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An overview on etiopathogenesis of canine pyometra and its management

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Abstract
Pyometra (pus in the uterus) is a common disease entity in intact female dogs during the luteal phase. Progesterone appears to be a crucial component in the pathogenesis of pyometra. Pyometra in canines results from hormonal imbalance; sequelae of cystic endometrial hyperplasia. Although the etiopathology of its primary aspect is unknown; however, the intact bitches experience hormonally mediated alterations in the endometrium as a result of recurrent and sustained estrogen responses followed by extensive intervals of progesterone dominance. When the endometrium is damaged by bacterial invasion, alterations in endometrial steroid receptors can cause pyometra.

Keywords: Canine, *E. coli*, Neutrophilia, Pus

Introduction
Pyometra (chronic purulent metritis/pyometra complex) is a pathological condition of the uterus that occurs due to hormonal disturbance in intact female dogs during the diestrual phase, clinically characterized by sanguineous to mucopurulent discharge after 4-8 weeks of estrus, lethargy, depression, anorexia, vomition, diarrhea, polyuria, polydipsia, abdominal distension [1, 2, 3]. It is one of the most common uterine infections that occurs in all age groups of bitches but it is more commonly seen in bitches which are >6 years of age [4]. Mostly canine pyometra is closely associated with other conditions of the uterus like mucometra, and hydrometra. This review mainly highlighs the etiopathogenesis, advanced diagnostic methods and the treatment methods involved in treating canine pyometra.

Incidence/Prevalence
The precise incidence is very difficult to define in intact bitches. Yet some studies pointed out the incidence of 2-15% in different breeds and age groups [5, 6]. Breeds reported to have high risk of pyometra includes Rottweiler, Saint Bernard, Chow Chow, Golden Retriever, Miniature Schnauzer, Irish Terrier, Airedale Terrier, Cavalier King Charles Spaniel, Rough Collie and Bernese Mountain dog [7]. In India, the breeds which show a higher risk of development of pyometra include Labrador, Spitz, German Shepherd, and Dalmatian; however, breeds such as Doberman, Dachshund, Great Dane, Pug, Boxer, Lhasa Apso, Cocker Spaniel, Saint Bernard, English Bulldog have been reported to have a lower risk of pyometra [7, 8], although the greatest prevalence of pyometra was seen in Pomeranian breed of dog [9]. Breed predisposition might be due to its susceptibility to diestrual hormonal disorder or higher population of this breed or it may carry a higher genetic predisposition for pyometra. In general, breed differences may reflect true genetic differences or merely constitute a reflection of the different life spans in different breeds. Aged animals are found to be more susceptible than younger ones, as with the age functional obsolescence of endocrine glands due to increasing endometrial alterations [9, 10]. The occurrence of close pyometra is less common than open pyometra [11, 12, 13, 14]. Nulliparous bitches have been found to be at increased risk compared to primiparous and it may be due to the removal of the original endometrium after pregnancy and the new lining has a different sensitivity to estrogen as well as progesterone [15].

Table 1: Incidence of canine pyometra in different age groups

Age (years)	Incidence %
<3	4.92 [11]
4-9	46.54 [15]
9-15	36.88 [11]
>15	0.46 [16]

Etiopathogenesis

Although complete pathogenesis of canine pyometra is not fully understood, however it has been reported that t hormonal imbalance plays a crucial role in its onset. Progesterone (P_4) hormone is the predominant hormone during the diestrus phase of the reproductive cycle and it is well known that this hormone not only that stimulates the endometrial growth and its secretion (uterine milk) but also reduces myometrial contractibility which ultimately favors the attachment and proliferation of bacteria to the epithelial cells of the uterus [17, 18]. Another school of thought suggests that progesterone leads to immunosuppression due to a reduction in the maturation of antigen-presenting dendritic cells [19]. Uterine secretion attracts the growth of many opportunistic pathogens like *E. coli* (Most common in canine pyometra), Klebsiella, Staphylococci and Streptococci (Tab. 2) involved in mixed infection [9, 20] which secrete endotoxin and ultimately lowers the uterine defense mechanism [21]. (Fig. 1)

Table 2: Microorganisms isolated from uterine contents of bitches with pyometra

Microorganisms	**Incidence %**
Escherichia coli	74.1-90[22,23]
Staphylococcus kloosii	1-40[22,23]
Streptococcus spp.	1-30[22,23,24]
Pseudomonas aeruginosa	2-20[22,23]
Klebsiella pneumoniae subsp. *Pneumonia*	3[22]
Citrobacter diversus	3[22]

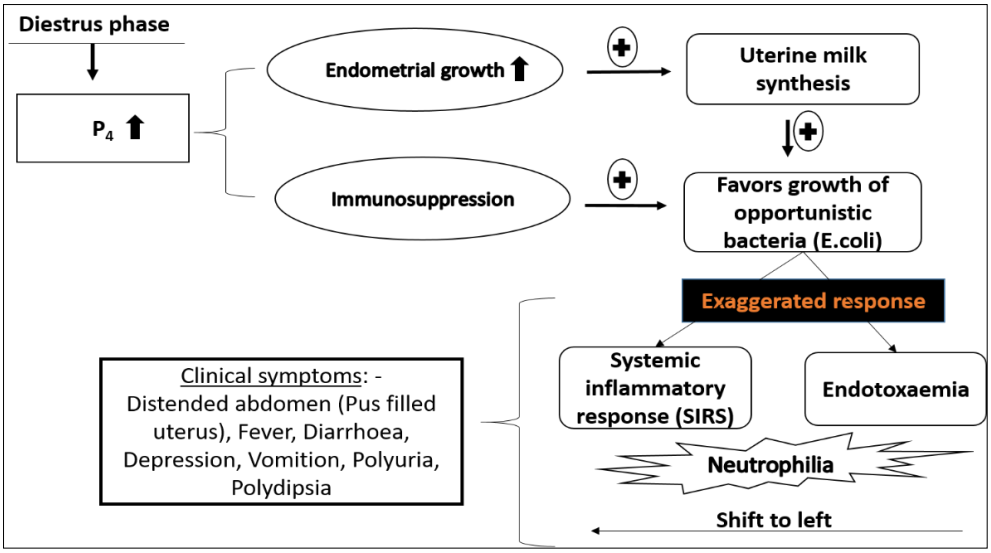

Fig 1: Detail Pathogenesis of Canine Pyometra.

Innate immunity of an animal responds to bacterial endotoxin attack by germline-encoded pattern recognition receptors, toll-like receptors (TLRs), which initiate the non-specific immune response with the recruitment of inflammatory cells, including neutrophils [25]Circulating toxin induces a systemic inflammatory response, this exaggerated response damage the glomerulus cell, reduces its efficacy to filter nitrogen that ultimately leads to an elevated level of blood urea nitrogen (BUN), creatinine. This toxin also affects the biliary duct system and causes cholestasis in long-standing cases of pyometra [18] (Fig. 2).

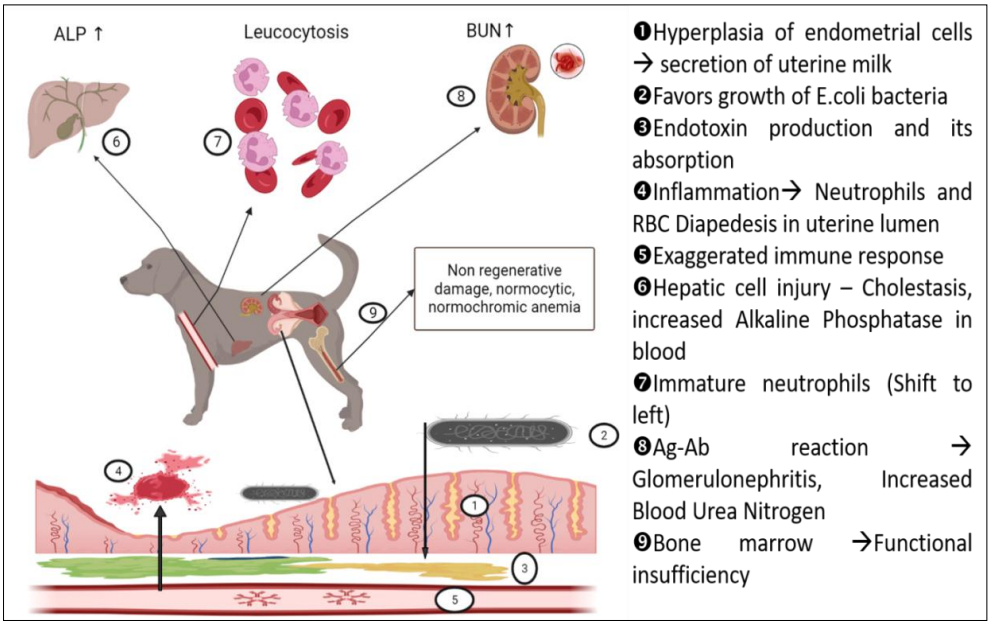

Fig 2: Systemic pathological changes in canine pyometra.

Clinical signs

The most common clinical signs in bitch suffering from pyometra are the gradual inappetence to anorexia and frequent vomition [13]. Common features in the open cervix pyometra of affected animals are polyuria, polydipsia and the foul-smelling odor coming from vaginal discharge (sanguineous to mucopurulent) [26]. Abdominal distension with pain, fever, hyperemic mucous membranes and sternal recumbency are other common clinical symptoms [27]. Vaginal discharge sticking to the hair of the tail and perineum is one of the significant findings associated with open pyometra [13].

Diagnosis

The presumptive diagnosis of pyometra is made based on the history, clinical signs, diagnostic imaging, hematology and biochemistry results. Differentiating CEH with mucometra from pyometra is often an important aspect of the diagnosis because treatment recommendations may be different for the breedable animal.

History and Physical Examination

Most bitches with pyometra have a history of recent estrus with an average interval from the onset of proestrus to a diagnosis of CEH-pyometra is 35 days (20-70 days) [2]. Pyometra is considered a diestral disorder but sometimes can occur during anestrus when progesterone is at baseline concentrations. Cases that occur during anestrus may be due to the persistence of abnormal events that occurred during diestrus, a non-ovarian source of progesterone, or incomplete luteolysis resulting in prolonged low levels of progesterone. Frequently bitches with pyometra have a history of treatment with exogenous progestins for contraception or exogenous estrogens administration for pregnancy termination [10]. Many cases concurrently have estrogen secreting cystic follicles, ovarian neoplasia, or a history of prolonged estrus. The clinical signs of pyometra include vaginal discharge, fever, polydipsia, polyuria, and vomition. Other signs include lethargy, anorexia, dehydration, tachycardia, tachypnea, and pale or hyperemic mucous membranes. Abdominal palpation may reveal pain or a large tubular structure. Purulent, mucoid or hemorrhagic discharge oozing out from the vagina [28].

Pyometra is classified further as open-cervix or closed-cervix, based on the patency of the cervix. Vaginoscopy is the first step in the diagnosis as a vaginal speculum examination to rule out any abnormality or foreign body as the source of the vulvar discharge. Before obtaining the cytology specimen, swabbing of cranial vagina culture and antibiotic susceptibility testing reveals the presence of degenerate neutrophils and bacterial flora in case of infection [29].

Diagnostic Imaging

Ultrasonography (USG) is the most useful diagnostic imaging modality for pyometra. USG and Abdominal radiographs may also reveal uteromegaly [30]. USG can also evaluate endometrial integrity, uterine wall thickness, uterine distention and cystic endometrial glands as well as differentiate pregnancy and neoplasia from pyometra. An Ultrasonograph of a uterus with pus reveals convoluted tubular horns containing an anechoic or hypoechoic fluid; the fluid also may have a slow, swirling pattern. Endometrial glands are increased in size and number in cases of CEH without pyometra, which appears as 1-2 mm anechoic areas within the endometrium [31] while cystic structures with thickened endometrium are diagnostic for CEH with or without pyometra [32]. The luminal contents are usually homogenous and echo-dense due to pus particles [33]. A high blood rate and low vascular resistance have been reported in bitches suffering from pyometra than normal diestrus ones by using Doppler [29]. Other potential conditions to rule out include pregnancy less than 42 days (more than 42 days after the luteinizing hormone surge fetal skeleton should be visible), mucometra, hydrometra, CEH and uterine neoplasia.

Laboratory Findings

Neutrophils with a range from 15,000 to 60,000 cells/ml are seen in canines and shift to the left neutrophilia is more pronounced in closed cervix pyometra. Animals with pyometra often have an increased percentage of the immature form of neutrophils (band neutrophils) [34]. Pyometra cases often have anemia that is characterized as non-regenerative, normochromic and normocytic and may be due to red blood cell diapedesis into the uterus or toxic suppression of erythropoiesis due to bone marrow affection [35]. Reduced levels of Hb, PCV, total erythrocyte count (TEC) and platelets along with an elevated level of erythrocyte sedimentation rate (ESR), total leucocytes count (TLC) and polymorphonuclear (PMN) cells point out toxaemic condition in bitch[10]. Biochemical studies revealed that an acute-phase reaction occurs in canine pyometra that leads to increased protein levels in the blood and there is ultimately an antigen-antibody (Ag-Ab) reaction that forms the complex [36], which adheres to the glomerulus and reduction in renal clearance function, leads to a rise in the blood urea nitrogen and hyperproteinemia [32]. As albumin is small in size compared to globulin, there is more excretion of albumin and a low amount of excretion of globulin (hyperglobulinemia) [37]. Hypoalbuminemia is another common finding due to sepsis [38]. Elevated creatinine and blood urea nitrogen levels reflect renal damage. Azotemia may be due to dehydration (prerenal) or reversible renal tubular damage. *E. coli* lipopolysaccharide (LPS) endotoxin causes reduced sensitivity or complete insensitivity to the antidiuretic hormone at the distal convoluted tubules and collecting ducts, which impairs concentrating ability and results in isosthenuria or hyposthenuria. Cytotoxic necrotizing factor–positive *E. coli* also causes reversible hepatocellular damage or hypoxia because of dehydration resulting in increased aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase [24]. An enzyme 3β-hydroxysteroid dehydrogenases involved in the P_4 synthesis from cholesterol is upregulated in the endometrium of bitches with the cystic endometrial hyperplasia-pyometra complex [39]. Various inflammatory mediators like cytokines, C-reactive proteins (CRP), serum amyloid A (SAA) and haptoglobin [40] serve as prognostic markers in the case of pyometra although further research is required to establish these markers in pyometra.

Treatment

The medical approach is mainly done with systemic and intrauterine use of medicines for non-threatening causes or owner desire to breed although ovariohysterectomy remains the choice of treatment for the canine pyometra.

Intravenous fluid therapy is required for the correction of dehydration to stabilize body condition {60 ml/kg + (%dehydration X bodyweight/100)}. Antioxidants are important to manage the immunocompromised cases of pyometra [31]. General treatment includes broad-spectrum antibiotics, fluid therapy along with immunostimulants.

Previous studies revealed that amoxicillin with clavulanic acid at the dose of 25 mg/kg/day is effective in subsiding infection [10]. Non-nephrotoxic antibiotics must be employed for the pyometra treatment.

Specific treatment with hormones is given to evacuate the uterine pus, nullify the effect of progesterone and stimulate immunity. Prostaglandins and antiprogestins are the standard treatments for post-estrous metritis/pyometra in the bitch. Prostaglandins-F2 alpha (PGF2α) possesses luteolytic and uterotonic activity and has been used to treat pyometra with repeated doses. Most authors recommend the use of subcutaneous administration of natural prostaglandins at the dose rate of 150-200 µg/kg/day for more than 10 days showed good results [26, 42]. The clinical status of animals treated with PGF2 alpha does not usually start to improve until at least 48 h after the start of treatment, and may even deteriorate. Antiprogestin therapy is employed to reduce progesterone activity on the endometrium [43, 44]. Progesterone blocker such as mifepristone [45] or aglepristone [46, 47] has proved better protocol as aglepristone competitively binds progesterone receptors and decreases intrauterine progesterone concentration. Another successful protocol in which aglepristone combined with a short duration (6 days) antibiotic proved efficacious as a progesterone receptor antagonist [48]. Satisfactory resolution of the disease is characterized by a reduction in uterine lumen diameter and decreased vaginal discharges. The administration of very low doses of prostaglandins (cloprostenol 1 µg/kg, SC) from days 3–7 also has promising findings [49]. Another recent protocol used for the treatment of pyometra is the administration of third-generation GnRH antagonist acyline @ 330 µg/ kg orally (single dose) with amoxicillin-clavulanate @ 12.5 mg/kg twice a day, orally for seven days provided promising results [29].

Conclusion

Despite faster advancement in veterinary research and development, a satisfactory treatment for canine pyometra is still yet to be developed. One of the many causes of this condition is a lack of comprehensive information about the etiopathogenesis of canine pyometra due to the complex nature of the disease. An early diagnosis followed by appropriate intervention is also requisite for successful treatment. In addition, there is a need to promote immunotherapy alongside specific pyometra therapy to improve the prognosis of the disease.

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