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Pathogenesis, diagnostic and therapeutic aspects of canine pyometra

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Abstract
Pyometra is a potentially fatal condition with a wide range of severe sequelae, including sepsis, septic shock, peritonitis, and widespread bacterial infection. Pyometra is more frequently affects middle-aged to old bitches and hormonal and bacterial factors are fundamental in the pathogenesis of the disease. Ultrasonography and vaginal cytology are basic diagnostic procedures that aid in disease differentiation. Surgical ovariohysterectomy is the safest and most successful therapy for pyometra because it eliminates the source of infection and avoids recurrence. In younger and healthy breeding animals with open cervix pyometra and no additional uterine or ovarian diseases, medical (pharmacologic) therapy may be an option.

Keywords: Endometritis, hyperplasia, progesterone, pyometra

1. Introduction
Pyometra is a uterine inflammation with mucopurulent to hemorrhagic discharge aggregation within the uterine lumen synonymous with bacterial infection, resulting in systemic illness. The theory that pyometra is secondary to cystic endometrial hyperplasia (CEH) was confirmed by an early and highly important research focused on experimental induction of CEH and pyometra in neutered and hormonally-treated bitches and hence the disorder was called "CEH – pyometra complex". Pyometra is a disease that occurs after the diestrus (Santana *et al.*, 2020) [31]. Clinical symptoms of pyometra usually appear 15-20 days after LH peak, but they may also appear during proestrus, post-mating or even anestrus (Pretzer, 2008) [28]. Cystic endometrial hyperplasia is a subclinical condition marked by endometrial gland proliferation, which results in the development of fluid-filled cysts and luminal uterine contents (Batista *et al.*, 2013) [2]. Another common hyperplastic change affecting the canine endometrium, pseudoplacentational endometrial hyperplasia (PEH), has been identified as an endometrial alteration that typically occurs during the diestrus (Schlafer and Gifford, 2008) [33].

2. Predisposing factors
Incidences of pyometra have been reported from 2 to 55.17% (Hagman, 2000; Ravishankar *et al.*, 2004) [15, 29]. Summer season has high pyometra morbidity (Laurusevicius, 2009; Antonov *et al.*, 2015) [24, 1]. Pyometra occurs most common in middle-aged to older females with a higher incidence in Bernese Mountain Dog, Collie, Rottweiler, Cavalier King Charles Spaniel, Golden Retriever, Bullmastiff, and Dogue de Bordeaux. Other variables, such as parity, increase the probability of developing pyometra, with nulliparous bitches having a greater risk, accounting for 75% to 77.78% of all pyometra cases (Gupta *et al.*, 2013) [14].

3. Causes of pyometra
The hormonal disruption followed by bacterial infection is crucial in the disease's etiopathogenesis. Furthermore, intact bitches are exposed to progesterone regularly during the diestrus, which is also crucial for the development of pyometra. Increased progesterone concentration after ovulation stimulates endometrial (endometrial hyperplasia) development and glandular secretion lead to uterine glandular secretion buildup, which gives suitable media for bacterial growth. When compared to the diestrus, the uterus has a higher degree of innate immune response to *Escherichia coli* during estrus (Sugiura *et al.*, 2004) [38]. *Escherichia coli* was isolated in 62% to 90% of pyometra cases (Singh, 2017) [35]. In a progesterone-stimulated endometrium, *E. coli*, which are natural inhabitants of the vaginal flora, have a greater capacity

to attach to specific receptors. Bacteria and their compounds can cause both local and systemic inflammation. Pyometra has been attributed to endotoxemia and bacteremia, with widespread infection affecting many organs (Hagman *et al.*, 2006; Karlsson *et al.*, 2013) [16, 22]. The condition is a medical emergency, and it's critical to seek veterinary help right once since a patient's health might quickly deteriorate.

3.1 Classification of pyometra

Pyometra is classified into two forms (a) less advanced or open-cervix (b) advanced or close-cervix cases of pyometra. The purulent uterine exudate is drained through the cervix in cases with open-cervix pyometra, resulting in a sanguineous purulent malodorous vulvar discharge that is readily recognized. The uterine horns are slightly too strongly swollen, and there is minor to severe intraluminal mucopurulent exudate. In contrast, in cases of close-cervix pyometra, the cervix remains closed and the purulent exudate is stored inside the uterus, increasing the likelihood of endotoxemic exposure and even uterine breakup. The uterus swells significantly and fills with copious quantities of fetid purulent exudates (Schlafer and Foster, 2016) [32].

4. Pathogenesis of canine pyometra

The pathogenesis of pyometra in the bitch involves estrogen stimulation of the uterus, followed by prolonged intervals of progesterone dominance. Endometrial expansion, uterine glandular secretions, and reduced myometrial contractions are all caused by progesterone. Progesterone reduces myometrial contractility, reduces uterine blood supply, and impairs neutrophilic migration into the uterus (Schlafer and Foster, 2016) [32]. Increased progesterone concentration (>40 ng/ml) after ovulation stimulates endometrial (endometrial hyperplasia) development and glandular secretion contribute to uterine glandular secretion aggregation, which provides an excellent medium for bacterial growth. Progesterone's detrimental effect on the maturation of antigen-presenting dendritic cells can also lead to a weakened immune defense (Wijewardana *et al.*, 2015) [41]. Furthermore, progesterone alters the endometrial innate immune response to bacterial infections by inhibiting the release of interferon (IFN), Toll-like receptors (TLR) 4 and TLR2 (Sugiura *et al.*, 2004; Silva *et al.*, 2012) [38, 34]. Furthermore, mucin coats the endometrial surface, especially Muc1, a protein that protects the endometrium from infection by preventing bacterial adhesion (Gipson *et al.*, 1997; DeSouza *et al.*, 2000) [12, 8]. Reduced Muc-1 endometrial expression during the diestrus can predispose to bacterial infections by allowing bacteria to bind to the endometrial epithelium and colonize the uterine area (Kida *et al.*, 2006; Ishiguro *et al.*, 2007) [23, 19]. Bacterial development is often aided by leukocyte suppression in the progesterone-primed uterus. Recently, bitches with cystic endometrial hyperplasia–pyometra complex were shown to have increased expression of 3-hydroxysteroid dehydrogenase in uterine endometrial tissue (Gultiken *et al.*, 2016) [13]. These results suggested that, despite normal circulating hormone levels, local progesterone synthesis may be involved in the pathogenesis and facilitate the growth of pyometra. Development of CEH is thought to be initiated due to estrogen stimulation followed by prolonged progesterone influence (De Bosschere *et al.*, 2001; Smith, 2006) [6, 37]. There is evidence that insulin-like grow factor 1 (IGF-1) may play a role in the development of CEH (De Cock *et al.*, 2002) [7].

5. Clinical findings

In open cervix pyometra, bitches are less systemically ill than closed cervix pyometra. A malodorous, sanguineous to mucopurulent vaginal discharge is the most prevalent clinical feature in females with open-cervical pyometra. Bitches with closed-cervix pyometra, on the other hand, are usually quite sick when they show, with depression, lethargy, polyuria, polydipsia, vomiting, diarrhoea, and perhaps abdominal distension. Closed cervix pyometra is commonly associated with fever and death may result from toxaemia alone or from peritonitis caused by uterine rupture.

5.1 Pathological findings

Llazani *et al.* (2021) [25] reported that leucocytosis with neutrophilia and left shift are characteristic findings in pyometra together with normocytic, normochromic anaemia. A lymphoplasmacytic and neutrophilic interstitial inflammatory infiltrate with aggregation of intraluminal neutrophils and eosinophilic amorphous fibrinous exudates classify advanced cases of pyometra (Santana *et al.*, 2020) [31]. CEH is distinguished by endometrial thickening and mild to extreme ectasia of endometrial glands, resulting in various cystic structures but endometrial luminal and glandular epithelia are single layered and cuboidal (Schlafer and Gifford, 2008; Santana *et al.*, 2020) [33, 31]. In cases of PEH, the endometrium is also thickened, and there may be variable degrees of endometrial glandular ectasia. Importantly, PEH has been identified as a distinct endometrial hyperplastic distinct from CEH, despite the fact that both occur during the diestrus. Indeed, a recent analysis found no substantial link between CEH and pyometra, while pyometra is strongly linked to PEH.

6. Diagnosis

Pyometra is best diagnosed via ultrasonography and common findings include an enlarged uterus with convoluted, tubular horns filled with anechoic to hypoechoic fluid (Bigliardi *et al.*, 2004) [3]. In pyometra, luminous components are often homogeneous, but they can also be echodense with sluggish, swirling patterns (Nyland and Mattoon, 2002) [27]. If the uterine luminal contents are echodence, mucometra is suspected, and hydrometra is suspected if the luminal contents are anechoic in conjunction with a lack of clinical symptoms compatible with pyometra. The most consistent result in the bitches with pyometra was leucocytosis. This may be attributed to increased tension on the body's defensive mechanisms, which in turn created more leucocytes to fight the infection (Nath *et al.*, 2009a) [26]. Peripheral leukocytosis (often reaching 30,000 cells/mm^3), degenerative left turn, and toxic neutrophils are all common clinical findings. In about 50-75% of cases, clinical blood chemistry shows a slight to moderate rise in Alanine aminotransferase (ALT) and Alkaline phosphatase (AP) concentrations. Measurement of circulating inflammatory mediators such as acute phase proteins, cytokines, or tryptophan metabolites may be used to monitor systemic inflammation (Fransson *et al.*, 2004; Dbrowski *et al.*, 2015; Karlsson *et al.*, 2012) [11, 21]. Automated methods for the acute phase protein C-reactive protein, which is frequently markedly increased in pyometra, are available, which is beneficial for rapid calculation and regular laboratory usage (Hillström *et al.*, 2014) [18]. Increased expression of a group of proteases, namely matrix metalloproteinase, secretory leukocyte peptidase inhibitor (SLPI), prostaglandin synthase enzymes, cyclooxygenase-2

(COX2) and calprotectins of the S100 family, namely S100A8 and S100A9, was a central feature in the pyometra uterus (Hagman *et al.*, 2009; Voorwald *et al.*, 2015) [17, 40]. In the cytokine populations, the bitches with pyometra had a significant increase in interleukin (IL)-1L-β, IL-6, IL-8, IL-10, 1L-15, 1L-18, and tumour necrosis factor (TNF-α) (Karlsson *et al.*, 2012) [21]. Furthermore, in the endometrium of pyometra positive bitches, a distinct up-regulation in expression of IL-6, IL-8, COX2, and prostaglandin F synthase (PGFS) was observed, particularly in the more extreme cases of endometrial atrophy (Singh *et al.*, 2018) [36]. The level of interaction and nature of material influence the ultrasonographic characteristics of pyometra. Mild intervention can be seen as a mixed anechoic to hypoechoic tubular arrangement in a longitudinal segment of ultrasonography.

6.1 Differential diagnosis of pyometra

Mucometra, hydrometra, or pyometra are all conditions that cause uterine fluid retention and enlargement. Mucometra and hydrometra are described by the storage of sterile mucous or serous fluid in the uterus, respectively. The degree of hydration of the fluid is the contrast between these conditions. Pyometra, unlike mucometra and hydrometra, has an inflammatory component and is linked to bacterial infection. On cytologic analysis of the vaginal discharge, neutrophils, which are typically degenerative and present in large numbers, are frequently detected in pyometra. However, in case of mucometra, cytology may indicate fewer neutrophils, with or without degenerative alterations, red blood cells, endometrial cells (typically with foamy cytoplasm), and varying levels of amorphous debris. In case of hydrometra, red and white blood cells, a moderate quantity of endometrial cells, little mucus, and amorphous debris reveal during cytological examination.

7. Treatment

Surgical treatment is the most effective treatment in older or closed cervix pyometra cases because the source of infection and bacterial products are removed and recurrence prevented. Prior to surgery, the patient is stabilized with enough intravenous fluid therapy to avoid hypotension, hypoperfusion, shock, dehydration, acid-base balance and electrolyte abnormalities, coagulation disturbances, and organ maladies (Fantoni and Shin, 2017) [9]. In younger and healthy breeding animals with open cervix pyometra and no additional uterine or ovarian diseases, medical (pharmacologic) therapy may be an option. The progesterone blocker aglepristone is commonly used for treatment of pyometra. Aglepristone binds to progesterone receptors in a competitive and effective manner, without enhancing the hormone's effects. Cervical relaxation is generally achieved within 48 hours, with few and minor side effects (Trasch *et al.*, 2003; Jurka *et al.*, 2010; Contri *et al.*, 2015) [39, 20, 4]. Aglepristone was more often used in conjunction with a relatively short course of antimicrobial treatment which yielded positive outcomes (Contri *et al.*, 2015) [4]. In order to treat pyometra, dopamine agonists or prolactin antagonists such as bromocriptine (20 mcg/kg) or cabergoline (@ 5 mcg/kg) are combined with prostaglandin are helpful. $PGF_{2\alpha}$ has been shown to be effective in the treatment of pyometra. To prevent side effects, the dose should begin with a lower dosage (50µg/kg) and gradually increase it to a higher dosage (250µg/kg). It is important to be aware of the potential side effects of PG therapy such as hypersalivation, panting, and vomiting. According to Fieni *et al.* (2014) [10], cloprostenol sodium had an 84% recovery rate compared to 60% for aglepristone. The lushing effect of uterine material caused by cloprostenol contraction of the myometrium results in less secretion of endotoxins into the bloodstream, and is primarily responsible for the rapid and pronounced improvement of clinical symptoms of bitches with open pyometra. Fertility rates following aglepristone therapy are greater in younger (less than 5 years old) bitches that have no other uterine or ovarian disease (Jurka *et al.*, 2010; Ros *et al.*, 2014) [20, 30]. The prognosis for survival and fertility is considered guarded to good.

8. Conclusion

Pyometra is a common disease in middle-aged bitch. In the clinical history, a recent season with a vaginal discharge and signs of renal disease are common. Mortality is low but can be very high in septic shock. Ultrasonography is used to confirm the diagnosis. Peritonitis, endotoxemia, and systemic inflammatory response syndrome are all prevalent pyometra consequences that are associated with more serious diseases. It is a highly fatal disease and the prognosis is poor if the diagnosis of pyometra is not made at the early stage.

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