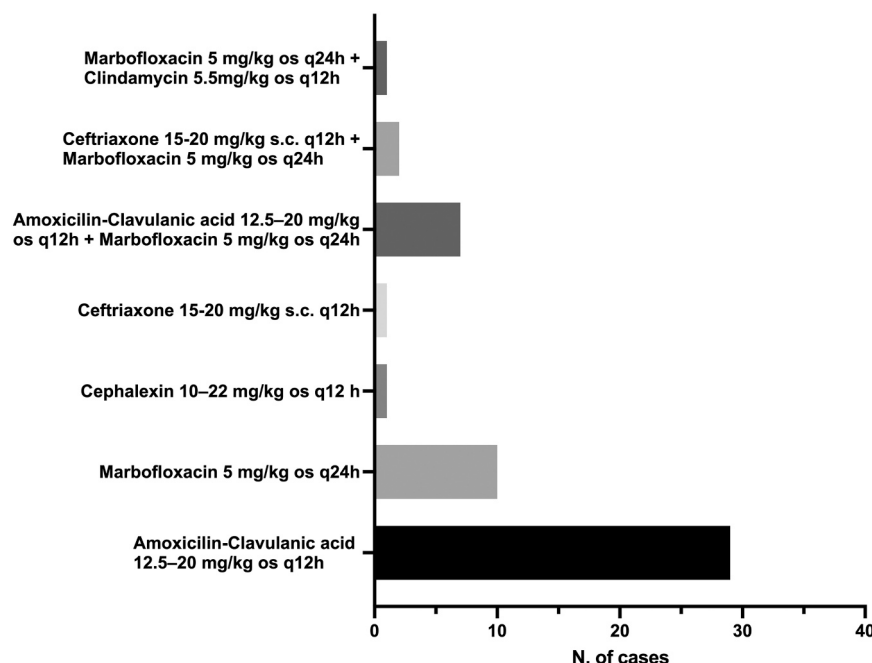


Fig. 3. Frequency of different antibiotic therapies prescribed to the bitches at hospital discharge, and treatment schedule.



Fig. 4. Effectiveness of the antimicrobial agents used at different times (pre-surgery, at surgery/during hospitalization, post-surgery) against the isolated bacteria. White square: antibiotic administration, green square: susceptible bacteria, orange square: intermediate susceptibility, red square: resistant bacteria. Cases with peritonitis/abdominal fluids are marked with an '*'. The case with negative bacterial culture is not reported.

then be susceptible to the antibiotic in use. Lastly, if the clinical condition improves, it is not necessary to change the antimicrobial according to *in vitro* results.

A judicious antimicrobial use would suggest to 'hit hard, hit fast and get out quickly' (Boothe and Boothe, 2015). When used, the duration of administration of a postoperative antibiotic should remain within the 7-day period during which the altered haematologic and immunologic parameters improve (Bartoskova et al., 2007). In private practice settings, postoperative oral antibiotics are part of the treatment protocol of pyometra in most cases (McCallin et al., 2022), and a standard 5-day postoperative treatment with trimethoprim-sulfonamide post-operatively is used at the Veterinary Teaching Hospital of the University of Helsinki (Ylhäinen et al., 2023) for uncomplicated pyometra cases. Specific literature is not helpful on this issue and only general recommendations are given: after an initial empirical antibacterial choice, which should consider that the most frequently isolated bacterial species is *E. coli*, treatment should be adjusted according to culture and susceptibility testing, in the event of resistance to therapy (Yoon et al., 2017; Hagman, 2023).

Our data confirm that *Escherichia coli* is the most frequently isolated bacterium, often in pure culture (Hagman, 2023). Percentages of isolation range from 69 (36 cases; Melo et al., 2022) to 86 (93 bitches; Borresen and Naess, 1977) or 90 (48 cases; Fransson et al., 1997).

Resistance profiles of bacteria can differ in different studies. A recent paper reported 100 % susceptibility of *E. coli* pyometra isolates to amoxicillin-clavulanic acid (Rocha et al., 2022); however, this result is not comparable to our findings because agar gel diffusion method was used instead of broth microdilution. Interestingly, *E. coli* was more susceptible to ceftazolin than to amoxicillin-clavulanic acid in our investigation.

The *E. coli* isolates in our study showed high susceptibility to fluoroquinolones. However routine use of this class of antimicrobials should be discouraged and is restricted to life-threatening infections, at least in Swedish legislation (Turkki et al., 2023). Surgically treated pyometra is usually not a life-threatening condition and OVH is the key to treatment. Fluoroquinolones should then not be the first choice in uncomplicated pyometra cases. Our results show that it is not even necessary to change the antibiotic on the basis of bacteria susceptibility results when clinical conditions are improving.

Bacterial culture in pyometra does not seem to be routinely performed (Lavin & Maki, 2023), both for economic reasons and because of the timing of the results, as these generally become available when the bitch has already recovered and has usually already been discharged from hospital, as in our study. However, in case of treatment failure, it is crucial to rely on microbiological test results.

In agreement with the extensive literature on spontaneous canine pyometra, the results of this study confirm that it is an infection of the uterus of middle- to older aged intact bitches, and that the prognosis is good after surgical removal of the pus-filled organ in association with antibiotic treatment (Hagman, 2023). Potentially life-threatening complications such as sepsis and peritonitis can occur (Jitpean et al., 2014; Turkki et al., 2023), and mortality is reported to be between 1 % (Jitpean et al., 2014) and 3 % (McCobb et al., 2022). Wound infection may also occur (Jitpean et al., 2014). Leukocytosis with neutrophilia is a typical finding; leukopenia is a marker of more severe conditions or complications, and may be due to endotoxin-induced bone marrow depression and leucocyte sequestration in the uterine lumen (Jitpean et al., 2014). A reduced leukocyte count, when associated to lower blood

glucose level, may be signs of sepsis. Hospitalization is longer if the infection has spread to the abdominal cavity, involving peritoneum and/or internal organs, either due to uterine rupture or possible leakage of pus through the oviducts (Rubio et al., 2014). In our study, when peritonitis, or abdominal fluid were present, recovery took longer and the number of days in hospital increased, up to a maximum of 8 days. Broad-spectrum antimicrobial agents are recommended for use in pyometra, such as amoxicillin-clavulanic acid, cephalosporins, enrofloxacin (Turkki et al., 2023), and amoxicillin-clavulanic acid and cephazolin are indeed the antibiotics that were administered to the bitches in the uncomplicated cases in our investigation with good results.

There are not shared and objective criteria for deciding when to continue antibiotic administration in the days following pyometra surgery, and prescribing antibiotics at discharge to prevent complications may be questionable and the issue needs to be investigated (Ylhäinen et al., 2023).

Notwithstanding the fact that gonadectomy is a common practice in female dogs, there is a general consensus in recent years that it should be discouraged unless strictly necessary for population control or owner's management reasons, and considered as it is, the cause of hormonal deprivation (Hart et al., 2020). This may imply that the incidence of reproductive pathologies, pyometra for first, will increase in the future; further studies are needed to define the best treatment plans, also with the objective of limiting the use of antibiotics to absolutely necessary cases, without increasing the risks for the patient.

Conclusions

Our results confirm that pyometra has a good prognosis following OVH and antibiotics administration, and that antibiotics do not need to be changed based on the bacteriological examination results if the clinical conditions are already improving, even in cases complicated by peritonitis or abdominal fluid. Our study did not aim to evaluate the outcome without antibacterial postoperative administration or with a shorter course, although this would be a noteworthy issue. Reducing postoperative antibiotic prescribing should be a goal of the VTH, but more consistent data are needed for pyometra cases.

CRedit authorship contribution statement

Ada Rota: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization. **Alessia Bertero:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Michela Corro:** Writing – review & editing, Resources, Methodology, Investigation. **Elena Spagnolo:** Writing – review & editing, Investigation. **Tiziana Nervo:** Writing – review & editing.

Declaration of Competing Interest

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Data Availability

The data analysed in the current study are available from the corresponding author on reasonable request.

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