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A retrospective study of bitches with pyometra and mucometra medically treated with aglepristone

Linnea Ros

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A retrospective study of bitches with pyometra and mucometra medically treated with aglepristone

En retrospektiv studie av tikar med pyometra och mucometra som behandlats medicinskt med aglepriston

Linnea Ros

Supervisor: Ragnvi Hagman, Department of clinical sciences

Assistant Supervisor: Bodil Ström Holst, Department of clinical sciences

Examiner: Odd Höglund, Department of clinical sciences

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ABBREVIATIONS

OHE	Ovariohysterectomy
CEH	Cystic endometrial hyperplasia
h	Hour
im	Intramuscular
iv	Intravenous
MD	Missing data
NAD	Nothing abnormal detected
PAD	Pathological anatomical diagnosis
PGF _{2α}	Prostaglandin F _{2α}
po	Per os
sc	Subcutaneous
Temp	Temperature
WBC	White blood cell count

SUMMARY

Pyometra is a common and life threatening disease of intact bitches. The disease is caused by a hormonal influence on the uterus in combination with a bacterial infection. The most common treatment is ovariohysterectomy, but several medical options are available to maintain fertility or avoid surgery and anaesthesia. Drugs that can be used for medical treatment are for example progesterone-receptor antagonists, prostaglandins and dopamine agonist. The present study focused on treatment with the progesterone-receptor antagonist aglepristone in combination with antimicrobial therapy. There are few studies evaluating the long-term outcome after medical treatment with aglepristone, and the outcome and recurrence risk varies.

The aim of this study was to evaluate long-term recovery and fertility after treatment with aglepristone in bitches with pyometra. In this study 30 bitches with pyometra or mucometra that were admitted to and treated at the University Animal Hospital (UDS), Swedish University of Agricultural Sciences (SLU) during a 9-year-period were included. The UDS data records were studied retrospectively and the outcome followed up by telephone interviews with the owners. The bitches were treated with aglepristone at a dose 10 mg/kg sc with a median of 4 times (12/28 bitches). All but one bitch were also treated with antimicrobial drugs for a mean duration of 22 days and the most frequently used antimicrobial drug was enrofloxacin. *Escherichia coli* were the most commonly isolated bacteria. None of the bacterial strains cultured were resistant to enrofloxacin, but 9 % were resistant to trimetoprim/sulfa.

The outcome was determined up to 6 years after treatment. The success rate, determined as a clinically healthy status, was 77 % (23/30 bitches), and the recurrence rate was 43 % (10/23 bitches) defined as recurrence of the disease. The mean time until recurrence was 11 months after the end of treatment. After treatment, 71 % (n = 10) of the 14 mated bitches produced puppies, and five of them produced two to four litters. The bitches that did not have a successful treatment were ovariohysterectomized, in all cases but one which was euthanized. In conclusion, medical treatment with aglepristone in combination with antimicrobial therapy was successful in 77% of the bitches studied and the recurrence rate was 43%.

SAMMANFATTNING

Pyometra är en vanlig sjukdom hos intakta tikar. Sjukdomen orsakas av hormonell påverkan på livmodern i kombination med sekundär bakteriell infektion. Den vanligaste behandlingen är ovariohysterektomi, men det finns flera enbart medicinska alternativ som används för att bevara fertiliteten samt undvika kirurgi och narkos. Denna studie har utvärderat behandling med aglepriston, en progesteronreceptor-antagonist. Det långsiktiga resultatet av medicinsk behandling med aglepriston har inte undersökts i Sverige. Behandlingsresultaten varierar mellan studier gjorda i olika länder, vilket kan bero på olika patienturval och antimikrobiellt resistensmönster.

Målet med denna studie var att undersöka det långsiktiga behandlingresultatet och fertiliteten efter aglepristonbehandling av tikar med pyometra i Sverige. I denna studie ingick 30 tikar med pyometra som behandlades med aglepriston på Universitetsdjursjukhuset (UDS), Sveriges lantbruksuniversitet under en nioårsperiod. Hundarnas journaler studerades och behandlingsresultatet följdes upp via telefonintervjuer med djurägarna. Tikarna behandlades i medeltal 4 gånger med aglepriston i dosen 10 mg/kg sc. Alla utom en tik behandlades också med antibiotika under i genomsnitt 22 dagar och det vanligaste använda preparatet var enrofloxacin. Ingen av de 11 bakteriestammar som isolerades var resistent mot enrofloxacin men mot trimetoprim/sulfa var 9 % (n = 1) resistent. *Escherichia coli* var den bakterie som isolerades från flest av de provtagna tikarna.

Uppföljning av behandlingresultatet gjordes som längst 6 år efter avslutad behandling. Behandlingen var framgångsrik (definierat som kliniskt frisk status) hos 77 % (23/30) av tikarna och andelen som fick återfall efter genomgången framgångsrik behandling var 43 % (10/23). Medeltiden innan återfall var 11 månader efter avslutad behandling. Efter genomgången behandling fick 71 % (n = 10) av de 14 tikar som parades valpar, och fem av dessa fick två till fyra valpkullar. De tikar där behandlingen inte var framgångsrik genomgick kirurgisk ovariohysterektomi, utom i ett fall där tiken istället avlivades. Enligt resultaten av denna studie var medicinsk behandling med aglepriston framgångsrik hos de flesta (77 %) behandlade tikar men andelen som fick återfall efter avslutad behandling var relativt hög (43 %).

INTRODUCTION

Pyometra is a potentially life threatening disease that is common among intact bitches. In average 19 % of insured Swedish bitches are diagnosed with the disease before they reach the age of 10 years (Jitpean et al., 2012). In a colony of Beagles that lived more than 4 years, 15,2 % were diagnosed with pyometra during their life-span (Fukuda, 2001). In Sweden, the dog population is mainly intact (Egenvall et al., 1999), which is why pyometra is a very frequent disorder in comparison to the situation in other countries where most bitches are spayed (Diesel et al., 2010). The pathogenesis of pyometra is not fully understood but hormonal influence of estrogen followed by subsequent progesterone stimulation during a relatively long period of time (metoestrus) (Dow, 1959b), in combination with bacterial infection is believed to cause the disease. The bacteria found in the uterus originate from the urinary tract or normal flora of each bitch, and *Escherichia coli* is the most common isolate (Dow, 1959a, Bassessar et al., 2009, Dow, 1958, Hagman and Greko, 2005, Hagman and Kuhn, 2002). Pyometra mainly affects middle-aged to older bitches and is generally diagnosed during the luteal phase of the estrus cycle (Dow, 1957, Dow, 1958, Hagman and Greko, 2005).

Ovariohysterectomy (OHE) is the treatment of choice for pyometra and is considered to be safe and effective (Borresen, 1975, Dow, 1957). To maintain fertility or if surgery or anesthesia should be avoided, there are also several medical treatment alternatives available. Examples of drugs that can be used for medical treatment of pyometra include progesterone-receptor antagonists (aglepristone, mifepristone), prostaglandins (dinoprost, cloprostenol), dopamine agonists (cabergoline) or different combinations of these drugs (Gilbert et al., 1989, Gabor et al., 1999, Jurka et al., 2010, Gobello et al., 2003, Corrada et al., 2006). Few studies have evaluated the long-term outcome after medical treatment, and for aglepristone, the time of evaluation varies from after the following estrus (Metcalf and Vischer, 2006, Breitkopf et al., 1997), after one year (Trasch et al., 2003), after two years (Fieni, 2006) or up to 54 month after treatment for a few bitches (Jurka et al., 2010). In one of the studies, the authors kept in contact with 3 successfully treated bitches for up to 6 years after treatment (Fieni, 2006). Treatment outcome may differ depending on varying antimicrobial resistance in different countries, but there is little focus on the choice of antimicrobial drugs used as adjunctive treatment of pyometra (Hagman and Greko, 2005, Bassessar et al., 2009). Additionally, the selection of bitches for medical treatment varies between different countries, which also might affect the outcome (Fieni, 2006, Rootwelt-Andersen and Farstad, 2006). So far the overall outcome after aglepristone treatment of pyometra in Sweden has not been studied.

The aim of this study was to investigate the long-term outcome (recovery and fertility) after medical treatment with aglepristone in bitches with pyometra in Sweden.

1 LITERATURE REVIEW

1.1 Background

Pyometra means “pus in the uterus”, but many names have been and are used to describe the condition such as pyometritis, purulent metritis, hypoplastic endometritis, chronic cystic metritis and cystic hyperplasia-pyometra complex (Dow, 1957, Ewald, 1961). The pyometra can be either open (with vaginal discharge present) or closed (no notable vaginal discharge depending on the functional status of the cervix). The cystic hyperplasia-pyometra complex can be divided into four distinct groups as suggested by Dow (1957, 1959a) after he had studied 100 cases histologically. Cystic endometrial hyperplasia (CEH) was generally present in pyometra uteri, but CEH could also be found in many older bitches without any signs of pyometra (Dow, 1958).

1.2 Pathogenesis

Escherichia coli is the most commonly isolated bacterium from the uterine content in bitches with pyometra (Meyers-Wallen et al., 1986, Bartoskova et al., 2007, Hagman and Greko, 2005). In one study of 100 bitches with pyometra, the mean age was 8,2 years (Dow, 1957), but there are breed variations reported for at which age the disease occurs (Egenvall et al., 2001). All cases of pyometra occurred during the luteal phase, 5 to 80 days after estrus, in one study (Dow, 1957). Acute endometritis also generally occurs from 5 to 90 days after estrus (Dow, 1958). The majority, 88%, of the dogs with cystic hyperplasia-pyometra complex were in metoestrus, and histological examination showed that 96 % had corpora lutea, and 19 % had cysts present in the ovaries, but only 2 cases had ovarian cysts in absence of corpora lutea (Dow, 1959a). These studies show that pyometra generally occurs during metoestrus.

To understand the pathogenesis, early attempts to induce CEH-pyometra in ovariectomized bitches by experimental administration of estrogen were made but did not succeed. In contrast, progesterone was effective, as cystic glandular hyperplasia of the endometrium could be observed after administration. A combination of the synthetic estrogen stilbestrol followed by progesterone also induced similar changes. If the dose of progesterone was increased, acute endometritis developed. Repeated treatments with high doses of progesterone in ovariectomized bitches also led to acute endometritis, indicating that CEH is a precursor for endometritis. The influence of progesterone in the pathogenesis is also supported by that two bitches with clinical signs of endometritis, had a relief of their clinical signs, emptied their uteri of fluid, and histological neutrophils were replaced by plasma cells after the progesterone administration ceased (Dow, 1959b).

In 1978 one study was published in which it was concluded that there were no evidence of high or long history of progesterone secretion in peripheral plasma in bitches with pyometra (Chaffaux and Thibier, 1978). Newer research reports indicate that it is not the concentration of progesterone in the circulation that is important in the pathogenesis but the number of progesterone receptors and the sensitivity to hormone stimulation (Fieni, 2006, Gobello et al., 2003). Progesterone and estradiol levels vary during the estrus cycle. Progesterone increases

the endometrial epitheliums secretions, inhibits relaxation of cervix (Dow, 1957), inhibit uterine contractions and negatively affects the immunity of the uterus (Jena et al., 2013). Progesterone concentrations can be used to determine the stage of the estrus cycle in the bitch (Table 1).

Table 1. Progesterone and estradiol levels during the estrus cycle (De Bosschere et al., 2001)

	Progesterone ng/mL	Estradiol-17 β pg/mL
Anoestrus	<0,5	<25
Proestrus	<1	>25
Estrus	>1	>25
Metoestrus	>0,5	<25

The relationship between CEH and pyometra is still not fully understood. More recently, it was suggested that CEH and pyometra are two different conditions, and the results of one study showed that CEH does not have to be followed by pyometra, and that pyometra could develop regardless of previous CEH (De Bosschere et al., 2001). Though both conditions are quite similar, one difference is that there is an inflammatory reaction and clinical signs present in bitches with endometritis-pyometra, but not in those with CEH-mucometra (De Bosschere et al., 2001). Another study of the same research group showed different expressions of estrogen- α receptors and progesterone receptors in the uteri of cases diagnosed with pyometra-endometritis and CEH-mucometra, indicative of two separate conditions rather than a disease complex (De Bosschere et al., 2002).

1.3 Clinical signs

Clinical signs that can be observed in bitches with pyometra are anorexia, lethargy, abdominal distension, illness, listlessness, polydypsia, polyuria, vomiting and fever and, in case of an open cervix pyometra, purulent discharge from the vulva (Dow, 1957, Jurka et al., 2010).

Laboratory findings such as leucocytosis, neutrophilia with a left shift monocytosis, and anemia are common in bitches with pyometra (Dow, 1959b).

1.4 Treatment

1.4.1 Surgical treatment

Ovariohysterectomy (OHE) is the treatment of choice and is associated with a mortality rate of 3,2 % (Gibson et al., 2013). Surgical treatment (OHE) in bitches with pyometra leads to fast recovery of hematological and immunological disturbances (Bartoskova et al., 2007).

1.4.2 Uterine drainage

Other treatment methods are uterine drainage and lavage. In one study of eight bitches with pyometra the uteri were flushed with a 5 % povidone-iodine and saline mixture in combination with systemic antimicrobial treatment. The vaginal discharge had stopped by day four in all but one bitch, in which the vaginal discharge continued until day 12 of treatment. All bitches subsequently had normal estrus cycles, were mated several times and in all but one case they produced puppies with normal litter size (De Cramer, 2010).

In one study, catheters were inserted into the uterine horns through the cervix, and left in place for 5 to 15 days to facilitate uterine drainage. The bitches were also treated with antimicrobials and/or in three cases ergometrine. Treatment was successful in 83 % (10/12) of the bitches, but one of these bitches had an early relapse of the disease. The two bitches that did not have a successful treatment had persistent vaginal discharge. Of the remaining nine successfully treated bitches, six were mated at the first estrus following treatment and five of them had puppies (Funkquist et al., 1983).

1.4.3 Aglepristone

Aglepristone is a steroid sex hormone antagonist that binds competitively to the progesterone receptor with high-affinity. Of the antiprogestins, aglepristone (RU46534), mifepristone (RU38486) and onapristone (ZK98299), it is only aglepristone (Alizin vet, Virbac, Montpellier, France) that is registered for veterinary use (Hoffmann and Schuler, 2000). In Sweden aglepristone is registered with the indication of abortion in bitches up to 45 days after mating (Fass vet, Läkemedelsindustriföreningens Service AB, 2013-11-04, Sweden). The results of several studies on aglepristone, all with sc route of administration, are presented in the following text.

In one study 52 bitches with pyometra were treated with aglepristone. The dose of aglepristone was 10 mg/kg on day 1, 2 and 7. The treatment was combined with the antimicrobials amoxicillin/clavulanic acid or enrofloxacin for a minimum of 7 days. The recovery rate was 92,3 % after 21 days. The recurrence rate was 9,8 % (4/41) within 3 months and 26,8% (11/41) within at least one year after treatment (Trasch et al., 2003).

In another study of pyometra 24 bitches were treated with aglepristone at the dose 10 mg/kg sc on day 1, 2, 7 and 14 in combination with amoxicillin/clavulanic acid for 7 days. The bitches were divided into two groups depending on age and all were mated in the first following estrus. The results showed that 57,1 % (8/14) of bitches <5 years got puppies when mated on the first following estrus, while 0 % (0/9) of the mated bitches >5 years did. Of the bitches in the older group 30 % (3/10) had recurrence of the disease after the next estrus and were treated by OHE, whereas none of the younger bitches had recurrence that early. In the younger bitches data was collected 36 to 54 month after treatment and by those dates 23 % (3/13) had had puppies. The older bitches were not possible to follow up long-term (Jurka et al., 2010).

Another report of 41 bitches with pyometra treated with antimicrobials and aglepristone at the dose 10 mg/kg on day 1; day 1 and 2; or day 1, 2 and 8 had a successful outcome in 83 % (34/41) of the bitches 30 days after treatment (Metcalf and Vischer, 2006).

In two studies, low doses of aglepristone were used to treat pyometra. In one of these studies, six bitches were treated with 6 mg/kg of aglepristone twice daily on day 1 and once daily on day 2, 3 and 4. The bitches had almost no uterine contents on day 6 when they were subjected to OHE (Blendinger et al., 1997). In the other study, seven bitches were treated with aglepristone at the dose 5 to 6 mg/kg on day 1, and 3 mg/kg once daily on day 2, 3, 4, 8, 12 and 16. In one bitch the dose was changed to 6 mg/kg every 2nd day from day 4. Within 12 days, six of the seven bitches had completely emptied their uteruses of its content. Six bitches were followed-up to the next estrus and no recurrence was observed. Two dogs were mated and produced healthy puppies. (Breitkopf et al., 1997)

Aglepristone has been shown effective as a treatment for both closed and open cervix pyometra (Gurbulak et al., 2005, Fieni, 2006). This is supported by a study in which seven of eight bitches with closed-cervix pyometra were treated with aglepristone and antimicrobials successfully and without any recurrence for at least one year after the treatment (Trasch et al., 2003). Additionally another study showed similar results in 12 bitches with closed-cervix pyometra treated with aglepristone and antimicrobials in which all had recovered on day 14 after treatment (Domoslawska et al., 2010).

1.4.3.1 Aglepristone and cloprostenol

Aglepristone can also be used in combination with a low dose of cloprostenol to reduce the side effects of the drug (Fieni, 2006). This treatment combination has been evaluated in several studies.

In one study comparing the treatment of aglepristone (at the dose 10 mg/kg on day 1, 2 and 8 and if necessary also on day 14 and 28) with aglepristone (at the same dose as the previous group) in combination with cloprostenol (1µg/kg daily on day 3 to 7), the success rate at day 90 was 60% (12/20) and 84% (27/32) respectively. In total 54,5 % of the 33 bitches, had side effects such as nausea (12/33) and vomiting (6/33). Follow-up data were available in 23 bitches of which 13 % (3/23) had a recurrence of pyometra 7 to 12 months later, and 19 % (4/21) has recurrence at 19 months after treatment. Five bitches were mated at the first estrus after treatment and four conceived. Three bitches were followed for 6 years without recurrence and with normal estrus (Fieni, 2006).

The combination of aglepristone and cloprostenol was also evaluated in a study of 15 bitches that were treated with aglepristone (at the dose 10 mg/kg on day 1, 3, 8 and if necessary day 15) and cloprostenol. Cloprostenol (at the dose 1µg/kg) were either given on day 3 and 8, or on day 3, 5, 8, 10, 12 and 15 if necessary. The success rate was 100 % (all 15 bitches recovered), either after 15 (n=10) or 29 (n=5) days. No side effects were observed. Recurrence rate at the next estrus was 21 % (3/14). One of the bitches was mated and had puppies (Gobello et al., 2003).

1.4.3.2 Aglepristone and intrauterine antimicrobials

In one study (Gurbulak et al., 2005) on 24 bitches there were no statistically significant difference in recovery rate in bitches with open or closed cervix pyometra treated with only aglepristone (6/13 recovered) compared to bitches treated with both aglepristone and intrauterine antimicrobials (9/11 recovered). However it was shown that there was a significantly higher recovery rate in bitches with closed-cervix pyometra treated with aglepristone and intrauterine antimicrobials (4/5 recovered) compared with the once with closed-cervix pyometra that were only treated with aglepristone (1/6 bitches recovered).

1.4.3.3 Side effects of aglepristone

Several studies have reported that no side effects were observed in bitches with pyometra after treatment with aglepristone (Blendinger et al., 1997, Breitkopf et al., 1997, Gobello et al., 2003). However, some side-effects of aglepristone treatment for termination of pregnancy have been reported such as anorexia in 36 %, weight loss in 5 %, polydipsia in 5 % and local swelling in 9 % (Pettersson and Tidholm, 2009).

1.4.4 Prostaglandins

Another medical treatment option for bitches with pyometra is prostaglandins. Prostaglandins (PGs) are hydroxyacids derived from the fatty acid arachidonate with a variety of actions in the body (Burke, 1982). The use of PGF_{2α} results in contraction of the myometrium, increased cervix relaxation, and after five days of diestrus it has a luteolytic action and reduces serum concentrations of progesterone (Gobello et al., 2003). PGF_{2α} is registered for equines and bovines in Sweden (Dinoprost, Dinolytic vet, Orion Pharma Animal Health, Sweden, Sollentuna) with the indications synchronizing heat, treatment of anestrus, abortion, and treatment of chronic metritis and pyometra (Fass vet, Läkemedelsindustriföreningens Service AB, 2013-11-05, Sweden). Several studies have been performed on treatment of bitches with pyometra with prostaglandins, and below follows a short summary of the main findings.

In one relatively early report, bitches with pyometra or metritis were treated with PGF_{2α} at the doses 22, 110, 220 or 441 µg/kg and the two lowest doses were found ineffective. PGF_{2α} were given once a day during two following days and had a positive outcome in some cases, but longer treatments were needed for most bitches. The treatment protocol was adjusted to 250 µg/kg sc every 24 hours for 3 to 10 days and another dose administered 3 to 5 days after vaginal discharge was last observed. Two bitches diagnosed with metritis after mating were treated for three and four days respectively, and had a successful outcome as they both had puppies at expected time. Side effects seen in most patients were loose feces, vomiting, salivation, ataxia, collapse, hyperpnoea and constriction or dilatation of the pupil. Follow up data showed that 5 of 9 bitches had puppies after their first or second following estrus (Burke, 1982).

In another study of 17 bitches with pyometra or postpartum endometritis were given PGF_{2α} at the dose 100 µg/kg, 250 µg/kg or 500 µg/kg sc once every day for a maximum of 5 days. If the dog had not recovered 1 to 2 weeks later the treatment was repeated; and in one case it was repeated three times. The success rate was 76 % (13/17). Of the ones that were mated 82 % (9/11) had puppies. The two bitches that did not conceive had a recurrence within 5 weeks from estrus. The two bitches that were not mated were clinically healthy. Side effects observed in the group with the lowest dose were restlessness, hyper salivation, vomiting and defecation in 20 % (1/5) of the bitches. At the higher dose the same side effects and panting were observed in 3 to 7 of 8 bitches and in the group receiving the highest dose side effects were of the same kind as in the previous group and were observed in 1 to 4 of 4 bitches. All doses used in this study were effective and the authors of this study recommend the lower dose regime. One bitch had growth of *Escherichia coli* from blood culture after treatment with PGF_{2α} was initiated, but not before. The authors therefore recommended antimicrobial treatment in combination with the treatment with PGF_{2α}. (Nelson et al., 1982).

One study of 10 bitches that received PGF_{2α} at a dose of 500 µg/kg (n=8) or 250 µg/kg (n=2) sc of dinoprost once daily for three days in combination with antimicrobials during four weeks showed a success rate of 100 %. All ten bitches were mated on the following estrus but only two of them produced puppies. Forty per cent (4/10) of the bitches produced puppies during the first year following treatment, and 55 % (5/9) of the bitches that were followed up more than one year. The recurrence during the first year was 40 % (4/10) and these bitches were treated again with the same protocol, and they all had another recurrence. Of the bitches that were followed up more than one year 77 % (7/9) had a recurrence. Four bitches had recurrence at the first following diestrus and three had recurrence more than one year after treatment. Periglandular fibroplasia was found in uterine biopsies from two of the ten bitches before treatment started, and in another two by the time of their recurrence. One of these bitches had puppies whereas three did not, and all four ended up having OHE. Side effects observed during treatment were salivation, panting, restlessness, emesis and defecation (Meyers-Wallen et al., 1986).

In a retrospective study of 40 bitches treated with dinoprost and/or luprostirol (a synthetic PGF_{2α} analogue) at the dose 26,8 to 258 µg/kg 1 to 3 times a day, duration of treatment varied from 2 to 26 days. Broad spectrum antimicrobials were used until the bitches did not show any more clinical signs. Treatment was successful in 87 % (33/38) of the bitches. Follow-up 1 to 5 years after treatment showed that 25 % (5/20) had failed to reproduce and 45 % (9/20) had produced at least one litter. In 6 cases information about reproduction was not available. Relapse of pyometra-metritis had occurred in 10 % (2/20 bitches) and 10 % had to have OHE because of complications after the treatment. The authors advised that dogs with cardio-pulmonary lesions should start at a lower dose and be carefully observed before increasing the dose because of its bronchospastic effect (Gilbert et al., 1989).

Eight bitches with open pyometra were treated with PGF_{2α} at the dose 250 µg/kg for 5 to 6 days in one study. After 6 weeks OHE was performed in six of them and showed a normal uterus in five of the bitches but in one of them there were areas of 1 cm that were caseated

and very thin-walled. One of the two dogs that did not have OHE later produced puppies (Renton et al., 1994).

Seven bitches with pyometra were treated with dinoprost at the dose 100 µg/kg sc once every day for 7 days in one clinical study. All bitches recovered and six came in estrus, where of these four also conceived. The recurrence rate was 42,9 %. During treatment 71 to 100 % of the bitches showed the side effects vomiting, panting, restlessness, hyperpnoea, defecation and urination. In the same study there were also 7 bitches with pyometra that were treated with cloprostenol at the dose 1 µg/kg sc once daily for 7 days. In this group all bitches recovered but only two came into estrus and of these one conceived. The recurrence rate was 85,7 %. Side effects observed in this group were vomiting, panting, restlessness and hyperpnoea in 29 to 57 % of the bitches (Jena et al., 2013).

One study used dinoprost at a low dose of 20 µg/kg im three times daily for a maximum of eight days, combined with antimicrobials for four weeks to treat 10 bitches with pyometra. On the 8th day the uterus was still enlarged in 3 dogs and these were ovariohysterectomized. None of the other bitches had recurrence during the following 10 months. Five of the bitches were mated and had puppies. No side effects were observed (Arnold et al., 1988).

Intravaginal PGF_{2α} at the dose 150 µg/kg once or twice daily in combination with amoxicillin or gentamicin im injections were used to treat 17 bitches with pyometra or metritis in another study. The duration of treatment was 3 to 12 days. By this time 88 % (15/17) of the animals had recovered, but two bitches had to be ovariohysterectomized because of deteriorating general condition. No recurrence was observed at the next estrus within 12 month after treatment. No side effects were observed (Gabor et al., 1999).

A study of 14 bitches with pyometra in which eight bitches were treated with PGF_{2α} (Lutalyse®) at the dose 100 µg/kg sc twice daily for 5 to 13 days, and six bitches with PGF_{2α} at the dose 150 µg/kg intravaginally once daily for 6 to 11 days. The first group had a success rate of 75 % and the second group had 100%. Both groups were also treated with broad spectrum antimicrobials. The side effects restlessness, salivation and hyperpnoea were seen in all bitches in both groups. In the first group the following side effects were also observed vomiting (7/8), defecation (5/8) and urination (6/8). The bitches that received intravaginal PGF_{2α} also showed the side effects vomiting (2/6) and defecation (1/6) (Nishi et al., 2004).

Uterine rupture was reported after administration of dinoprost at the dose 230 µg/kg im in a bitch with pyometra and vaginal discharge (Jackson, 1979). In one study (Nelson et al., 1982) a response to treatment with PGF_{2α} took at least 48 hours and therefore was recommended to use with caution when treating seriously ill bitches. Nelson et al. (1982) do not recommend treatment in bitches with closed cervix because of the risk for contents from the uterus leaking in to the peritoneal cavity. This recommendation was based on the findings of one bitch in the study with closed cervix had to have OHE 4 hours after the first injection because her general condition was getting worse and where vaginal discharge was found in the abdominal cavity during surgery. The outcome in bitches with closed-cervix pyometra was also not so good, with only 25 % (1/4) bitches having a successful outcome (Nelson et al., 1982).

To summarize, prostaglandins are an effective treatment alternative for treating pyometra, but with many side effects reported.

1.4.4.1 Cloprostenol

Cloprostenol is a synthetic prostaglandin analog and compared to natural prostaglandins it is much more effective in causing luteolysis and maintaining uterotonic action (Corrada et al., 2006). Only bitches without liver or kidney dysfunction should be treated with cloprostenol, and close clinical contact during the treatment has been suggested (Fieni, 2006).

One study including 24 bitches with pyometra divided the bitches into four different groups with different treatment protocols. Group 1 was treated with 1 µg/kg cloprostenol im once daily for up to 7 days in combination with antimicrobials im. This group had a recovery rate of 83 % (5/6 bitches). The second group was treated with the same protocol for cloprostenol but received intrauterine administered antimicrobials. In the second group the recovery rate was 83 % (5/6 bitches). The third group also received cloprostenol with the same protocol used as in the previous groups, in combination with antimicrobials administered im but they were also treated with intrauterine povidone iodine. In this third group all 6 bitches recovered. The fourth group was treated with antimicrobials im and intrauterine povidone iodine. In the fourth group the recovery rate was 67 % (4/6 bitches) (Khan et al., 2007).

1.4.5 Cabergoline in combination with cloprostenol

Cabergoline (Galastop vet, Ceva Animal Health, Sweden, Lund) is a dopaminergic agonist and its effect is anti-prolactinergic. Another dopaminergic agonist is bromocriptine and these two drugs are both ergotamine-derivative alkaloids that have a direct effect on the lactotrophic cells of the anterior pituitary gland through the D₂-dopamine receptors, and therefore inhibit prolactin secretion. Cabergoline has mainly been used for milk suppression in dogs, but prolactin has a role during the latter half of the luteal phase as a luteotropic hormone, which makes it useful in inhibiting luteal action of progesterone and therefore also useful for treatment of pyometra or mammary tumors and for pregnancy termination (Gobello, 2006). Below follows a summary of three studies of bitches with pyometra treated with cabergoline.

In one of the studies, 22 bitches with pyometra were treated with 5,0 µg/kg cabergoline daily, 5,0 µg/kg cloprostenol on day 3, 6 and 9, and potentiated sulfonamide twice daily during the treatment period. Cabergoline was administered for 10 days in all bitches except in two that needed treatment until day 13, and one bitch that was treated until day 12 and then was subjected to OHE. The two bitches that were treated longer than 10 days also had an additional dose of cloprostenol on day 12. There were no side effects recorded after the cabergoline treatment, but after the first dose of cloprostenol all 22 bitches retched and vomited, 45 % (10/22) had abdominal straining, 18 % (4/22) had diarrhea and 73 % (16/22) started panting. After the second treatment 77 % (17/22) of the bitches showed signs of side effects, and after the third 41 % (9/22) showed signs of side effects. At the next estrus 11 bitches were mated and 64 % (7/11) of them produced litters. The recurrence rate of pyometra

was 18 % (4/22) during the luteal phase after the first estrus after treatment (England et al., 2007).

Cabergoline at a dose 5µg/kg and cloprostenol at a dose 1µg/kg once daily during 7 days in combination with antimicrobials were used in one study of 29 bitches with pyometra (n=14) or endometritis (n=15). For eight bitches it was necessary to continue the cloprostenol treatment until day 14. Treatment was successful in 69 % (20/29 bitches) by day 7, and 83 % (24/29) of the bitches as evaluated after 14 days. Side effects, diarrhea and vomiting, were observed in 31 % (9/29) of the bitches after cloprostenol treatment. Recurrence was observed in 25 % (6/24) of the bitches after the following estrus. Two bitches were mated after treatment and one of them conceived (Corrada et al., 2006).

In the earlier mentioned study by Jena et al. (2013) there were seven bitches that received treatment with a combination of cabergoline at the dose 5 µg/kg po once daily and cloprostenol at the dose 1 µg/kg sc once daily for seven days. All 7 bitches recovered and all of them came in estrus, and 5 subsequently conceived. The recurrence rate was 29 % (2/7 bitches). The side effects vomiting, panting, restlessness and hyperpnoea were observed in 29 to 43 % of the bitches (Jena et al., 2013).

The combination of cabergoline in combination with cloprostenol seems to be an effective treatment method as it has a good success rate.

1.4.6 Testosterone propionate

Treatment of pyometra with testosterone propionate is currently not used in Europe but is mentioned in this literature overview since it was previously used for this purpose.

In one study testosterone propionate was used to treat pyometra in ten bitches, at the dose 25 mg im twice every week, and in some cases combined with penicillin. Most bitches were treated for about three weeks and the success rate was 70 % (7/10 bitches). One bitch (14 %) had a recurrence at the next estrus (Spy, 1966).

2. MATERIAL AND METHODS

2.1 Animals

A retrospective study was performed at the Department of Clinical Sciences, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden, using data on bitches with pyometra or mucometra admitted to the University Animal Hospital (UDS), SLU, and that were medically treated with aglepristone (Alizin vet[®], Virbac, France) for a minimum of two consecutive days. Data were collected from all medically treated bitches (n=34) diagnosed with pyometra from the time when aglepristone (Alizin vet[®]) was registered for this purpose in Sweden (June 2004) until February 2013.

2.2 Data collection

The journal system of UDS (Trofast AB, Västerås, Sweden) was used to identify patients with the diagnostic codes “KA4121” (pyometra) (n= 32) and “KA4192” (mucometra) (n= 2) combined with aglepristone (Alizin vet, Virbac, Montpellier, France). One patient was excluded because it was destined for surgical treatment and only treated with aglepristone for one day when it was stabilized before surgery.

All owners were interviewed by phone by the author (LR) during September to October 2013 for retrieval of data on subsequent history, fertility and long-term outcome. For more specific information about breeding the Swedish Kennel Club (SKK) registry was used to obtain exact dates of parturition and number of registered puppies.

All data from the UDS journals, journal copies from other veterinary clinics, owner interviews and SKK data were inserted in an excel file (Microsoft Office, Redmond, USA). The data were then processed in excel and adapted to fit into tables (see Tables 1 to 9).

The first day a bitch was treated with aglepristone is in this study referred to as “day 1”. Any previous days are referred to as “day -1”, “day -2” and so on, i.e. there was no day 0.

2.3 Studied variables

Clinical signs data were based on what the owners had observed before and during the time of the first visit at the UDS. The clinical examination findings were based on the veterinarian’s physical examination on the same occasion. Blood samples were obtained from 23 of the 30 bitches between day -3 and 2, and in one of the bitches at day -10 as calculated from the start of aglepristone treatment (day 1). In 11 cases results from bacterial cultures of sterile cotton swab samples from the cranial vagina were available, as performed at the Section of Bacteriology, National Veterinary Institute (SVA), Uppsala, Sweden (9 cases); from Skövde Animal Clinic, Skövde, Sweden (1 case) and from Enköpings Animal Clinic, Enköping, Sweden (1 case). In 2 bitches bacterial culture results from urine samples were available, as performed at the National Veterinary Institute (SVA), Uppsala, Sweden and University Animal Hospital (UDS), Uppsala, Sweden.

Side effects noted were based on clinical signs observed at the UDS and information retrieved from the owners before and after treatment. In 2 cases *post mortem* reports were available (Department of Pathology, SLU), and in one case diagnosis was based on macroscopic and histological examination of the uterus and ovaries performed at the National Veterinary Institute, Uppsala, Sweden. Details of all the studied variables are illustrated in Table 3.

3 RESULTS

Thirty-four bitches were identified from the journal system as treated with aglepristone. Four of the bitches were treated with other hormonal drugs as well, and were excluded from the

study and their individual results described separately from the ones treated with only aglepristone.

The 30 bitches included in the study were of 26 different breeds (three German Shepherds, two long-haired Collies, two English Springer Spaniels, and one of the following Alaskan Malamute, Australian Cattle dog, Australian Shepherd, Bearded Collie, Boston Terrier, Dachshund, Doberman Pinscher, Drever, French Bulldog, Golden Retriever, Great Dane, Hovawart, Irish Terrier, Irish Wolfhound, Japanese Spitz, Neapolitan Mastiff, Perro de agua Espanol, Pug, Shiba Inu, Staffordshire Bullterrier, Standard Poodle and Yorkshire Terrier) and one bitch was of mixed breed. The age range was 11 months to 14 years when treatment started (mean \pm SD age $5,3 \pm 3,8$ years) and the weight range was 3 to 64 kg (mean weight 23 kg). The four bitches that had received other hormonal treatment as well were of the breeds Golden Retriever, Swedish Elkhound, Bearded Collie and Kerry Blue Terrier and they were between 1,7 to 4,1 years when treatment started.

The diagnose were based on history, clinical examination and laboratory findings. Abnormal vaginal discharge and a fluid-filled uterus identified by ultrasonography in all but four cases. Three bitches were initially examined by radiography, and ultrasonography performed 2 to 14 days into treatment. In one case the diagnosis was based merely on clinical signs and physical examination demonstrating purulent vaginal discharge and a moderately depressed general condition. This bitch was examined by ultrasonography 10 days after treatment was initiated.

Not all treatments were fully performed at UDS and data regarding aglepristone injections, laboratory analyses, ultrasonography, radiography, antimicrobial treatments and bacterial culturing were obtained from journal copies from other veterinary clinics. Similarly, information about any surgical treatment, previous uterine disease, recurrence of pyometra after treatment and pregnancies/whelping and number of puppies were as far as possible also obtained and verified through journal copies from other veterinary clinics after submission from the owners.

Six bitches could not be found in the SKK registry because of missing information. Of these bitches, five had never had puppies and one had just had one litter (subsequent caesarian section at UDS) according to their owners.

3.1 Treatment protocols

The bitches were treated with aglepristone (Alizin vet[®], Virbac, Montpellier, France) [30 mg/ml] at the dose 10 mg/kg sc. The treatment with aglepristone was combined with administration of antimicrobials, in all animals but one (bitch number 28). Information about the antimicrobial drugs administered during the study time is shown in Table 2. The duration of clinical signs before treatment was initiated varied between 1 and 49 days, but in 76 % (22/29 bitches) treatment had started within 7 days after clinical signs were first observed. In one bitch information was not available about duration of clinical signs prior to diagnosis. The number of aglepristone injections each bitch received was between one and five, and the median was four injections (in 12/28 bitches). The bitch that only had 1 injection had a

successful outcome, but of the 6 bitches that had 2 injections, 3 were admitted to surgery (OHE) ≤ 7 days after treatment was initiated and did not receive any injections after that. Data on the number of injections administered was missing in 2 bitches.

Table 2. Information about used antimicrobial drugs

Product name	Substance	Dose	Admi- nis- tration	Inter- vall
Baytril vet ^{1, 2, 3}	Enrofloxacin	5 mg/kg	sc	q24 h
Baytril vet ^{1, 2, 3}	Enrofloxacin	5 mg/kg	po	q24 h
Vetrimoxin vet ^{4, 5, 6}	Amoxicillin	10 mg/kg	po	q12 h
Bimoxyl vet ^{4, 7, 8}	Amoxicillin	15 mg/kg	sc	q24 h
Doktacillin ^{9, 10, 11}	Ampicillin	10-40 mg/kg	iv	q6-8 h
Synulox vet ^{12, 13, 14}	Amoxicillin/ Clavulanic acid	7 mg/kg resp 1,75 mg/kg	sc	
Marbocyl vet ^{15, 16, 6}	Marbofloxacin			
Ampivet vet ^{17, 2, 3}	Ampicillin	15-25 mg/kg	po	q6-12 h
Tribrissen vet ^{18, 19, 20}	Sulfadiazin, trimetoprim			
Bactrim forte ^{21, 22, 11}	Sulfametoxazol, trimetoprim			
Flagyl ^{23, 24, 11}	Metronidazol			
<i>1 Bayer Animal Health</i>	<i>9 Meda</i>			<i>17 Boehringer Ingelheim Vetmedica</i>
<i>2 Copenhagen</i>	<i>10 Solna</i>			<i>18 Intervet</i>
<i>3 Denmark</i>	<i>11 Sweden</i>			<i>19 Boxmeer</i>
<i>4 Ceva Animal Health</i>	<i>12 Orion Pharma Animal Health</i>			<i>20 Netherlands</i>
<i>5 Libourne Cedex</i>	<i>13 Helsinki</i>			<i>21 Roche</i>
<i>6 France</i>	<i>14 Finland</i>			<i>22 Stockholm</i>
<i>7 Dublin</i>	<i>15 Vetoquinol</i>			<i>23 Sanofi</i>
<i>8 Ireland</i>	<i>16 Lure</i>			<i>24 Bromma</i>

Other drugs given before or during treatment are listed in Table 3. Additionally, many bitches were sedated before ultrasound examination.

The four dogs that had had other hormonal treatments as well as treated with aglepristone were as follows: one bitch was treated with dinoprost at the dose 100 $\mu\text{g}/\text{kg}$ on day -6 from the start of aglepristone treatment, one bitch received dinoprost at the dose 26 $\mu\text{g}/\text{kg}$ on day 2, 3 and 4 after aglepristone treatment was initiated, one bitch received treatment with dinoprost at the dose 200 $\mu\text{g}/\text{kg}$ at day -3, -1 and 1, and the dose 68 $\mu\text{g}/\text{kg}$ every eight hour on day 2 to 4 and once on day 5, and one bitch was treated with oxytocin at the dose 2,6 μg iv once on day -8 and day -5, and twice day -7 and -6 from the start of the aglepristone treatment. From day -6 to -1 the bitch was also treated with oxytocin nose spray, 6,7 μg four times per day. There was also another dog that received other hormonal treatment besides aglepristone, and it is dog number 11, that had received treatment with cabergoline for pseudopregnancy day -2 and -1 and had at that time not showed any symptoms of pyometra yet.

Table 3. Other drugs given before or during treatment with aglepristone

Drug	Substance
Rimadyl vet ^{1, 2, 3}	Carprofen
Vetoryl ^{4, 5, 6}	Trilostane
Metacam för hund ^{7, 8, 9}	Meloxicam
Norocarp ^{10, 11, 12}	Carprofen
Previcox ^{13, 14, 15}	Firocoxib
Metadon Recip ^{16, 17, 18}	Methadone
Temgesic ^{19, 20, 6}	Buprenorfine
Prednisolon Pfizer ^{21, 22, 18}	Prednisolone
Medrol ^{21, 22, 18}	Metylprednisolone
Hipracin vet ^{23, 24, 18}	Synthetic oxytocin
Syntocinon ^{25, 26, 18}	Oxytocin
Dinolytic vet ^{1, 22, 18}	Dinoprost
Galastop vet ^{27, 28, 18}	Cabergoline

1 Orion Pharma Animal Health	15 France
2 Helsinki	16 Recip
3 Finland	17 Solna
4 Dechra Veterinary Products	18 Sweden
5 Staffordshire	19 RB Pharmaceuticals
6 Great Britain	20 Slough, Berkshire
7 Boehringer Ingelheim Vetmedica	21 Pfizer
8 Ingelheim/Rhein	22 Sollentuna
9 Germany	23 Nordvacc Läkemedel
10 N-vet	24 Hägersten
11 Newry	25 Swedish Orphan Biovitrum AB
12 Northern Ireland	26 Stockholm
13 Merial Norden	27 Ceva Animal Health
14 Lyon	28 Lund

3.2 Clinical signs

All bitches had vaginal discharge before treatment with aglepristone i.e. open cervix pyometra. Six bitches were still in oestrus when clinical signs of pyometra started, 8 were just after to four weeks after oestrus, 10 were 5 to 9 weeks after oestrus and 2 were more than 10 weeks after oestrus. Two bitches showed clinical signs of pyometra 7 weeks and 8 month after whelping, respectively. For two bitches information was not available for time since last oestrus. Six of the bitches had been mated before they developed clinical signs of pyometra. Of the four bitches that had had other hormonal treatment as well (and were excluded from the study), two had been mated before they developed clinical signs of pyometra.

The general condition was good in 67 % (20/30) of the bitches and in the remaining 33 % it was moderately depressed. According to the owners the general condition was good in 40,7 % (11/27), moderately depressed in 55,6 % (15/27) and severely depressed in 3,7 % (1/27) of the bitches. Inappetence was noted in 46 % (13/28) of the bitches, polyuria in 40 % (8/20), polydipsia in 30 % (8/27), vomiting in 25 % (6/24) and diarrhea in 17 % (4/24). At the first visit to UDS, 38 % (10/26) of the bitches had a body temperature of 39 °C or above, 50 %

(7/14) were dehydrated, 52 % (12/23) had abdominal pain and 7 % (2/27) had mildly hyperemic mucus membranes. WBC was over the reference range for healthy dogs in 33 % (7/21) of the bitches and neutrophils were increased or decreased in 52 % (11/21) of the tested bitches. For more details on clinical examination and laboratory variables see Table 4.

Table 4. Clinical information about the bitches when they were first presented at the clinic

ID	Age	Weight	Time since heat (weeks)	Inapp	PU	PD	Vomiting	Diarrhea	Gc	Gc owner	Temp	Deh.	Abd. pain	Muc.	WBC	Neutrophils
1	2,7	55,5	8	Yes	-	Yes	-	-	Moderate	Moderate	38,8	No ⁸	No ⁹	NAD	N	N
2	1	17,1	4	No	No	No	No	-	Good	-	38,8	No	No	NAD	H	S H
3	1,2	29,5	0	No	-	No	No	No	Good	Good	38	-	Yes	NAD	N	N
4	7,3	14,7	0	Yes	Yes	Yes	-	-	Moderate	Moderate	39,2	-	-	NAD	-	-
5	6,6	23,1	6 ¹	No	No	No	-	No	Good	Good	39,5	-	No	NAD	N	N
6	13,8	3,4	4	No	Yes	No	No	No	Good	Moderate	39,5	Yes	-	NAD	N	B H
7	14,1	8,5	8	Yes	Yes	Yes	Yes	No	Moderate	Serious	38,1	Yes	Yes	-	N	N
8	6,2	31,2	A.w ²	No	No	No	-	-	Good	Moderate	38,6	-	-	NAD	-	-
9	1,6	7,6	8	-	-	-	No	No	Good	Good	38,8	-	-	NAD	-	-
10	10,4	12,3	0	Yes	-	Yes	No	No	Good	Good	37,9	Yes	Yes	NAD	N	N
11	6,8	17,5	8	No	-	No	No	No	Moderate	Moderate	38,6	-	No	NAD	N	N
12	3,4	7,9	0	No	No	No	No	No	Good	Good	MD	-	-	-	-	-
13	1,4	22	7	Yes	No	No	No	No	Good	Good	39	-	No	NAD	-	-
14	4,8	20,4	0	Yes	-	No	Yes	No	Moderate	Moderate	39,5	- ⁸	Yes	NAD	H	H
15	4,7	44,3	0	No	No	No	No	No	Good	Moderate	38,6	No	Yes	Mildly hyperemic	N	N
16	3,1	18,2	2 ¹	Yes	-	No	No	Yes	Good	Moderate	40	Yes	No	NAD	H	H
17	4,9	26,5	6 ¹	Yes	No	No	Yes	No	Good	Good	38,7	-	No	NAD	H	S H
18	3,3	63,5	3,5	No	-	No	-	-	Moderate	Moderate	39	No	-	NAD	-	-
19	4,4	7,8	- ^{1,3}	Yes	-	No	No	No	Good	Moderate	37,5	Yes	No	NAD	N	H
20	3,8	22,8	1	-	-	No	Yes	Yes	Good	Moderate	39	-	No	NAD	H	H
21	1,2	10,6	8	Yes	Yes	Yes	No	No	Moderate	Moderate	-	-	Yes	NAD	H ¹⁰	H ¹⁰

ID	Age	Weight	Time since heat (weeks)	Inapp	PU	PD	Vomiting	Diarrhea	Gc	Gc owner	Temp	Deh.	Abd. pain	Muc.	WBC	Neutrophils
22	2,8	17,7	2 ¹	No	No	-	No	No	Good	-	38,3	No	No	NAD	-	-
23	2,3	30	31 ⁴	Yes	No	Yes	No	No	Moderate	Moderate	40	-	Yes	NAD	N	HB LS ¹¹
24	9,4	61	3,5	Yes	Yes	Yes	Yes	No	Moderate	Moderate	38,4	Yes	Yes	Mildly hyperemic	H	H
25	11,4	4,8	- ⁵	No	Yes	No	-	-	Good	Good	-	-	Yes	MD	-	-
26	10,3	24,8	12	Yes	Yes	Yes	No	Yes	Moderate	Moderate	-	Yes	Yes	NAD	N	N
27	2,9	12	A.w ⁶	No	Yes	No	No	Yes	Good	Good	38,3	-	Yes	NAD	N	N
28	0,9	28	8	No	No	No	No	No	Good	Good	<39	-	Yes	NAD	N	N
29	5	29	3,5 ¹	No	No	-	No	No	Good	Good	39,6	No	No	NAD	-	-
30	6,2	26	7	No	No	No	Yes ⁷	No	Good	-	38,1	No	-	NAD	N	B H

Age = years of age, Weight = kilograms, Time since heat = time since last heat until clinical signs (weeks), Inapp = inappetence, PU = Polyuria, PD = Polidipsia, Gc = general condition, Gc owner = general condition according to the owner, Temp = rectal temperature (°C), Deh. = dehydration, Abd pain = abdominal pain on palpation, Muc = Mucus membranes, 0 = still in heat, A.w. = after whelping, H = High, L = Low, N = Normal, - = Missing data, B = Band neutrophils, S = Segmented neutrophils, Yellow = the bitch has had another hormonal treatment as well

¹ mated

² 7 weeks since delivered a dead puppy

³ visiting the clinic for pregnancy check with ultrasound

⁴ should have been 7 weeks ago but the owner did not notice anything

⁵ owners never noticed her having estrus

⁶ caesariansection 8 month previously, should have been in heat 2 months ago

⁷ after Medrol treatment

⁸ but was dehydrated on day 2

⁹ but had abdominal pain day 2

¹⁰ blood sample taken 10 days before diagnosis, but was ill of unknown reason then

¹¹ Toxic neutrophils

3.3 Bacterial culturing and antimicrobial drugs

Bacterial culturing obtained from cranial vaginal swab at the start of aglepristone treatment (in two cases 11 and 21 days, respectively, before aglepristone treatment started) was available in 11 bitches, and from urinary samples in 2 bitches (in one case 18 days before aglepristone treatment begun). The culture results are shown in Table 5 together with the antimicrobial resistance. In one bitch with *Escherichia coli* the results from resistance was not available and is therefore not presented in the tables. The bacteria found in 13 tested bitches were *Escherichia coli* (n=6), *Staphylococcus intermedius* (n=2), β -hemolytic *Streptococcus* (n=2), *Pseudomonas aeruginosa* (n=1) and *Escherichia fergusonii* (n=1). In 3 bitches the results were negative and two different bacteria were found in 2 bitches. Of the 3 bitches with negative cultures, 2 had already started treatment with antimicrobial drugs before the sample was taken (1 respective 15 days earlier), which may have affected the bacterial growth. Complete bacterial antimicrobial resistance pattern are shown in Table 6. In Table 7 the same information as in Table 6 are listed but only for cultures of *E.coli*.

Table 5. Bacteria cultured and their resistance to antimicrobial drugs listed. S=sensitive, I= intermediate sensitivity, R= resistant

Antimicrobial drug	Ec	Ec	Ec	Ec	Ef ¹	Ec ¹	Si ²	Si	S	S ³	P ³
Penicillin	R	R	R	R	R	R	R	R	S	S	R
Ampicillin	R	S	I	S	S	S	R	R	S	S	R
Cefalotin	R	R	-	R	I	I	S	S	S	S	R
Amoxicillin/Klavulansyra	R	S	I	S	S	S	S	S	S	S	R
Oxacillin	R	R	-	R	R	R	S	S	S	S	R
Fusidinsyra	R	-	-	R	R	R	S	S	R	R	R
Klindamycin	R	R	R	R	R	R	S	S	S	S	R
Nitrofurantoin	S	S	S	S	S	S	S	S	S	S	R
Polymyxin B	S	-	-	S	-	-	-	-	R	-	-
Erytromycin	R	R	-	R	R	R	S	S	S	S	R
Gentamicin	S	S	S	S	S	S	S	S	S	I	S
Trimetoprim/sulfa	S	I	S	S	S	S	S	I	S	S	R
Tetracyklin	I	I	-	I	I	S	R	S	R	S	R
Enrofloxacin	S	S	S	S	S	S	S	S	I	I	I
Streptomycin	-	S	-	-	S	S	S	S	-	I	R
Mecillinam	-	-	S	-	-	-	-	-	-	-	-
Cefalexin	-	-	I	-	-	-	-	-	-	-	-

Ec = *Escherichia coli*, Ef = *Escherichia fergusonii*, Si = *Staphylococcus intermedius*, S = β -hemolytic *Streptococcus sp*, P = *Pseudomonas aeruginosa*, - = Missing data

¹ The isolated bacteria came from the same bitch

² Culture from urinary sample

³ The isolated bacteria came from the same bitch

Table 6. Total resistance of cultured bacteria

Antimicrobial drugs	Resistant %	Sensitive %	Intermediate %	Number of animals
Penicillin	82	18	0	11
Ampicillin	36	55	9	11
Cefalotin	40	40	20	10
Amoxicillin/Clavulanic acid	18	73	9	11
Oxacillin	60	40	0	10
Fusidinsyra	78	22	0	9
Klindamycin	64	36	0	11
Nitrofurantoin	9	91	0	11
Polymyxin B	33	67	0	3
Erytromycin	60	40	0	10
Gentamicin	0	91	9	11
Trimetoprim/sulfa	9	73	18	11
Tetracyklin	30	30	40	10
Enrofloxacin	0	73	27	11
Streptomycin	14	71	14	7

Table 7. Antimicrobial resistance of 5 *Escherichia coli* isolates from 5 bitches with pyometra to commonly prescribed drugs

Antimicrobial drugs	Resistant %	Sensitive %	Intermediate %	Number of animals
Penicillin	100	0	0	5
Ampicillin	20	60	20	5
Cefalotin	75	0	25	4
Amoxicillin/Clavulanic acid	20	60	20	5
Oxacillin	100	0	0	4
Klindamycin	100	0	0	5
Erytromycin	100	0	0	4
Trimetoprim/sulfa	0	80	20	5
Tetracyklin	0	25	75	4
Enrofloxacin	0	100	0	5

The antimicrobial drugs that were used in each bitch, and information about cultured bacteria, are listed in Table 8. The time of use of antimicrobial drugs was up to 53 days, with a mean duration of treatment of 22 days. Eleven of the bitches had also received antimicrobial drugs 1 to 30 days before aglepristone treatment started. The most frequently used antimicrobial drug was enrofloxacin (n=24).

Table 8. Treatment and outcome

ID	Age	Days with clinical signs before treatment	Number of treatments with aglepristone (on day)	Antimicrobial drugs used	Duration of antimicrobial treatment (days)	Successful treatment	Recurrence	Time before recurrence	Follow-up time	At the end of the follow-up time
1	2,7	1	2 (day 1,2)	E	7	No	-		6 d	OHE
2	1	13	5 (day 1,2,8,15,27)	Amo, T	40	Yes	Yes	1st 4, 2nd 17	2 y	Intact
3	1,2	1	4 (day 1,2,7,14)	Amp, E	21	Yes	No		1 y, 6,5 m	Intact
4	7,3	2	2 (day 1,2)	E	13	No	-		12 d	OHE
5	6,6	3	4 (day 1,2, 10, 17)	Amo	8	Yes	Yes	1st 11, 2nd 18	1 y, 7 m	OHE
6	13,8	2	4(day 1, 2,8,16)	E	22	Yes	Yes	16	1 y, 4 m	Dead ⁷
7	14,1	24	4 (day 1,2,9,16)	T	20	No	-		23 d	Dead ⁸
8	6,2	49	3 (day 1, 2, 9)	E, Amo	22	Yes	No		3 y, 8 m	Intact
9	1,6	21	4 (day 1, 2,MD, 16)	E	22	Yes	No		6 y	Intact
10	10,4	<7	4 (day 1,2, 9, 16)	Amp, E	18-21	Yes	Yes	9,5	9,5 m	Dead ⁹
11	6,8	1	4 (day 1, 2, 9, 18)	Amo	10 ²	No	-		1 m	OHE
12	3,4	1	3 (day 1, 2, 8)	E	20	Yes	Yes	21	1 y, 10 m	OHE
13	1,4	1	5 (day 1, 2, 9, 16, 23)	E	30	Yes	No		6 y	Intact
14	4,8	<7	3 (day 1, 2, 9)	E	23	Yes	Yes	1st MD, 2nd 72	6 y	Dead ¹⁰
15	4,7	2	4 (day 1, 2, 8,15)	E	21	Yes	No		2 m	Dead ¹¹
16	3,1	1	2 (day 1,2)	E	8	No	-		1 w	OHE
17	4,9	None ¹	MD (day 1,2, MD)	E, M	15 ³	Yes	Yes	17,5	1 y, 6 m	OHE
18	3,3	2,5	3 (day 1,2, 12)	E, Amo	33	Yes	No		3 y, 3 m to 4 y, 3 m ⁶	Dead ¹¹
19	4,4	14 ¹	3 (day 1,2 and 8)	E	22	Yes	No		3 y, 1 m to 5 y, 1 m ⁶	Dead ¹¹

ID	Age	Days with clinical signs before treatment	Number of treatments with aglepristone (on day)	Antimicrobial drugs used	Duration of antimicrobial treatment (days)	Successful treatment	Recurrence	Time before recurrence	Follow-up time	At the end of the follow-up time
20	3,8	1	2 (day 1,2)	Amo	4	No	-		4 d	OHE
21	1,2	<7	4 (day 1,2,9,20)	E	36	Yes	No		4 y, 6,5 m	Intact
22	2,8	10	5 (day 1,2,8,15,28)	E	33	Yes	No		2 y, 7,5 m	Intact
23	2,3	<7	4 (day 1,2,8, 15)	E	29	Yes	No		4 y, 7,5 m	Intact
24	9,4	7	4 (day 1,2,10,23)	E	36	Yes	Yes	4	5 m	Dead ¹²
25	11,4	7	MD (day 1,2, MD)	E	11 ³	Yes	Yes	9	11 m	Dead ¹³
26	10,3	7	4 (day 1,2,8, 15)	E	21	Yes	Yes	3	4 m	OHE
27	2,9	7	2 (day 1,2)	E	23 ⁴	Yes	No		5 m	Dead ¹¹
28	0,9	2	1	None	0	Yes	No		3 y, 9,5 m	Intact
29	5	1	2 (day 1.2)	E, T	33 ⁵	Yes	No		1 y	OHE
30	6,2	18	3 (day 1, 2,8)	Amo, E	53	No	-		<2 m	OHE

MD = Missing data, E = Enrofloxacin, Amo = Amoxicillin, Amp = Ampicillin, T = Trimsulfa, M = Marbofloxacin, d = days, m = months, y = years

¹ Not so many clinical signs, had UL for pregnancy control and then saw the fluid filled uterus

² Treatment with antimicrobial drugs started 18 days after aglepristone treatment because of mastitis. During the month before the pyometra the bitch had been treated with antimicrobial drugs for about three weeks.

³ MD on exact time of treatment

⁴ Treatment with metronidazol is mentioned once in the journal but not dose or time

⁵ Was first treated with antimicrobial drugs for 21 days, then had a bacterial culture and after 13 days started treatment with the other antimicrobial drug mentioned for 12 days.

⁶ The owner was not sure of the time, this is the possible time

⁷ Did not respond to treatment, also had other diseases, was euthanized

⁸ Did not respond to treatment, was euthanized

⁹ Recurrence with severely affected general condition, not a good candidate for surgery, was euthanized

¹⁰ Euthanized because of having a 2nd recurrence

¹¹ Euthanized because of other disease

¹² MD about the reason

¹³ Recurrence that did not respond to treatment with Cabergoline, was euthanized

3.4 Outcome

In 77 % (23/30) of the bitches treated with aglepristone, treatment was successful, defined as return to a clinical healthy status. The seven bitches that did not have a successful outcome were ovariohysterectomized in all cases but one (a bitch that was 14 years old and was euthanized instead). Recurrence was observed in 43 % (10/23) of the bitches. The first recurrence after treatment occurred from 3 to 21 months (in average 11 months) after the treatment. In one bitch information was not available about the exact time of recurrence. A second recurrence was observed in 3 bitches 17 to 72 month after the first pyometra, all the other 7 bitches that had had a recurrence had either had OHE or was euthanized ≤ 2 month because of the recurrence or other reasons. The possible follow up time for the bitches was between 3 days and 6 years. At the end of the study period 11 of the 30 bitches had been ovariohysterectomized, 9 bitches remained intact and 10 had died. More details about the outcome are illustrated in Table 8.

If the bitches were divided into two age groups as in the study by Jurka et al. (2010) the success rate was 84 % in the group that was ≤ 5 years (16/19) and 64 % (7/11) in bitches >5 years. In the younger group the recurrence rate was 25 % (4/16) compared to 86 % (6/7) in the older age group.

Twenty bitches had their ovaries evaluated by ultrasonography between day -10 and 16. A comparison was made between two groups; one with ovarian cysts and one without, to see if the success of the treatment differed and if the recurrence was different in the two groups. Bitches evaluated as possible having cysts were included in the group with cysts. In the group with cysts 70 % (7/10) of the bitches had a successful treatment compared to the group without cysts that had a success rate of 100 % (10/10). The recurrence rate was 43 % (3/7) in the bitches with ovarian cysts, and 50 % (5/10) in the other group.

3.5 Puppies and mating

Before having the pyometra, 23 % (7/30) of the bitches had produced at least one litter. Two of the bitches had produced two litters and three bitches had had caesarian section. Eight bitches had been mated without getting pregnant at some point before the pyometra and six of these had been mated just before pyometra developed. Of the bitches that did not conceive after mating two had produced litters earlier and data about conceiving was not available in one of these bitches. After treatment 71 % (10/14) of the mated bitches produced puppies. Five produced 1 litter, four produced 2 litters and one produced 4 litters. See Table 9 for more details.

Table 9. Information about mating and puppies after the pyometra

ID	Mated and empty	Litter number, number of puppies (number of dead puppies)
2	Yes 2 times	None
8	No	3rd: 1 puppy (2 dead)
9	MD	1st: 4 puppies (1 dead), 2nd: 3 puppies, 3rd: 3 puppies (and 1 malformed), 4th: 2 puppies
12	No	2nd: 2 puppies, 3rd (1 dead, 1 malformed, 1 that died after 24 hours, 1 that died after 5 days)
13	No	1st: 9 puppies, 2nd: 4 puppies
14	Yes several times	No
17	Yes 2 times	No
18	Yes 2 times	No
19	No	2nd: 5 puppies, 3rd: 4 puppies (1 dead)
21	No	1st: 6 puppies
22	No	1st: 5 puppies, 2nd: 6 puppies
23	No	1st 8 puppies
27	No	2nd: 4 puppies, had caesarian section (the 1st time she also had caesarian section)
29	No	1st: 4 puppies

3.6 History

The owners were asked if they had observed any problems with vaginal discharge or pyometra before the initial visit to UDS - and all but one responded that they had not, though according to the journal and journal copies at least three of them had been searching veterinary care for vaginal discharge previous to the visit.

3.7 Findings during ovariohysterectomy

The findings during OHE or *post mortem* are listed in detail in Table 10. Of the 11 bitches that had OHE and information available, pathological findings were observed in 10 of the uteruses.

Table 10. Findings during Ovariohysterectomy (OHE) or post mortem exam

ID (no)	Time since Day 1	Recurrence before OHE	Findings
1	6 days	-	Uterus \approx 2 cm diameter, pyometra
4	12 days	-	Large uterus (1,4 kg), 3-8 cm diameter
5	1 year and 7 month	Yes	Uterus 1- 2 cm diameter, hard and pus-filled, pyometra
11	1 month	-	Uterus \approx 1,5 - 2 cm diameter pus-filled, pyometra
12	1 year and 10 month	Yes	Cysts in ovaries and uterus, 0,2 -2 cm diameter, uterus 2 cm in diameter, lumen coated with white/yellow discharge and blood clot
15	2 month	No	Post mortem ¹ : Uterus NAD macroscopically
16	1 week	-	Uterus 2 - 3 cm diameter, lumpy, normal color
17	1 year and 6 month	Yes	Large uterus, pyometra
20	4 days	-	Pyometra
26	4 month	Yes	A pus-filled ampulla in corpus uteri. PAD: pyometra and likely adenomyosis
27	5 month	No	Post mortem ¹ : 4 weeks <i>post partum</i> , fresh scaring from four puppies, one small thickening. Histological: ovaries NAD, several follicles and corpora lutea
29	1 year	No	Normal uterus 2 weeks after oestrus
30	<2 month	-	Uterus normal size, contains no fluid, CEH

Day 1 = The first day of aglepristone treatment, PAD = Pathological anatomical diagnosis, NAD = Nothing Abnormal Detected, CEH = Cystic endometrial hyperplasia

¹ Was euthanized for other reasons than pyometra

3.8 Side effects

Side effects after aglepristone administration were anxiety (3/28 bitches), loss of appetite (2/28 bitches), vomiting (1/28 bitches) and skin necrosis or reaction (1/28 bitches). The three anxious bitches also showed one or more of the following side effects panting (n = 2), diarrhea (n = 2), abdominal cramps (n = 1) or polydipsia (n = 1). Data were missing in two cases. Twenty-three of the owners could not recall any side effects from the treatment, though in three of these patients side effects were noted in the journals, and are included in the results.

3.9 Other diseases

Previous diseases that were recorded were urinary tract infection (4 bitches), urinary calculi (2 bitches), skin problems (2 bitches), Cushing's disease (1 bitch), Addison's disease (1 bitch), hypothyroidism (1 bitch), mammary tumors (1 bitch) and sensitive stomach (1 bitch).

Diseases that were recorded before, during or after treatment were ortopedical/neurological or motional other diseases (9 bitches), pseudo pregnancy (5 bitches), otitis (2 bitches), heart

murmurs (2 bitches), cataract (2 bitches), keratoconjunctivitis sicca (2 bitches), conjunctivitis (1 bitch) and tumors (1 bitch).

Diseases that developed after treatment were symmetrical lupoid onychodystrofi (SLO) (1 bitch), ventricular torsion (1 bitch) and chronic renal insufficiency (1 bitch). Information about later developed diseases was not available in one case. Some of the bitches are included in several of the above mentioned categories (had several concurrent problems).

3.10 The four excluded bitches

The results for the four bitches that were excluded from the study because of additional hormonal treatment are presented in the following text. One bitch had been treated with antimicrobial drugs three times for vaginal discharge the last year before being treated with aglepristone and other hormones at the UDS. The antimicrobial drug treatment varied from 2 to 43 days, and the number of aglepristone injections each bitch got were between 2 to 5. The treatment was successful in 2/4 bitches and recurrence were observed in 1/2 bitches. The two successfully treated bitches were mated and had 3 and 4 litters, respectively. Side effects observed were skin reactions (2/4) and after dinoprost administration one bitch vomited once. Of the four bitches that received other hormonal treatment as well no other diseases were recorded other than that one bitch later developed SLO.

4 DISCUSSION

The overall success rate of medical treatment with aglepristone for pyometra was 77 % (23/30 bitches) defined as clinically healthy status of the bitch. This proportion is somewhat lower than was reported in three other studies of medical treatment with aglepristone. In these studies the success rates were 92 %, 83 % and 100 %, respectively (Trasch et al., 2003, Metcalfe and Vischer, 2006, Jurka et al., 2010). The present success rate was, however higher than one report of 60 % (Fieni, 2006). These differences in success rates could perhaps be explained by different selection of candidates for medical treatment, due to traditions and routines in different countries where the studies were performed. Additionally, the individual patients selected could have influenced the results, i.e. minor studies may have false low recurrence rates because of few studied bitches. Some of the bitches in our study had shown clinical signs for quite a while before treatment with aglepristone was initiated, which may have influenced the outcome in a negative way rather than if treatment had been started earlier in the development of the disease. Early treatment is expected to give better result as the uterus has been exposed to infection for a shorter time and generalized inflammation or sepsis less likely to affect the bitch systemically and with complications more likely to occur. It is also possible that antimicrobial resistance could be the cause of treatment failure in some of the bitches. The results from bacterial culturing (9 bitches) showed that one bitch had *Escherichia coli* resistant to amoxicillin, which was the antimicrobial drug initially chosen for treatment but the drug was changed to trimethoprim-sulpha after the antimicrobial resistance test results were available. One bitch from which both *Streptococcus* and *Pseudomonas* were

isolated was initially treated with enrofloxacin and the bacterial antimicrobial resistance test showed that the bacteria were only intermediate sensitive for this drug. The antimicrobial treatment was therefore complemented with amoxicillin that the *Streptococcus* was sensitive to but the *Pseudomonas* was resistant to. One bitch was treated with enrofloxacin and the antimicrobial resistance examination showed that the bacterial isolate was intermediate sensitive for this drug, but sensitive to amoxicillin and the antimicrobial drug treatment was therefore changed to amoxicillin. These findings show that bacterial culturing is of importance when choosing the optimal antimicrobial drug for medical treatment of pyometra.

When only the bitches with ultrasonographically evaluated ovaries and uteri were compared, the 10 bitches without ovarian cysts had a 100 % success rate compared to the 10 bitches with ovarian cysts that had the success rate 70%. The recurrence rate was 43 % in bitches with cysts compared to 50 % in bitches without cysts. The presence of hormone producing ovarian cysts could have affected the outcome in a negative way because during metoestrus the progesterone is often high and with a cyst that produces estrogen the uterus is exposed to both progesterone and estrogen which may induce pyometra. The treatment outcome with consideration to presence of ovarian cysts or not on ultrasonography has not been evaluated in studies of medically treated bitches with pyometra before.

In bitches younger than five years of age, the success rate here was 84 % (16/19) whereas it was lower (64 %, 7/11) in bitches over five years of age. A success rate of 84 % is comparable to the 92 % success rate in the long-term study by Träsch et al. (2003), though one study showed no difference in short term results in younger and older dogs (Jurka et al., 2010). All treated bitches in this study had an open pyometra (vaginal discharge present), but this did not improve the treatment result in studies treating both opened and closed pyometra (Jurka et al., 2010, Breitkopf et al., 1997) except in one study (Metcalf and Vischer, 2006) where a higher success rate in bitches with open (85 %) compared to closed (75 %) pyometra was shown.

The recurrence rate in this study was 43 %, with a follow-up time up to 6 years. In another long-term study the recurrence rate was reported to be 27 % within one year after treatment (Träsch et al., 2003). In that study the mean age of included bitches was 6,9 years (compared to 5,3 years in the present study) so the “better” outcome in that study cannot be explained by including more bitches of a younger age. In another study the recurrence rate was 30 % in bitches older than five years as evaluated by the following estrus and there was no recurrence in bitches that were five years or younger at the start of treatment (Jurka et al., 2010). The relatively higher recurrence rate in the present study could be due to the longer follow up time (up to 6 years as compared to one year or the next estrus, respectively) (Träsch et al., 2003, Jurka et al., 2010). Especially as the mean time for recurrence in this study was after 11 month and therefore it can be assumed that more bitches would have had a recurrence recorded if they had been followed up for a longer period of time also in the other studies. If the bitches were divided into two groups depending on their age, bitches younger than five years had a recurrence rate of 25 % compared to 86 % in bitches older than 5 years. Because the long-term outcome of medical treatment for pyometra varies greatly depending on the age of the bitch, owners should be informed of the recurrence risk as high as 86% in bitches older

than five years since these results differ from what has previously been reported. As for comparisons between different drugs for medical treatment for pyometra, prostaglandin treatment recurrence has been reported to be 15 % at the following estrus (Nelson et al., 1982), 40 % during the first year after treatment and for bitches followed more than one year it was 77 % (Meyers-Wallen et al., 1986), 10 % (Gilbert et al., 1989), 86 % (Jena et al., 2013), 0 % (Arnold et al., 1988) and 0 % (Gabor et al., 1999), respectively. The follow up times in these studies varied from by following estrus to up to five years after treatment, and most of them had a shorter follow up time than one year. The recurrence rate in this study of 43 % gives a more true estimate of the actual recurrence rate since it is based on a long-term evaluation of the outcome.

In three bitches a second recurrence was observed 18 to 72 months after the first pyometra treatment. All the other 7 bitches that had had a recurrence either were ovariohysterectomized or euthanized within 2 months because of the recurrence or for other reasons. The prognosis for repeated medical treatment of recurring pyometra was thus poor as the disease recurred again in all of the three bitches that were medically treated for a recurring pyometra. Though based on very few bitches, these results indicate that medical treatment of a recurring pyometra is associated with a poor prognosis.

Some of the bitches (n = 6) in this study had been mated before developing pyometra. This could possibly be because many of the bitches selected for medical treatment were destined for breeding. It is less likely that mating can cause pyometra in a healthy uterus since experimental attempts to induce the disease by inserting bacteria in the uterus during estrus have failed (Nomura et al., 1988).

In studies where a combination of aglepristone and cloprostenol was used for medical treatment of pyometra, the success rates were reported to be 84 % (27/32) (Fieni, 2006) and 100 % (15/15) (Gobello et al., 2003), respectively. These success rates are higher than in the present study but comparable with the results of some other studies (83-100%) where only aglepristone was used (Trasch et al., 2003, Metcalfe and Vischer, 2006, Jurka et al., 2010), the numbers of bitches included in the studies were from 24 to 52. A low number of bitches in a study can give a false high or low results depending on the individuals selected to the study, as one single bitch makes a big difference in percentage. Treatments combining cabergoline and cloprostenol have had a success rate of 83 % (Corrada et al., 2006) which is also comparable to the aglepristone treatment results mentioned above, but side effects were seen in 31 % of the bitches.

Treatment with $\text{PGF}_{2\alpha}$ has showed a success rate of 76 % (Nelson et al., 1982), 100 % (Meyers-Wallen et al., 1986) and 87 % (Gilbert et al., 1989). Though the side effects reported are more frequently observed and more severe (Burke, 1982, Nelson et al., 1982, Meyers-Wallen et al., 1986, Jena et al., 2013) than those reported for aglepristone (Blendinger et al., 1997, Breitkopf et al., 1997). When $\text{PGF}_{2\alpha}$ was administrated intravaginally in one study (Gabor et al., 1999) the success rate was 88 %, which is comparative to after iv administrated $\text{PGF}_{2\alpha}$ with the difference that there were no side effects observed in the study were $\text{PGF}_{2\alpha}$ was administered intravaginally. Because the success rate does not differ very much, but the side effects are more frequent and severe for $\text{PGF}_{2\alpha}$ treatment than for aglepristone (Nelson et

al., 1982), the author hereby states that aglepristone treatment is a better choice. Lower doses of cloprostenol has been used for treatment of pyometra with good result (Khan et al., 2007) and could maybe be a good option in countries where aglepristone is not available.

In this study 71 % (10/14) of the bitches became pregnant and whelped after treatment compared to 57 % (8/14) bitches less than five years old and none (0 %) of 9 bitches over five years of age in another pyometra study (Jurka et al., 2010). Our results can also be compared to other studies in which bitches treated with prostaglandin conceived in 5/9 (56 %) of the cases (Burke, 1982), 9/11 (82 %) (Nelson et al., 1982), 9/14 (64 %) (Gilbert et al., 1989) and 5/5 (100 %) of the treated cases (Arnold et al., 1988). In one study of bitches treated with cabergoline in combination with cloprostenol puppies were produced in 7/11 of mated bitches (64 %) (England et al., 2007). Compared to the results in those studies the results after mating are good in this study.

There were only two bitches here that were five-years or more when treatment begun and later were mated, therefore it is no comparison done between bitches older or younger than five years.

The mean duration of antimicrobial treatment was 22 days in the present study, which is longer than in some other studies (7 days and in some cases 5 days, respectively) (Jurka et al., 2010, Fieni, 2006). The maximum or mean duration was not defined in some studies which makes it difficult to compare different antimicrobial drug treatment periods in relation to outcome between different studies (Metcalf and Vischer, 2006, Träsch et al., 2003). This raises the question if antimicrobials are not an important part in treating pyometra medically, or whether antimicrobials are merely important for prevention of the infection progressing to sepsis? It might be possible that the progesterone antagonist is most important to cure the disease, and that antimicrobial therapy could perhaps be limited to fewer days than currently recommended? The optimal duration of antimicrobial therapy should be studied further considering the risk of antimicrobial resistance and that one of the bitches in the present study were treated for up to 53 days.

The overall antimicrobial resistance demonstrated in the present study is lower than in isolates found in another study from bitches with pyometra (Bassessar et al., 2009). The difference could be partly because of different bacteria isolated, and partly because of different methods were used for evaluating antimicrobial resistance, and that the isolates were only judged sensitive or resistant and not intermediate in the other study.

The *E.coli* that was isolated in this study had a resistance that was comparable with isolates in another study (Hagman and Greko, 2005) of *E. coli* strains isolated from uteri from 80 bitches with pyometra. The proportion of *E. coli* strains resistant to different antimicrobial drugs in that study was ampicillin 10 %, streptomycin 5 %, tetracycline 4 % and enrofloxacin 4 % compared to in this study 20 %, 0 %, 0 % and 0 %, respectively.

The most frequently used antimicrobial drug here was enrofloxacin. From the 1st of January 2013, in Sweden, all antimicrobials containing quinolones (such as enrofloxacin) are only allowed to be used if no other antimicrobials have effect, the condition is life-threatening or if

the disease or infection site makes testing for resistance impossible. The choice of antimicrobial must also be motivated in the journal and be strengthened by science and experience (SJVFS 2012:32, saknummer D9, § 8). Therefore veterinarians in Sweden will have to use other antimicrobial drugs instead of enrofloxacin in the future. The resistance to enrofloxacin in this study was 0 % even though it was most frequently used. Trimetoprim/sulfa could be a good option in the future as the resistance was 0 % in *E.coli*.

Because this study was retrospective, there are some limitations such as some information being forgotten by the owners, as illustrated with the information about previous problems with vaginal discharge or pyometra which were recorded in the journals but the owners failed to remember. When the information from the owners differed from that in the journals, the information in the journal was considered being most correct to avoid this loss of memory bias, since the journal data was recorded in real-time during the visit at the UDS.

One interesting finding was that one of the bitches (Standard poodle) (and one of the four excluded bitches that were treated with other hormones as well, a Kerry Blue Terrier) later in life developed SLO (after 5,5 years and <4 years), which is not a very common disease. There is no logical explanation for a connection between pyometra and SLO, other than both diseases involving an inflammatory response. It could be a coincidence or perhaps some weakness in the immune system that pre-disposes for both these diseases. No other reports of the relation between SLO and pyometra are currently published.

One factor that makes it more difficult to compare the different studies of medical treatment of pyometra are the different definitions of success used, and how to determine what is actually a favorable outcome. Is it a high recovery rate? As seemed by return to clinical healthy status or the ability to produce puppies? Or is it the absence of recurrence? In the present study the definition of successful treatment was a healthy status after treatment because this is sometimes the only goal when selecting medical treatment and it is a necessity for breeding the bitch again.

If the owner wants to breed the bitch or surgery or anesthetics wants to be avoided in a bitch less than five years old with pyometra, treatment with aglepristone can be a good option since it was here reported to be successful in 23 of 30 bitches treated. If the bitch is five years or older the chance for a successful treatment is lower and the risk for recurrence higher. Based on the high risk of recurrence (in all of three previously treated bitches), further treatment with aglepristone at a recurrence of pyometra is not recommended.

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