

Pyometra in Bitches: A Review of Literature

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Abstract

Pyometra is a frequently diagnosed bacterial infection of the uterus in intact, sexually mature bitches, leading to the accumulation of purulent material in the uterine lumen. Approximately one third of the anoestrous bitches can be diagnosed with pyometra. Closed-cervix pyometra is particularly dangerous, because septicaemia and toxæmia may develop rapidly and if left untreated can result in death of the patient. Due to the insidious nature of the disease and its sometimes equivocal clinical signs, patients are often presented in poor condition for anaesthesia and surgery.

Keywords: Pyometra, uterus, bitches

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INTRODUCTION

Pyometra is a frequently diagnosed bacterial infection of the uterus in intact, sexually mature bitches, leading to the accumulation of purulent material in the uterine lumen. Approximately one third of the anoestrous bitches can be diagnosed with pyometra. Closed-cervix pyometra is particularly dangerous, because septicaemia and toxæmia may develop rapidly and if left untreated can result in death of the patient [1].

Due to the insidious nature of the disease and its sometimes equivocal clinical signs, patients are often presented in poor condition for anaesthesia and surgery. This disease is known to lead to systemic inflammation potentially affecting multiple organs of the body, including the heart [2]. The mortality rate in pyometra is assessed as 4% despite modern treatment, which could be due to impairment of kidneys.

In routine practice, no attempt is made to rule out the involvement of kidneys in pyometra [3]. Early diagnosis and therapeutic intervention may prevent severe complications associated with advancing sepsis. For this purpose, it is crucial to identify diagnostic or prognostic biomarkers that can be used in clinical practice [4]. It appears that, several researchers have contributed to the subject on pyometra in bitches and the data have been accumulating over a period of decades and

every time, novel information is added. Of late, the direction of research appears to be reoriented towards identification of biomarkers for objective diagnosis of renal involvement in bitches with pyometra. The available literature on pyometra in bitches has been reviewed under the following broad headings.

INCIDENCE AND SIGNALMENT

A genetic predisposition for existence of pyometra was also suspected [5]. An increased incidence in breeds such as Golden Retriever, Irish Terrier, Saint Bernard, Rottweiler Dogs was reported by Antonov *et al.* and Jitpean *et al.* [6, 7]. However, no association between the incidence of pyometra and breed of the animal has been observed [8].

The age of bitches diagnosed with pyometra ranged from as young as four months to as old as 16 years of age [9]. Canine pyometra was more often observed in older and most frequently in 7–8 years old bitches and an increased incidence in nulliparous bitches and in bitches greater than four years of age [10].

However, it was established that, the risk of pyometra increased with age in domestic dogs [11]. No difference was observed between the age and occurrence of open or closed type of pyometra [12]. However, there has been a global consensus on the association between nulliparity and pyometra [13].

CLINICAL SIGNS

The clinical signs in pyometra are more or less conspicuous. The clinical features of pyometra were versatile [10] and pyometra should be included in the differential diagnosis for any intact bitches regardless of the presenting signs [1]. The onset of clinical signs in pyometra was gradual and insidious with vomiting more common in severely affected patients [7, 12]. In open cervix pyometra, bitches were less systemically ill [9], but, polyuria and polydipsia with a purulent vaginal discharge were common features [13]. The discharge was malodorous, sanguineous to mucopurulent in nature [14].

Abdominal pains, pyrexia, hyperaemic mucus membranes [15] sternal recumbency [16] were the other frequently encountered clinical signs. A frequent and serious consequence of pyometra in bitches was endotoxaemia and progression to systemic inflammatory response syndrome [17]. Abdominal palpation reveals enlarged uterus but uterine horn is unclear due to tense abdomen [18].

HAEMATOLOGY

Anaemia and leucocytosis with neutrophilia besides increased number of immature forms were the common haematological findings reported by almost all authors. The increase in white blood cells (WBCs) was always due to an increase in neutrophils of which up to 35% were immature forms [1, 7, 16, 19, 20]. The number of immature forms when exceeded, the segmented neutrophils indicated the severity of inflammation and suppurative nature of the disease [21]. However, a considerable proportion of bitches with pyometra can have normal leucocyte counts [22]. It is important to note that leucopenia associated with pyometra yields a very poor prognosis [4].

Anaemia in dogs affected with pyometra could be due either to toxic depression of bone marrow and or loss of red cells into the uterine lumen. Diapedesis of erythrocytes into uterine lumen and a shortened life span of circulating erythrocytes associated with iron deficiency could also result in anaemia [23, 24]. The total leucocytosis was higher in close pyometra, than that in open pyometra and toxic states led to a nonregenerative normocytic,

normochromic anaemia with a degenerative shift to left [25]. Bitches with pyometra were found to have a nonregenerative anaemia, which was either normocytic normochromic or microcytic hypochromic type [26].

The dehydration in pyometra is one of the complications that has to be addressed so as to proceed either for stabilization or for surgery. A packed cell volume (PCV) of 36–40% was considered to reflect the existence of border line anaemia that was being masked by dehydration [27]. Increase in total leucocyte count and a decrease in lymphocyte count were directly proportionate to the severity of the disease in bitches with pyometra. Due to suppressed lymphocyte activity, bitches affected with pyometra should be managed as immunocompromised patients and immune stimulants must be considered for therapy [27]. The altered haematological parameters such as leucocytosis with neutrophilia can be expected to return to their normal ranges by seven to fourteen days after hysterectomy [13, 28].

SERUM BIOCHEMISTRY

Blood Urea Nitrogen, Serum Creatinine and Plasma Proteins

Blood urea nitrogen values were used for expressing prognosis of pyometra. Recovery chances were best when blood urea nitrogen values were below normal and prognosis was poor when blood urea nitrogen values were above 90 mg percent [29]. Renal dysfunction was recognized as a feature of canine pyometra [30] and was assessed by hyperproteinemia [31]. Contrary to these observations, lower concentration of serum proteins, creatinine were also occasionally reported [23].

Serum concentrations of urea nitrogen and creatinine were valuable, when the glomerular filtration rate was greater than 75% but were not sensitive enough for detection of early renal damage [32]. Normal serum urea and creatinine levels indicating normal kidney function in all the affected bitches with pyometra have also been reported [4]. Serum blood urea nitrogen and creatinine concentrations were not usually found elevated, unless prerenal azotemia developed as a consequence of dehydration. In surgically

treated animals, azotemia resolved promptly after fluid therapy and surgery, confirming the prerenal nature of azotemia [9, 19].

Hypergammaglobulinemia and hypoalbuminemia were documented in bitches diagnosed with pyometra [1, 33, 34]. The increase in albumin and globulins was attributed to dehydration and chronic antigenic stimulation of the immune system. Serum biochemical analysis and urinalysis were the mainstay diagnostic tests for initial detection and estimation of severity of kidney disease in dogs. Increases in serum creatinine concentration were mild and often remained within reference ranges, until approximately 60–75% of all nephrons were no longer functional [39].

Serum Enzymes

A significant increase in Aspartate amino transaminase and a decrease in Alanine amino transaminase were observed in bitches affected with pyometra [26, 28]. The elevated levels of serum Alanine amino transferase and Gamma glutamoyl transpeptidase, in all bitches affected with pyometra were found to return to their respective reference values either after medical treatment or following ovariohysterectomy [12, 29].

Abnormally increased levels of serum alkaline phosphatase are seen in more than 76% bitches affected with pyometra [13]. Elevated serum alkaline phosphatase and alanine amino transferase concentrations following ovariohysterectomy in bitches with pyometra were thought to reflect hepatocellular damage in response to toxemia, or diminished hepatic circulation due to dehydration [30]. Gamma glutamoyl transpeptidase is less useful as an indicator of acute renal damage in dogs than alkaline phosphatase [19, 33].

Biomarkers

Urinary enzymes such as Gamma glutamoyl transpeptidase, N acetyl B-D Glucosaminidase and B-Glucuronidase were significantly higher in dogs with renal damage and hence were more sensitive and reliable test for assessing early renal damage than serum creatinine or BUN concentrations [36]. Pelander recorded mild-to-moderate cardiac Troponin I in dogs

with pyometra before and after surgery although its clinical importance was uncertain. Increases in urine N-acetyl- β -D-glucosaminidase and gamma-glutamoyl transpeptidase indices allowed for earlier detection of renal tubular damage in dogs [37]. It can be suggested that haematology and blood biochemical examination must be carried out in every case of pyometra in order to predict time of hospitalization and postoperative care [8].

URINALYSIS

It appears that, very few reports are available on urinalysis in bitches affected with pyometra. This could be due to the fact that, findings of urinalysis were less consistent, as dehydration affected urine specific gravity. The decreased ability of the renal tubules to concentrate urine was attributed to the decreased specific gravity of urine and clinical signs of polyuria and polydypsia [25]. Albuminuria was a common finding in bitches affected with pyometra [17]. Proteinuria in dogs might result from glomerulonephritis and infection due to inflammatory response from where glomerular leakage of proteins would occur [38]. Urine protein and creatinine ratio exceeding 1.0 appears to have clinically relevant histological lesions and requires monitoring after ovariohysterectomy [39].

BACTERIOLOGICAL STUDIES

Pyometra in bitches is a bacterial infection and inflammation with pus accumulating in the uterus resulting in a life-threatening systemic illness in advanced cases [40]. The main bacterial organism responsible was *Escherichia coli* and it was thought to be the natural inhabitant of the vaginal flora that gained entrance to the uterus during proestrus and estrus [41–46].

The healthy uterus is capable of eliminating entering bacteria without further development of uterine pathologies [47]. It was suggested that the urinary tract might serve as a bacterial reservoir and bacteria ascend into the uterus during a susceptible stage in the estrous cycle [48]. However, the type of bacteria isolated from the vagina did not necessarily represent the bacterial species isolated from the uterus in pyometra [49].

Cytotoxin necrotizing factor (CNF) in *E. coli* infection was showed to increase endothelial damage and provoke a greater inflammatory reaction in pyometra [50]. *E. coli* in bitches with pyometra could lead to systemic inflammatory response syndrome [51]. High blood concentrations of endotoxin have been related to death of the affected bitches [1]. Certain serotypes of *E. coli* such as 02, 04, 06, and 075, were more commonly associated with pyometra than others and the presence of cytotoxin necrotizing factor (CNF) was associated with more severe endometrial changes [52]. The disseminated bacterial infection or thrombo-emboli might spread the infection to different organs such as brain, myocardium, kidney or uvea, causing severe malfunctions. Early diagnosis and therapeutic intervention might prevent severe complications associated with advancing sepsis in dogs with pyometra [17].

Bacterial colonization of the ovarian bursa in dogs with clinically suspected pyometra was carried out and it was reported that the biological importance of these isolations remained unclear. The bacteria from the ovarian bursa were similar to those recovered from the uterine pus in half of the cases [3].

RADIOGRAPHY

Radiography might be used as an aid in diagnosing pyometra in bitches, but could be frequently inconclusive. Pyometra, mucometra, uterine torsion, the normal nonpregnant and early pregnant uterus were observed to possess same soft tissue or fluid opacity [53]. In the abdomen, a fluid filled organ with variable wall thickness and proliferative changes could be visualized as a sausage-like fluid filled tubular organ located beneath the descending colon and the urinary bladder could be identified [1, 44]. A fluid dense tubular structure in the ventral and caudal abdomen can be noticed on a plain lateral radiograph of the abdomen [18]. Diagnosis of pyometra could be best made with the aid of ultrasonography when compared to radiography [54].

ULTRASONOGRAPHY

The diagnosis of pyometra was best made with the aid of ultrasonography and findings typically included an enlarged uterus with

convoluted, tubular horns filled with anechoic to hypoechoic fluid [18, 28, 55]. Ultrasonographic imaging of the uterus presented a much more specific technique that allowed not only the type of pyometra to be recorded (showing whether it was localized, segmental or uniformly tubular in nature) but also integrity of uterine wall and content type [56]. It was considered as an accurate procedure for the qualitative and quantitative examination and diagnosis of canine pyometra [57, 58]. B-mode ultrasonography with B-mode scanner with a 5 MHz transducer was an efficient method to diagnose pyometra in bitches. A correlation between increase in viscosity of the secretion and echogenicity can also be found [59].

Ultrasonography was more efficient than radiography in diagnosing positive cases with 100% efficacy [54, 60]. The thickness of uterine walls and the characteristics of fluid might be determined, allowing differentiation between pregnancy, cystic endometrial hyperplasia, pyometra and mucometra. In pyometra, the uterine wall was usually thickened and the uterus distended to a variable extent with serous to viscid heterogenic fluid often presenting flocculation, whereas mucometra was characterized by thin uterine walls and hypoechoic fluid [19].

HISTOPATHOLOGY

Histopathology of uterine specimens was carried out by collecting samples for biopsy or at autopsy. Diffuse plasma cell infiltration of the endometrium was considered as a characteristic lesion in pyometra. The important histopathological changes in the uterus of bitches affected with pyometra included deposition of fibropurulent exudates in glandular lumen; squamous metaplasia of endometrium; vacuolation of cytoplasm of lining cells; inflammatory infiltrate consisting of neutrophils, lymphocytes, plasma cells and macrophages; distended uterine glands; and hyperplastic glandular epithelium as the frequent histopathological findings in pyometra-affected uterus [44, 61].

Pyometra in bitches affected all segments of nephron [26]. Renal biopsies from bitches affected with pyometra using light microscopy, electron microscopy and immune-

histochemistry revealed that the overall evaluation of renal tissue had no histological changes [62]. The renal lesions associated with pyometra were of either acute or subacute in nature [33]. Glomerular sclerosis and fibrosis was a coincidental finding in the histological sections obtained from aged bitches affected with pyometra [63]. Tubular and interstitial lesions were identified in the histopathology of kidney samples in bitches with pyometra, but histological features specific for glomerulonephritis were not prominent [64]. Tubulo-interstitial inflammation, lymphoplasmacytic interstitial infiltrates in periglomerular locations, and a higher prevalence of interstitial fibrosis were also recorded in the sections from the kidneys [19].

RENAL INVOLVEMENT AND BIOMARKERS

Diagnosis of renal dysfunction in pyometra requires urinalysis, serum biochemistry, complete blood count and sequential evaluation of serum creatinine levels [65]. Circulating creatinine and urea concentrations, and urine-specific gravity were the main parameters used to diagnose acute and chronic kidney disease [66]. Urinary enzymes such as Gamma-glutamyl transpeptidase, N-acetyl-p-D-glucosaminidase and f-glucuronidase were considered more sensitive and reliable tests for assessing early renal damage in dogs than serum creatinine or blood urea nitrogen concentrations [36, 67]. Acute phase proteins such as C-Reactive protein, Serum amyloid A component and hepatoglobin in bitches undergoing surgery for pyometra were useful markers for monitoring the postoperative period [68]. Urinary enzymes and urine protein:creatinine (UPC) were found useful in detecting renal lesions earlier than serum urea nitrogen and creatinine values [36].

The other biomarkers that were tried include, urinary enzymes such as Alanine amino peptidase, gammaglutamyl transpeptidase, Alkaline phosphatase, N-acetyl-P-D glucosaminidase, etc. [36], cardiac-specific Troponin I [2], Albumin, Immunoglobulin G, Retinol-binding protein, N-acetyl-b-D glucosaminidase [69], Creatinine, cystatin C (CysC), iohexol, and radiolabeled molecules [35]. KYNA, IDO, TRP, KYN values at the

time of suture removal after ovariohysterectomy in pyometric bitches was indicated so as to indicate their health status [41].

TREATMENT

Medical treatment of pyometra with compounds promoting expulsion of the uterine pus, in combination with antimicrobials can be tried based on the status of uterus and the general condition of the bitch [70]. Intra-uterine drainage was tried as a treatment modality of choice for pyometra in bitches. But, this was considered to result in high rate of recurrence [71]. The safest and most satisfied treatment of pyometra in bitches was ovariohysterectomy [72]. Prostaglandin therapy was suggested for young bitches with open pyometra [73]. Medical management of pyometra in bitches was associated with high rate of recurrence [74, 75]. Closed suction abdominal drains and a different administration route for prostaglandin F₂ alpha are promising enhancements in the treatment of pyometra [76]. Medical management of closed cervix pyometra was contraindicated due to potential life threatening complications [77] and it did not bring about the expected therapeutic outcome and therefore ovariohysterectomy was only the treatment of choice [28]. Several researchers tried medical management with drugs such as aglepristone [46], cloprostenol sodium [61], Amoxicillin-clavulanate with dopaminergic agonist, cabergoline [78, 80].

Pyometra had been most commonly treated by ovariohysterectomy, after stabilization by administration of intravenous fluids and broad-spectrum antibiotics. This was considered as recommended treatment in all bitches without significant reproductive value, or when the owner had no strong desire to breed the bitch. Due to the insidious nature of the disease and equivocal clinical signs, patients were often presented in poor condition for anaesthesia and surgery. Kidney function tests and liver enzymes were recommended to be evaluated [19]. Seriously ill bitches with pyometra could be treated with appropriate intravenous fluid therapy and broad spectrum antibiotics prior to ovariohysterectomy [1]. At the time of transection of the ovarian pedicle during

ovariohysterectomy, the ovarian bursa should not be opened in order to prevent potential intra-abdominal spread of bacteria [3].

COMPLICATIONS

The frequency of postoperative complications in ovariohysterectomy was more in small-sized breeds when compared to medium and large-sized breeds [79, 81]. Despite modern treatment routines, the mortality rate due to pyometra was still approximately 3–4% [82]. The development of leucocytosis, fever, vomiting and decrease in food consumption, progressive hypotension leading to shock and high rates of mortality following ovariohysterectomy in pyometric bitches was attributed to the release of bacterial endotoxins. The frequent and serious consequences of pyometra were endotoxaemia and progression into the systemic inflammatory response syndrome [17].

Specific complications following ovariohysterectomy in bitches with pyometra include peritonitis with ruptured uterus, urinary tract infection, surgical wound infection, uveitis, and cardiac arrhythmias in 25 per cent and prolonged postoperative hospitalization in 19% cases. Leucopenia was found to be associated with increased risk for peritonitis and prolonged hospitalization making leucopenia the most important biomarker to be aware of clinically [7].

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