

Medical Treatment of Pyometra and the use of Aglepristone

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Pyometra is a common disease in bitches over eight years of age. The disease generally occurs during the di-oestrous phase of the reproductive cycle (Blendiger *et al*, 1997). Currently, it is generally accepted that cystic endometrial hyperplasia(CEH)-pyometra complex is very closely associated with increased circulating blood progesterone concentrations (Noakes *et al*, 2001). Progesterone promotes multiplication of the glandular cells in the uterus, which may result in cystic endometrial hyperplasia. Progesterone also depresses local mechanisms to clear bacteria from the genital tract. Infections with *E.coli*, from the bitch's bowel and ascending the urogenital tract, have been identified as the most common bacterial component of the canine pyometra complex (Hagman *et al*, 2002, Wadas *et al*, 1996). Pyometra is associated with inflammation of the endometrium with the accumulation of purulent and/or haemorrhagic secretions in the uterus. Depending on the

degree of cervical opening, a vaginal discharge may be present. Without treatment the infection has high morbidity and mortality due to endotoxaemia and septicaemia (Hagman *et al*, 2006).

Surgical treatment of pyometra by ovariohysterectomy is curative. Anaesthetic and surgical risk may be increased due to the systemic effects of pyometra and these must be addressed before during and after surgery. Future breeding is not possible after ovariohysterectomy.

Due to the luteolytic and uterotonic properties of prostaglandin-F2 alpha (PGF2 α), the repeated administration of PGF2 α has been used to treat pyometra (Gilbert *et al*, 1989; Meyers *et al*, 1986). To avoid the risk of serious side effects, prostaglandins are only recommended for use in young bitches with no liver, kidney or cardiovascular disease. The duration of treatment and the onset of side effects related to the action of the prostaglandins on smooth muscle causing diarrhoea, salivation and vomiting do not make it an ideal single modality treatment option of pyometra.

Given the major role of progesterone in inducing CEH-pyometra complex, anti-progestins such as aglepristone³, could be expected to be useful in a medical treatment protocol. Aglepristone is a potent progesterone antagonist, with an affinity for progesterone receptors *in-vitro* three times greater than that of progesterone. Aglepristone binds to uterine progesterone receptors without producing the biological effects of progesterone. Aglepristone has been shown to effectively suppress the biological action of progesterone during gestation, interrupting gestation (Fieni *et al* 1996; Galac *et al*, 2000; Fieni *et al*, 2001a), causing cervical opening and inducing parturition (Fieni *et al*, 2001b). The molecule

³ Alizin, Virbac

has been effectively used in the treatment of uterine infections associated with the presence of a high level of plasma progesterone (Blendiger *et al* 1997, Breitkopf *et al* 1997, Hoffman *et al* 2001). Recent work has described the use of aglepristone to treat pyometra in bitches, as a short or medium term result after the initial acute recovery (Trasch *et al*, 2003) and including its combined use with cloprostenol (Gobello *et al*, 2003).

In a recent large clinical study (Fieni, 2006) the use of aglepristone alone and in combination with low doses of cloprostenol was evaluated in the treatment of metritis-pyometra in bitches. Sixty-seven bitches, aged 8.2 ± 3.5 years with a uterine infection were accordingly allocated into three groups; group 1: metritis (n=15), group 2: open pyometra (n=35) and group 3: closed pyometra (n=17). All bitches were injected subcutaneously three times with 10 mg/kg of aglepristone on days one, two and eight. It was the only treatment administered to bitches with metritis. In addition to this treatment, half the bitches with open and closed pyometra were injected daily from day three to day seven with 1 µg/kg cloprostenol⁴ subcutaneously. All pyometra bitches were concurrently treated with amoxicillin/clavulanic acid antibiotics⁵. All bitches were closely monitored with regular clinical and gynaecological examinations and full blood counts. The efficacy criteria were assessed as recovery of good general health, lack of vulvar discharge and lack of uterine lumen enlargement. If necessary an additional treatment with aglepristone was administered on day 14 and day 28. The final examination was on day 90.

At day 90, 80.6% (54/67) of all the bitches were cured including all of the bitches with metritis (15/15), receiving only aglepristone, the closed pyometra cases (17/17) had cervical opening within 48 hours of receiving aglepristone. In the bitches with open or closed

⁴ Estrumate, Schering-Plough Animal Health

pyometra, additional treatment with cloprostenol from days three to seven, significantly improved the global success rate at day 90 to 84.4% (27/32) compared to 60% (12/20) in bitches without cloprostenol ($p < 0.05$).

It was concluded that aglepristone alone was effective and safe to treat metritis and an effective means of inducing cervical opening in cases of closed pyometra. The combination of aglepristone and cloprostenol was more effective in the medical treatment of open and closed pyometra than aglepristone alone.

A review of records between 2001 and 2006 from Applecross Veterinary Hospital showed 56 cases (11 cats and 45 dogs) where aglepristone protocols had been used to treat pyometra. Five protocols had been used in treatment; a) Single – single subcutaneous injection of aglepristone 10 mg/kg on day 1, b) Standard - subcutaneous injections of aglepristone 10 mg kg⁻¹ on days 1 and 2, c) Extended - subcutaneous injections of aglepristone 10 mg/kg on days 1, 2 and 8, d) Standard + Cloprostenol – Standard protocol with daily subcutaneous cloprostenol 1 µg/kg starting between days 4 and 8 and continuing for a maximum of eight injections and e) Extended + Cloprostenol – Extended protocol with daily subcutaneous cloprostenol 1 µg/kg starting between days 4 and 8 and continuing for a maximum of eight injections. A successful outcome was based on resolution of clinical signs by day 30 after treatment with or without ultrasound confirmation of a normal uterus post treatment. All animals received concurrent medical therapy as appropriate including but not limited to antibiotics, intravenous fluids and nutritional support. The results are summarised in tables 1 and 2.

⁵ Synulox, Pfizer

For all treatment protocols 84.9% (28/33) and 75% (9/12) of bitches with open and closed cervix pyometra, respectively and 100% (11/11) of queens irrespective of cervical patency had successful outcomes. The numbers in each group are insufficient for meaningful statistical comparison. In successfully treated bitches 18.9 % (7/37) delivered pups at a subsequent oestrus after treatment and 10.8% (4/37) had recurrent pyometra at the next di-oestrus after treatment. In successfully treated queens 54.5 % (6/11) delivered kittens at a subsequent oestrus after treatment and one had recurrent pyometra five months after initial treatment. The remaining 26 bitches and four queens have not been mated, not conceived, undergone elective ovariohysterectomy or been lost follow up.

The reasons for failure of aglepristone protocols to achieve more successful outcomes in the bitch include the presence of focal multi-locular pyometra, client reluctance to pursue medical therapy and rapid clinical deterioration of systemic clinical status eg endotoxaemia requiring ovariohysterectomy. The bitches that underwent ovariohysterectomy within 48 hours of starting treatment did not indicate failure of aglepristone *per se* but reflected an inability to medically stabilise the patient until the aglepristone effect was expected.

The conservative treatment of pyometra with anti-progestins (such as aglepristone) will not replace ovariohysterectomy, particularly when medical stabilisation of the patient is unlikely in the first 24 hours.. However, it is a valuable alternative for the treatment of bitches used for breeding purposes, for dogs with risk of anaesthesia and for those dogs where, for whatever reasons, the owners object to ovariohysterectomy.

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Table 1: Number (%) of bitches and queens that achieved successful outcomes response based on aglepristone treatment protocols Applecross Veterinary Hospital (2001-2006).

Species	Single	Standard	Stand + PG	Extended	Ext + PG
Bitches	3/5 (60.0)	27/31 (87.1)	2/3 (66.7)	4/5 (80.0)	1/1 (100.0)
	Single	Standard	Stand + PG	Extended	Ext + PG
Queens	2/2 (100.0)	8/8 (100)	(0)	1/1 (100.0)	(0)

Table 2: Number (%) of bitches and queens that achieved successful outcomes in response to aglepristone treatment protocols based on cases from Applecross Veterinary Hospital (2001-2006)

Species	Open pyometra	Closed pyometra
Bitches	28/33 (84.9)	9/12 (75.0)
Queens	10/10 (100)	1/1 (100)