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Medical Treatment for Pyometra in Dogs

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Contents
Pyometra is a reproductive disorder very common in bitches over 8 years of age in which physiological effects of progesterone on the uterus play a major role. The traditional therapy for pyometra is ovariohysterectomy. The main advantage of ovariohysterectomy over medical management is that it is both curative and preventive for recurrence of pyometra. However, surgery is associated with the risk of anaesthesia and renders the bitch sterile. During the last 10 years, numerous medical treatments have been proposed to treat both open and closed cervix pyometra. The most effective medical treatment with minor side effects seems to be the repeated administration of aglepristone with or without the additional treatment with low doses of prostaglandins.

Introduction

Pyometra or chronic purulent endometritis is a common, metoestral disease mainly affecting bitches over 8 years of age (Chaistain et al. 1999; Egenvall et al. 2001). The disease generally occurs following oestrus and generally during the luteal phase, (Blendinger et al. 1997). The pathogenesis of pyometra is only partly understood, but it's generally acknowledged that primary hormonal imbalance or abnormal response to normal concentrations of oestrogens, and progesterone affects the epithelial cells of the uterus and facilitates bacterial adherence, colonisation and growth (Noakes et al. 2001; Hagman and Kühn 2002). Oestrogens increase the uterine cell growth and the endometrial vascularization. They increase the uterine sensibility and reaction to progesterone. Progesterone results in endometrial proliferation and uterine glandular secretion, decreased myometrial contraction and induces closure of the cervix (Borresen 1975; Smith 2006). Common bacteria found in the uteri of healthy bitches reflect the bacterial flora of the vagina and cervix. *Escherichia coli* is the pathogen most commonly isolated from bitches with pyometra (Chen et al. 2003; Hagman and Kühn 2002; Hagman et al. 2006).

The uterine response to the presence of bacteria is largely based on innate immunity. Conserved pathogen-associated molecular patterns (PAMPs) synthesized by microorganisms, such as lipopolysaccharide (LPS) for gram-negative bacteria, are recognized by germline-encoded pattern recognition receptors, toll-like receptors (TLRs), which initiate the non-specific immune response with recruitment of inflammatory cells, including neutrophil granulocytes (Horne et al. 2008).

The increase in progesterone concentrations during oestrus in the bitch may result in a less efficient non-specific immunity, decreasing the expression of TLR during oestrus and early dioestrus, and allowing the embryo implantation and development (Silva et al. 2012). The concomitant presence of bacteria such as *Escherichia coli* during these phases may induce the development of an infection. The bacteria adhere to the endometrium and stimulate the immune response. The expression of TLR2 and TLR4 receptors is increased (Silva et al. 2010), which stimulates the secretion of cytokines, cyclooxygenase-2 (COX-2) and prostaglandin E2 and F2α (Silva et al. 2012), causing local inflammatory response.

For metritis, the cervix is open and the inflammation moderate. The uterine horns are narrow in diameter and the lumen cannot be distinguished on ultrasound. In cases of open pyometra, the cervix is more or less open and the inflammation significant; the uterine horns are distended with purulent fluid, resulting in significant vulvar discharge.Vulvar discharge may be mucoid, purulent, sanguinopurulent or haemorrhage.

In some cases, the cervix remains closed (closed pyometra). There is no vulvar discharge, but the accumulation of purulent fluid distends the lumen of the uterus, and in late evolution, the endometrium is generally atrophied.

Pyometra is a medical emergency that requires rapid intervention to prevent overwhelming sepsis. Without treatment, the infection is fatal.

Indications for Medical Treatment

The traditional therapy for pyometra is surgical ovariohysterectomy which immediately removes the purulent contents of the uterus and suppresses the release of endotoxins. Drawbacks with surgery are the risk with anaesthesia and that it renders the bitch sterile.

Medical treatment may be indicated for:

- Breeding bitches,
- Bitches in very poor condition or old bitches, normothermic, in whom anaesthesia would be dangerous
- Cases where the owners want to keep costs at a minimum,
- To improve the general status of the bitch prior to surgery.

Medical treatment is contraindicated for pyretic or hypothermic bitches with suspected peritonitis.

The efficacy of medical treatment depends on the clinical presentation: metritis, open pyometra or closed pyometra and on the presence or absence of ovarian cysts.

General Treatment

The following general principles apply, irrespective of the chosen specific medical treatment:

- Use of an Elizabethan collar to prevent the ingestion of vulvar discharge,
- Antibiotic coverage with not nephrotoxic agents (e.g. amoxicillin-clavulanic acid 25 mg/kg/day) to prevent septicaemia for bitch in bad general health or for those close monitoring is not possible.
- Fluid therapy (60 ml/kg + % dehydration x body weight/100) to correct dehydration and treat toxic shock.

Table 1. Clinical treatment protocols for the treatment of open pyometra with prostaglandins

Specific	Complementary
Dosage	Antibiotics
PGF2α natural: 0.25 mg/kg	Association of sulfadoxine and trimethoprim:
Cloprostenol : 10 μg/kg	Borgal 7.5%® 30 mg/kg subcutaneously
Duration	Association amoxicillin and clavulanic acid:
Daily administration for 5–7 days	Synulox® 12.5 mg/kg twice daily per os
Check between 10–14 days	Elizabethan collar
Further treatment if necessary	Pre-treatment optional (cf. table 2)

Specific Treatment

Prostaglandins and antiprogestins are the standard treatments for post-oestrus metritis/pyometra in the bitch.

Prostaglandins

Luteolytic and uterotonic properties of prostaglandin-F2 alpha (PGF2α) have been used to treat pyometra with repeated doses.

Prostaglandin F2 alpha is indicated in the treatment for metritis or open pyometra in healthy young bitches with normal kidney and liver function, and in the absence of uterine hypertrophy. The use of prostaglandin in cases of closed pyometra is associated with the risk of peritonitis, following the forced passage of purulent fluid up the uterine tubes into the ovarian bursae and out into the peritoneal cavity, or through rupture of the uterine wall (Nelson et al. 1982).

Protocol

The efficacy of treatment is correlated to the repeated administration of injections for 8–10 days rather than the actual total dose administered. Comparison of the uterotonic effect of two different doses administered via intramuscular injection (250 μg/kg vs 50 μg/kg), in bitches in dioestrus, demonstrated that uterine contractions were equivalent. The highest dose was effective for 32 ± 3 min and the lowest, for 23 ± 3 min. (Burke 1982; Nelson et al. 1982; Schille 1986).

Side effects are dose-dependent (Wheaton and Barbee 1993), which is why most authors recommend using 100–250 μg/kg/day of natural prostaglandins (Nelson et al. 1982; Feldman et Nelson, 2004; Davidson 1993) or 10 μg/kg of cloprostenol (Tainturier and Treboz 1985) (Table 1).

The recommended duration of treatment, with one administration per day, is between 5–7 days (Tainturier and Treboz 1985). The efficacy of treatment is checked 10–14 days after the first treatment and if necessary a second treatment can be instigated. Blood tests have shown that septicaemia is present in 15% of bitches (Feldman et Nelson, 2004), which is why systemic antibiotics are recommended. Antibiotics will improve the general status of the bitch but cannot resolve the uterine infection on their own.

Given the increased vaginal discharge after prostaglandin administration, we recommend administering the drug early in the morning and hospitalizing the bitch for 4–6 h. To avoid the ingestion of purulent discharge, we also recommend the use of an Elizabethan collar or similar device.

Clinical evolution

The clinical status of animals treated with PGF2alpha does not usually start to improve until at least 48 h after the start of treatment, and may even deteriorate. Clinically, copious vaginal discharge can be observed for 48 h, it should then start to decrease. Initially, the vaginal discharge is purulent, becoming mucopurulent, and finally clear before resolving. In some cases, a haemorrhagic discharge may be seen 4 or 5 days into treatment. Ultrasonography reveals a rapid reduction in the diameter of the uterus over the first 24–48 h. The evacuation of pus from the uterus improves the animal's general status with recovery of appetite (Tainturier and Treboz 1985).

Efficacy

Felman and Nelson (1996) treated 103 bitches with metritis and open pyometra with natural prostaglandins and observed complete resolution in 93% of the cases. Two-thirds resolved after the initial 5-day treatment and the remaining third after a second series of doses. The administration of PGF2 alpha analogues (Cloprostenol: 10 μg/kg) for 5 days resolved 75% of cases. A second treatment 10 days later increased this cure rate to 90% (Tainturier and Treboz 1985). The efficacy of PGF2alpha is primarily due to its ability to induce uterine contraction. A luteolytic effect is also observed in 50% (Tainturier and Treboz 1985) to 80% (Nudelmann, 1992) of treated bitches. Prostaglandins are effective at normal or low serum concentrations.

Side effects

Short-term side effects are closely linked to the injection of prostaglandins and are due to prostaglandins action

on the smooth muscles; they appear within minutes of the injection and last approximately 1 h.

They include:

- Hypothermia for 1–2 h. The core body temperature can fall by 0.75–2°C. Further reductions may occur with the re-administration of prostaglandins
- Increased frequency of defecation and occasionally diarrhoea,
- Salivation and vomiting
- Depression or excitation with shivering.

The intensity of the side effects can be reduced using various techniques that limit the effect of prostaglandin on smooth muscle fibres.

- Administer progressive doses of prostaglandins: day 1: 0.10 mg/kg, day 2: 0.20 mg/kg and then 0.25 mg/kg (Feldman et Nelson, 2004).
- Use cloprostenol instead of natural prostaglandins at 10 μg/kg (Tainturier and Treboz 1985)
- Administer prostaglandins before feeding
- Administer a pre-treatment (Atropin, prifinium, metopimazine) 15 min before prostaglandins (Table 2)

These side effects necessitate the short-term hospitalization of the bitch.

Long-term efficacy

Fertility after medical treatment is acceptable with 75% (Sokolowski 1986) to 87% (Feldman and Nelson, 2004) of bitches becoming pregnant after treatment. Infertility was associated with chronic inflammation of the uterus with permanent hyperplasia. Recurrence after treatment is variable: 5% for Feldmann and Nelson (2004) in bitches that became pregnant just after the cure to 70% for Memon and Mickelsen (1993) over a period of 27 months. We therefore recommend mating the bitch at the first oestrus after cure because pregnancy has been shown to prevent uterine disease (Niskanen and Thrusfield 1998).

Antiprogestin

The cessation of progesterone activity on the endometrium can be induced by injecting an antiprogestin such as aglepristone (ALIZINE® - Virbac laboratories France) (Blendinger et al. 1997; Fieni et al. 2001a). Aglepristone is a progesterone receptor antagonist. Aglepristone competitively binds progesterone receptors and decreases intrauterine progesterone concentration. The antiprogesterone efficacy of aglepristone has been demonstrated in pregnancy termination and parturition induction (Fieni et al. 1996, 2001b). This property can be used to treat metritis and open or closed pyometra (Trasch et al. 2003; Fieni 2006; Jurka et al. 2010). As for prostaglandins, aglepristone is recommended, under strict medical control, for bitches in good general health. However, given its lack of uterotonic effect, aglepristone can be used with a closed cervix (Fieni 2006).

Table 2. Optional pre-treatment administered before prostaglandins to avoid side effects (Fieni et al. 1989)

Subcutaneous route	Atropine® atropine	0.025 mg/kg
	Prifinial® prifinium	0.1 ml/kg
	Vogalène® metopimazine	0.5 mg/kg

Protocol

Aglepristone inhibits the action of the progesterone on the uterus. An effective concentration of aglepristone must be maintained long enough to allow the uterine mucosa to recover.

Three different protocols using aglepristone alone have been described in the literature:

- Breitkopf et al. (1997) treated bitches over 16 days with two SC injections of 5–6 mg/kg of aglepristone on day 1 (12 h apart), then one SC injection of 3 mg/kg on days 2, 3 and 4, then one SC injection of 3 mg/kg every 4 days;
- Blendinger et al. (1997) used two injections of 6 mg/kg of aglepristone on day 1 (12 h apart) and then administered one injection of 3 mg/kg SC during 3 days;
- Fieni (2006) injected 10 mg/kg of aglepristone once SC on days 1, 2 and 8 and if the uterine lumen was still visible on ultrasonographic examination, another injection was performed on day 15.

To ensure optimal efficacy, the protocol must be adapted to the evolution of the pyometra and the cure of the bitch: aglepristone is injected subcutaneously at 10 mg/kg on days 1, 2 and 8. From day 8, the efficacy is checked before each administration. Satisfactory resolution of the disease is characterized by a reduction in uterine lumen diameter and decreased vaginal discharges. Treatment is discontinued once all discharge has ceased and the lumen has returned to its normal diameter. An additional treatment with aglepristone on day 15 and occasionally on day 30 may be necessary. As aglepristone has not direct uterotonic action and to improve the results we also recommend the administration of very low doses of prostaglandins (cloprostenol 1 μg/kg, SC) from days 3–7.

Clinical evolution

Clinically, for bitches with metritis or open pyometra, aglepristone injections induce progressively an increase in vaginal discharge for 2–7 days. Then, vaginal discharges go from being purulent to mucous and finally serous and at the same time decrease in quantity. The last sign that is observed, 2–4 weeks after the first aglepristone administration, is the cleaning of the vulva area by the bitch. For bitches with closed pyometra, the opening of the cervix induces a large amount of purulent discharge which is associated with immediate improvement in general condition and, in most cases, with increased appetite.

Efficacy (Fieni 2006)

For bitches with metritis (purulent uterine infection with no detectable dilation of the uterine lumen on ultra-

sound), treatment with aglepristone alone resulted in complete resolution in over half of the bitches (9/15 i.e. 60%) within 2 weeks, and all but one of the other cases, within 4 weeks (14/15 i.e. 92.8%).

In all of the bitches with closed pyometra, the two first doses of aglepristone induced opening of the cervix (18/18). The mean time to cervical opening was 25.8 ± 12.3 h. The shortest time was 4 h after the first administration of aglepristone, and none of the bitches showed cervical opening after 48 h. These results demonstrate that surgery is no longer the only possible treatment for closed pyometra.

For bitches with open or closed pyometra, additional treatment with cloprostenol from day 3–7 improved the overall success rate on day 90 to 84% (27/32) with cloprostenol vs 60% (12/20) with aglepristone alone. The recovery was quicker in bitches that had received additional treatment with cloprostenol, with a higher success rate of 22% (3/20 vs 12/33) on day 14 and 24.5% (9/20 vs 23/32) on day 28.

The efficacy of the treatment depended on the clinical presentation. For bitches treated with cloprostenol and aglepristone, although the success rate on day 14 was very low for bitches with closed pyometra (2/11 i.e. 18%) compared with those with open pyometra (10/21 i.e. 48%), the recovery rate on day 90 was higher for closed pyometra with a 90% 9/10) success rate compared with 80% (17/21) for bitches with open pyometra. This difference was also observed in bitches treated with aglepristone alone.

Of the 67 bitches treated, 17 had plasma progesterone concentrations below 3.18 nM. Treatment was successful in all bitches with low progesterone concentrations except for two bitches with open pyometra.

Side effects

Aglepristone has not been described to induce systemic side effects when used for treatment of pyometra (Fieni et al. 2001a). Administration of low doses of cloprostenol (1 μg/kg) does not induce side effects in healthy bitches (personal observation). For bitches treated with cloprostenol and aglepristone for infectious uterine disease, 44% (14/32) had no side effect. For the others, vomiting was the side effect most often observed, and it was strong in only six bitches.

This rate of side effects could be explained by the bad general condition of the bitches.

After treatment, pyometra was not observed at the next heat. Amongst the bitches that remained in our care, some of them had pyometra again 3 or 4 years afterwards, i.e. they had at least four heats without any trouble. Trasch et al. (2003) monitored bitches for 1 year after medical treatment and observed a recurrence rate of pyometra at the following heats in 18.9%, which is similar to the results of other studies (Gobello et al. 2003; Jurka et al. 2010).

The mean age of the bitches was 8 years, which could explain the recurrence of pyometra 2 years later. Some of them were successfully treated again using the same protocol. The best way to manage breeding bitches is to mate them at the next heat, firstly, because after treatment with aglepristone, fertility and prolificacy were normal or even higher (personal observation), and secondly, because pregnancy helps to prevent the pyometra.

Conclusion

In conclusion, aglepristone alone can be effective and safe for the treatment of metritis and to induce cervical opening in closed pyometra. The association of aglepristone and cloprostenol was effective in the medical treatment for open and closed pyometra. Nevertheless, careful case selection is important, and medical treatment is contraindicated in bitches with hepatorenal failure or peritonitis; clinical parameters should be monitored closely throughout treatment.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

Blendinger K, Bostedt H, Hoffmann B, 1997: Hormonal effects of the use of an antiprogestin in the bitches with pyometra. J Reprod Fertil Suppl **51**, 317–325.

Borresen B, 1975: Pyometra in the dog: a pathophysiological investigation. North Vet Med **27**, 508–517.

Breitkopf M, Hoffmann B, Bostedt H, 1997: Treatment of pyometra (cystic endometrial hyperplasia) in bitches with an antiprogestin. J Reprod Fertil Suppl **51**, 327–331.

Burke TJ, 1982: Prostaglandin F2a in treatment of pyometra-metritis. Vet Clin North Am **12**, 107–109.

Chaistain CB, Panciera D, Waters C, 1999: Association between age, parity, hormonal therapy and breed, and pyometra in Finnish dods. Small Anim Endocrinol **9**, 8.

Chen YMM, Wright PJ, Lee CS, Browning GF, 2003: Uropathogenic virulence factors in isolates of *Escherichia coli* form clinical cases of canine pyometra and fèces of healthy bitches. Vet Microbiol **94**, 57–69.

Davidson AP, 1993: Medical treatment of pyometra with prostaglandine F2a in the dog and cat. In: Bonagura JD, Twedt DC (eds), Kirk's Current Veterinary Therapy, Small Animal Practice, 12th ed., pp. 1081–1083.

Egenvall A, Hagman R, Bonnett BN, Hedhammar A, Olsson P, Lagerstedt AS, 2001: Breed risk of pyometra in insured dogs in Sweden. J Vet Inter Med **15**, 530–538.

Feldmann EC, Nelson RW, (eds), 2004: Cystic endometrial hyperplasia/pyometra complex. In: Canine and Feline Endocrinology and Reproduction, 3rd ed. WB Saunders Co, Philadelphia, PA, pp 852–867.

Fieni F, 2006: Clinical evaluation of the use of aglepristone to treat cystic endometrial hyperplasia-pyometra complex in bitches. Theriogenology **66**, 1550–1556.

Fieni F, Fuhrer M, Tainturier D, Bruyas JF, Dridi S, Siliart B, Gogny M, Dumon C, 1989: Utilisation d'un analogue de synthèse des prostaglandines: le cloprosténol dans l'avortement provoqué de la chienne. PMCAC **24**(4), 557–572.

Fieni F, Tainturier D, Bruyas JF, Badinand F, Berthelot X, Ronsin P, Rachail M, Lefay MP, 1996: Etude clinique d'une antihormone pour provoquerl'avortement chez la chienne: l'aglépristone. Rec Med Vet **172**, 359–367.

Fieni F, Martal J, Marnet PG, Siliart B, Bernard F, Riou M, Bruyas JF, Tainturier D, 2001a: Hormonal variation after early or mid-pregnancy termination in bitches with aglepristone (RU534). J Reprod Fertil Suppl **57**, 243–248.

Fieni F, Marnet PG, Martal J, Siliart B, Touzeau N, Bruyas JF, Tainturier D, 2001b: Comparison of two protocols to induce parturition in bitches with a progesterone antagonist: aglepristone (RU534). J Reprod Fertil Suppl **57**, 237–242.

Gobello C, Castex G, Klima L, Rodriguez R, Corrada Y, 2003: A study of two

protocols combining aglepristone and cloprostenol to treat open cervix pyometra in the bitch. Theriogenology **60**, 901–908.

Hagman R, Kühn I, 2002: *Escherichia coli* strains isolated from the uterus and urinary bladder of bitches suffering from pyometra: comparison by restriction enzyme digestion and pulsed-field gel electrophoresis. Vet Microbiol **84**, 143–153.

Hagman R, Kindahl H, Lagerstedt AS, 2006: Pyometra in bitches induces elevated plasma endotoxin and prostaglandin F2α métabolites levels. Acta Vet Scand **47**, 55–68.

Horne AW, Stock SJ, King AE, 2008: Innate immunity and disorders of the female reproductive tract. Reproduction **135**, 739–749.

Jurka P, Max A, Hawrynska K, Snochowski M, 2010: Age related pregnancy results and further examination of bitches after aglepristone treatment of pyometra. Reprod Dom Anim **45**, 525–529.

Memon MA, Mickelsen WD, 1993: Diagnosis and treatment of closed-cervix pyometra in the bitch. J Am Vet Med Assoc **203**, 509–512.

Nelson RW, Feldman EC, Stabenseld GH, 1982: Treatment of canine pyometra and endometritis by PGF2α. JAVMA **181**, 899–903.

Niskanen M, Thrusfield MV, 1998: Associations between age, parity, hormonal therapy and breed, and pyometra in Finnish dogs. Vet-Rec **143**, 493–498.

Noakes DE, Dhaliwal GK, England GC, 2001: Cystic endometrial hyperplasic/pyometra in dogs: a review of the causes and pathogenesis. J Reprod Fertil (Suppl. 57), 395–406.

Nudelmann N 1992: Pyomètre chez la chienne. In: Les indispensables de l'animal de compagnie. Reproduction. Ed. P.M.C.A.C., Paris, 187–192.

Schille VM 1986: Management of reproductive disorders in the bich and queen. In: Kirk RW (ed), Current Veterinary Therapy, Small Animal Pratice, 9th ed, W.B. Saunders, Philadelphia, 1225–1229.

Silva E, Leitao S, Henriques S, Kowalewski MP, Hoffmann B, Ferreira-Dias G, Lopes da Costa L, Mateus L, 2010: Gene transcription of TLR2, TLR4, LPS ligands and prostaglandin synthesis enzymes are up-regulated in canine uteri wih cystic endometrial hyperplasia-pyometra complex. J Reprod Immunol **84**, 66–74.

Silva E, Henriques S, Brito S, Ferreira-Dias G, Lopes da Costa L, Mateus L, 2012: Œstrous cycle-related changes in production of Toll-like receptors and prostaglandins in the canine endometrium. J Reprod Immunol **96**, 45–57.

Smith FO, 2006: Canine pyometra. Theriogenology **66**, 610–612.

Sokolowski JH 1986: In: Burke TJ (ed.) Small Animal Reproduction and Infertility: A Clinical Approach to Diagnosis and Treatment. Lea & Febiger, Philadelphia, 279–283.

Tainturier D, Treboz C, 1985: Traitement de la métrite chronique de la chienne par le cloprosténol, un analogue de la PgF2a. PMCAC, **20**, 239–244.

Trasch K, Wehrend A, Bostedt H, 2003: Follow-up examinations of bitches after conservative treatment of pyometra with the antigestagen aglepristone. J Vet Med A Physiol Pathol Clin Med **50**, 375–379.

Wheaton LG, Barbee D, 1993: Comparison of two dosages of prostaglandin F2α on canine uterine mobility. Theriogenology **40**, 111–120.

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