Pyometra in Small Animals

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KEYWORDS

- Endometritis • Cystic endometrial hyperplasia • *Escherichia coli* • Endotoxemia
- Aglepristone • Prostaglandin • Cabergoline • Bromocriptine

KEY POINTS

- Pyometra foremost affects middle-aged to older intact bitches and queens, usually within 4 months after estrus.
- Hormonal and bacterial factors are involved in the pathogenesis, and progesterone plays a key role.
- Cystic endometrial hyperplasia (CEH) is a predisposing factor, but pyometra and CEH can develop independently.
- Pyometra induces endotoxemia and sepsis, and early diagnosis and treatment increase the chances of survival.
- Diagnosis is based on clinical signs and findings on physical examination, hematology and biochemistry laboratory tests, and diagnostic imaging identifying intrauterine fluid.
- Surgical ovariohysterectomy is the safest and most effective treatment, as the source of infection is removed and recurrence prevented. Medical treatment can be an alternative in young and otherwise healthy breeding animals with open cervix and without other uterine or ovarian pathologies.

▶ Video content accompanies this article at http://www.vetsmall.theclinics.com.

INTRODUCTION

Pyometra, literally meaning "pus-filled uterus," is a common illness in adult intact female dogs and cats and a less frequent diagnosis in other small animal species.[1,2] The disease is characterized by an acute or chronic suppurative bacterial infection of the uterus post estrum with accumulation of inflammatory exudate in the uterine lumen and a variety of clinical and pathologic manifestations, locally and systemically.[3] The disease develops during the luteal phase, and progesterone plays a key role for the establishment of infection with ascending opportunistic bacteria. The pathogen most often isolated from pyometra uteri is *Escherichia coli*.[4–6] A wide range of clinical signs are associated with the disease, which can be life-threatening in severe cases. It is important to seek

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immediate veterinary care when pyometra is suspected because a patient's status may deteriorate rapidly and early intervention increases chances of survival. The diagnosis is generally straightforward but can be challenging when there is no vaginal discharge and obscure clinical signs. Surgical ovariohysterectomy (OHE) is the safest and most efficient treatment, but purely medical alternatives may be an option in some cases.

EPIDEMIOLOGY AND RISK FACTORS

Pyometra is an important disease, particularly in countries where elective neutering of healthy dogs and cats is not generally performed.[1,2,7] In Sweden, in average 20% of all bitches are diagnosed before 10 years of age and more than 50% in certain high-risk breeds. The disease generally affects middle-aged to older bitches, with a mean age at diagnosis of 7 years, and has been reported in dogs from 4 months to 18 years of age. The overall incidence rate is 199 per 10,000 dog-years at risk.[7] In cats, pyometra is not as common, which is believed to depend on less progesterone dominance due to seasonality and induced ovulation. In queens, 2.2% are diagnosed with the disease before 13 years of age, with an incidence rate of 17 cats per 10,000 cat-years at risk.[2] The mean age at diagnosis is 5.6 years, with an age range of 10 months to 20 years, and the incidence increases with age and markedly over 7 years of age.[2,8–10] A higher incidence in some dog and cat breeds indicates that they may have a genetic predisposition.[1,2,7,9] Exogenous treatment with steroid hormones, such as progestogens, or estrogen compounds that increase the response to progesterone, are associated with increased risk of the disease.[11,12] Pregnancy is slightly protective in dogs, an effect that is also influenced by breed.[13] Cystic endometrial hyperplasia (CEH) is believed to increase the uterine susceptibility for infection.[14,15] In cats, little is known about risk factors and protective factors but previous hormone therapy (ie, exogenous progesterone) is associated with an increased risk.[16]

ETIOLOGY AND PATHOGENESIS

The complex pathogenesis of pyometra is not yet completely understood but involves both hormonal and bacterial factors. Although most studies have been done in dogs, the development is believed similar in cats. The uterine environment during the luteal phase is suitable for pregnancy but also for microbial growth. Progesterone stimulates growth and proliferation of endometrial glands, increased secretion, cervical closure, and suppression of myometrial contractions.[14] The local leukocyte response and uterine resistance to bacterial infection also become decreased.[17–19] Circulating concentrations of estrogen and progesterone are not usually abnormally elevated in pyometra, and increased numbers and sensitivity of hormone receptors are believed to initiate an amplified response.[20,21] Simultaneous corpora lutea and follicular cysts are more often found in bitches with pyometra, supporting a synergistic hormonal effect.[22]

Progesterone-mediated pathologic proliferation and growth of endometrial glands and formation of cysts (ie, cystic endometrial hyperplasia [CEH]) is believed to predispose for pyometra but the 2 disorders can develop independently (**Fig. 1**).[23] Sterile fluid may accumulate in the uterine lumen, with or without CEH, which is defined as hydrometra or mucometra or, more rarely, hemometra, depending on the type of fluid and its mucin content. Clinical signs are generally subclinical or mild when there is no bacterial infection of the uterus.[3,24,25]

E coli is the predominant pathogen isolated from pyometra uteri, but other species may also occur (**Table 1**).[4,26–29] More than 1 bacterial species can be involved, and cultures are sometimes negative.[28,29] Emphysematous pyometra is caused by gas-producing bacteria.[30] A healthy uterus eliminates bacteria that have entered during
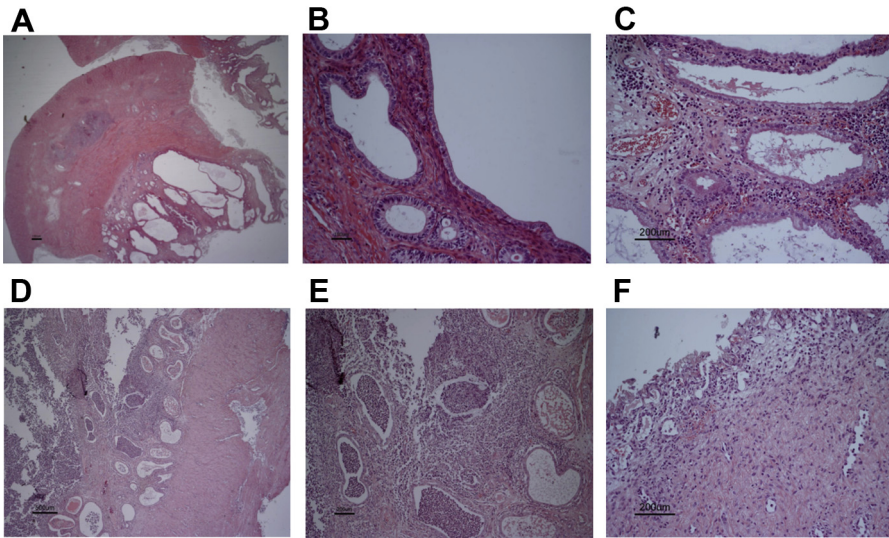
Fig. 1. Images of histologic examination findings in uterine tissues examples from dogs with CEH/pyometra. (*A*) CEH; (*B*) larger magnification of (*A*); (*C*) CEH–endometritis; (*D*) pyometra; (*E*) larger magnification of (*D*); (*F*) pyometra–atrophic endometrium.

cervical opening, but the clearance capacity varies depending on the estrus cycle stage. Experimental *E coli* infection during the luteal phase more often leads to CEH/pyometra compared with in other estrus cycle stages.[31] The infection is most likely ascending because the same strains are present in the gastrointestinal tract, but hematogenic spread could possibly also occur.[6,32,33] *E coli* are natural inhabitants

Table 1		
Bacterial species isolated from the uterus in bitches and queens with pyometra		
Organism	**Proportion in Bitches (%)**	**Proportion in Queens (%)**
Escherichia coli	65–90	71
Staphylococcus spp	2–15	8
Streptococcus spp	4–23	19
Pseudomonas spp	1–8	—
Proteus spp	1–4	—
Enterobacter spp	1–3	—
Nocardia spp	1	0
Pasteurella spp	1–2	<1
Klebsiella spp	2–14	<1
Mixed culture	4–16	—
No growth	10–26	20
Mycoplasma spp, *Enterococcus* spp, *Clostridium perfringens, Corynebacterium* spp, *Citrobacter* spp, *Moraxella spp, Edwardsiella* spp, and others	<1	<1

Data from Refs.[4,5,8–10,28,30,47,52–54,93]

of the vaginal flora[34] and have an increased ability to adhere to specific receptors in a progesterone-stimulated endometrium.[5] Certain serotypes of *E coli* are more common and often exhibit the same virulence traits as isolates from urinary tract infections.[35–37] The same bacterial clone can frequently be isolated from the uterus and the urinary bladder in pyometra.[5,6,33]

Bacteria and bacterial products are potent inducers of local and systemic inflammation. Endotoxin, lipopolysaccharide components of Gram-negative bacteria, such as *E coli,* are released into the circulation during bacterial disintegration and induces fever, lethargy, tachycardia, and tachypnea.[38] Higher endotoxin concentrations may cause fatal shock, disseminated intravascular coagulation, and generalized organ failure.[39,40] Pyometra has been associated with endotoxemia[40,41] and bacteremia,[42] and disseminated infection may affect various organs.[43,44] Approximately 60% of bitches and 86% of queens with pyometra suffer from sepsis (ie, life-threatening organ dysfunction caused by a dysregulated host response to an infectious process).[45,46] The illness is considered a medical emergency and it is important to seek immediate veterinary care because a patient's health status may deteriorate rapidly.

CLINICAL PRESENTATION

Typically, middle-aged to older animals are presented up to 2 months to 4 months after estrus with a history of various signs associated with the genital tract and systemic illness (**Table 2**). A continuous or intermittent mucopurulent to hemorrhagic vaginal discharge is often present but can be absent if the cervix is closed.[47] The systemic illness is often more severe if the cervix is closed, and the uterus may become severely

Table 2 History data and clinical signs in bitches with pyometra	
Case History and Clinical Signs	**In Percentage (%)**
Vaginal discharge[a]	57–88
Lethargy/depression[a]	63–100
Inappetence/anorexia[a]	42–87
Polydipsia[a]	28–89
Polyuria[a]	34–73
Vomiting	13–38
Diarrhea	0–27
Abnormal mucous membranes	16–76
Dehydration	15–94
Palpable enlarged uterus	19–40
Pain on abdominal palpation	23–80
Lameness	16
Distended abdomen	5
Fever	32–50
Hypothermia	3–10
Tachycardia	23–28
Tachypnea	32–40
Systemic inflammatory response syndrome	57–61

[a] Usually in greater than 50% of the bitches.
Data from Refs.[24,25,48,49,53,93,107]

distended.[48] Classic systemic signs are anorexia, depression/lethargy, polydipsia, polyuria, tachycardia, tachypnea, weak pulse quality, and abnormal visible mucous membranes. Fever, dehydration, vomiting, abdominal pain on palpation, anorexia, gait abnormalities, and diarrhea are present in approximately 15% to 30% of bitches with the disease.[47,49] The most common clinical signs in queens are vaginal discharge, lethargy, and gastrointestinal disturbances, such as anorexia, vomiting, and diarrhea (**Fig. 2**).[8,10] Vaginal discharge may absent or concealed by fastidious cleaning habits in up to 40% of affected queens.[9] Weight loss, dehydration, polydipsia/polyuria, tachycardia, tachypnea, abdominal pain on palpation, abnormal mucous membranes (pale, hyperemic, or toxic), and unkept appearance are other findings associated with feline pyometra.

DIAGNOSIS

The disease is easy to recognize in classic cases but can be more challenging when there is no vaginal discharge (ie, closed cervix), and the history and clinical picture are obscure. Pyometra should be a differential diagnosis in bitches and queens admitted with signs of illness after estrus, but the disease can occur at any time during the estrus cycle. The preliminary diagnosis is based on history and findings on physical and gynecologic examinations, hematology and blood biochemistry analyses, and ultrasonography and/or radiography of the abdomen. Bacteriologic culturing of the vaginal discharge is not helpful for the diagnosis because the same microbes are present in the vagina in healthy animals.[50] Careful abdominal palpation, to avoid rupture of a fragile uterus, may identify an enlarged uterus. Diagnostic imaging is valuable for determining the uterine size and to rule out other causes of uterine enlargement (**Fig. 3**A–G). Radiography frequently identifies a large tubular structure in the caudoventral abdomen. Ultrasonography has the advantage of detecting intrauterine fluid, even when the uterine diameter is within the normal range, and of revealing additional pathologic changes of the uterine tissue and ovaries, such as ovarian cysts or CEH, which may affect the outcome of medical treatment negatively (**Fig. 4**, Video 1). More advanced diagnostic imaging techniques are seldom necessary. Differential diagnoses include mucometra, hydrometra, and hemometra that may have similar clinical presentation and ultrasonography findings.[51] Vaginal cytology usually shows severe leukocyte degeneration, neutrophils and some macrophages, plasmacytes, and lymphocytes but bacterial phagocytosis is not always visible.[52] Vaginoscopy is

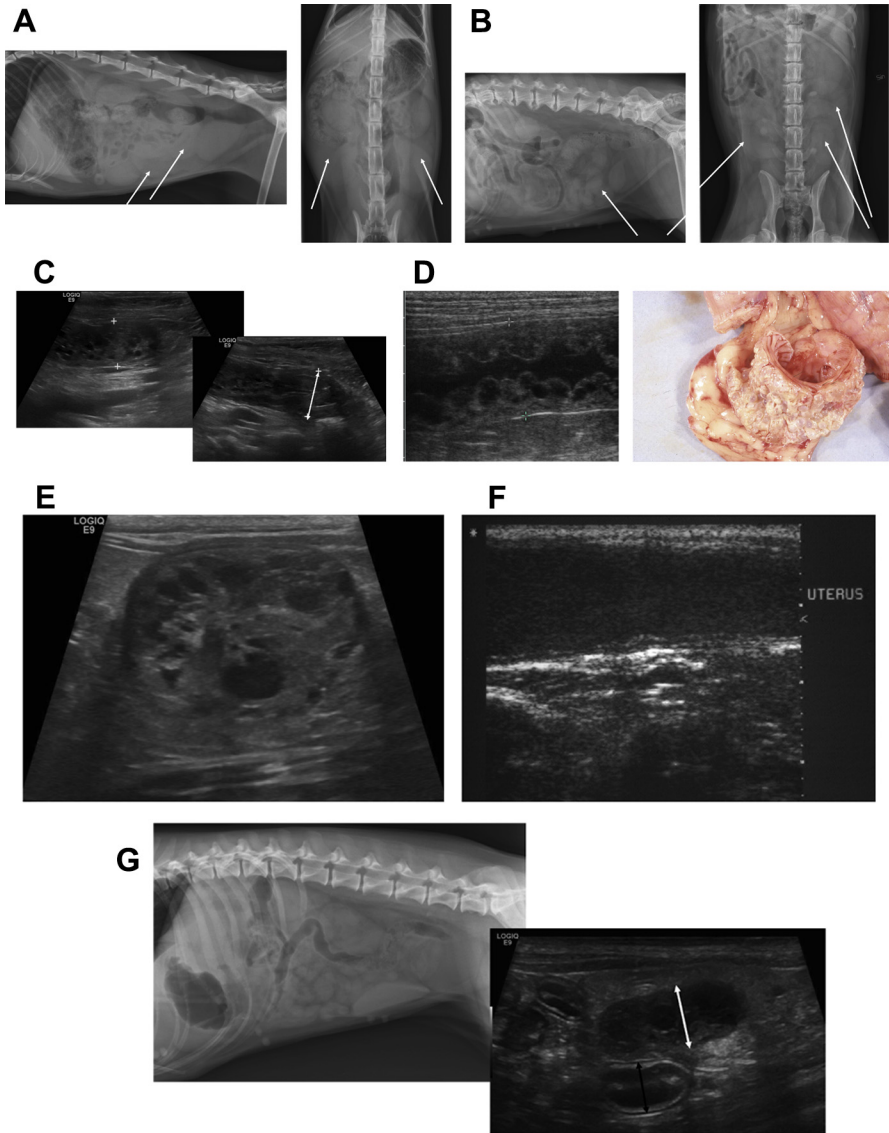**Fig. 2.** Purulent vaginal discharge in a queen with open cervix pyometra.

Fig. 3. (*A*) Uterine enlargement in a cat; diagnosis: pyometra. Tubular structures of soft tissue/fluid opacity (*arrows*). (*B*) Uterine enlargement in a dog; diagnosis: CEH. Tubular structures of soft tissue/fluid opacity (*arrows*). (*C*) Ultrasound images of CEH in a dog. Thickening of the uterine wall with multiple anechoic cystic structures, no intraluminal fluid. Uterine diameter was 2 cm. Cervix located between double-headed arrow. (*D*) CEH and pyometra—thickening of the uterine wall with multiple anechoic cystic structures; the intraluminal fluid was purulent. Both images in (*D*) are of the same uterus. The uterine diameter was 2 cm. (*E*) CEH in a rabbit. (*F*) Atrophic wall pyometra: enlarged uterus with a thin wall and echogenic intraluminal fluid. (*G*) Uterus or small intestines of the same diameter (radiograph to the left). Uterus between white double-headed arrows, CEH. Small intestine with typical layered appearance between black double-headed arrows.
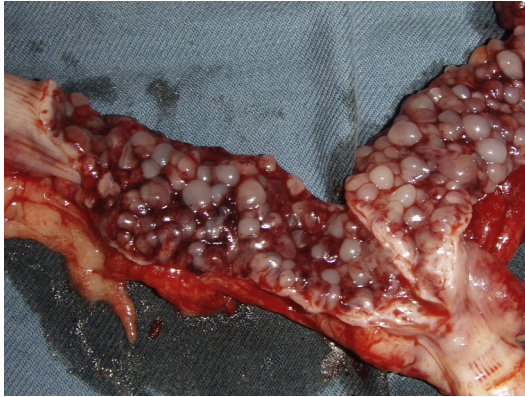
Fig. 4. Canine uterus with CEH and purulent appearance of the fluid in some cysts.

helpful for determining the origin of a vaginal discharge and to exclude other pathologies but is usually not performed in the emergent clinical setting. The diagnosis pyometra is verified by postoperative macroscopic and histologic examination of the uterus and ovaries, and microbiological examination of the uterine content.

CLINICOPATHOLOGIC TESTING—LABORATORY PARAMETERS

Hematology and biochemistry parameter abnormalities are generally investigated,[49,53] with additional tests performed depending on the health status (**Table 3**). Leukocytosis, with neutrophilia and left shift, and monocytosis are characteristic findings in pyometra together with normocytic, normochromic regenerative anemia. Renal dysfunction is common, to which endotoxemia, glomerular dysfunction, renal tubular damage and decreased response to antidiuretic hormone contribute.[54,55] Concomitant cystitis and proteinuria usually resolve after treatment of the pyometra, but severe proteinuria that remains may predispose for renal failure.[54] Circulating inflammatory mediators and acute phase proteins are generally increased.[56] A hypercoagulable state is usually present.[57]

TREATMENT ALTERNATIVES

Surgical treatment, OHE, is safest and most effective because the source of infection and bacterial products are removed and recurrence prevented.[53] Laparoscopically assisted techniques have been developed but are not commonly used and only in mild cases.[58] Medical management (solely pharmacologic) may be possible in young and otherwise healthy breeding animals or in a patient for which anesthesia and surgery is hazardous. In patients with serious illness or when complications, such as peritonitis or organ dysfunctions, are present or the cervix is closed, medical treatment is not recommended and surgery is the treatment of choice. Candidates for medical treatment need to be carefully selected for best prognosis for recovery and subsequent fertility.[59] Microbiological culturing and sensitivity testing are prerequisites for optimal selection of antimicrobial therapy, for which samples are obtained from the cranial vagina or postoperatively from the uterus.

SURGICAL TREATMENT

Prior to surgery, the patient is stabilized with adequate intravenous fluid therapy to correct hypotension, hypoperfusion, shock, dehydration, acid-base balance and

Table 3 Laboratory findings in bitches with pyometra	
Abnormality	**In No. of Bitches (%)**
Leukopenia	4
Leukocytosis	61
Neutropenia	4
Neutrophilia	55
Monocytopenia	3
Monocytosis	60
Anemia	55
Band neutrophils	40
Band neutrophils >3%	83
Trombocytopenia	37
Toxic changes present	9
Increased ALAT	22
Hypoalbuminemia	33
Decreased ALP	49
Increased ALP	37
Increased AST	64
Cholesterolemia	74
Hypernatremia	29
Hypochloremia	2
Hypochloremia	33
Azotemia	5
BUN decreased	10
BUN increased	5
Bile acids increased	21
Hypoglycemia	6
Hyperglycemia	4
Hypokalemia	4
Hypercalcemia	6
Hypokalemia	25
Hyperlactatemia	10
Urine enzymes increased	42
Bacteruria	25

Abbreviations: ALAT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate transaminase; BUN, blood urea nitrogen.
Data from Refs.[24,49,54]

electrolyte abnormalities, coagulation disturbances, and organ dysfunctions.[60] Monitoring and intervention in critically ill patients following parameters according to the "rule of 20" is recommended.[61] In moderately severely and severely ill patients, or if sepsis or serious complications are identified, intravenous broad-spectrum bactericidal antimicrobials are administered to prevent systemic effects of bacteremia and sepsis.[62] The initial choice of antimicrobial drug should be effective against the most common pathogen *E coli* and adjusted after culture and sensitivity results to a narrow-spectrum alternative.[62] The drug should not be nephrotoxic, and the dose,

route, and frequency of administration adjusted to ascertain optimal effect. In 1 study, 90% of *E coli* pyometra isolates were sensitive to ampicillin.[4] The frequency of antimicrobial resistance, however, may differ by geographic location, which needs to be considered, and national regulations concerning restriction of antimicrobial usage in pets should be followed.[27,32] In life-threatening peritonitis, severe sepsis, or septic shock, a combination of antimicrobials is usually recommended for covering a wider range of pathogens.[62] If the health status is close to normal or only mildly depressed and without complications or concurrent diseases, OHE is curative for pyometra per se, and antimicrobials not included in the perioperative supportive treatment.

Removal of the infection is key, and surgery should not be unnecessarily delayed due to the risk of endotoxemia and sepsis when the uterus remains in situ. Anesthesia and perioperative management are focused on maintaining hemodynamic function, gastrointestinal function and protection, pain management, cellular oxygenation, nutrition, and nursing care.[63] Certain drugs may alleviate the inflammatory response.[64] A standard OHE is performed with some modifications.[16,65] The uterus may be large, friable, and prone to rupture, and it is important to handle the tissues carefully (**Figs. 5–9**). The abdominal cavity should be protected from accidental leakage of pus via uterine laceration or the fallopian tubes/ovarian bursa opening by packing off the uterus with moistened laparotomy swabs (see **Fig. 9**). Vessels in the broad ligament are usually ligated. Purulent material is completely removed from the remaining cervical tissue stump, which is not oversewn. Urine for bacterial culturing can be obtained by cystocentesis when the bladder is exposed. The abdomen is routinely closed but if contaminated with pus this should be removed and the abdomen rinsed with several liters of warmed physiologic saline solution and a closed suction (or open) drainage considered.[63,65] Samples for bacterial culturing are acquired before abdominal closure if needed. For verification of the diagnosis, macroscopic and histopathologic examination of the uterus and ovaries is performed.

Intensive postoperative monitoring is essential, and in uncomplicated cases 1 day to 2 days of postoperative hospitalization is usually sufficient. The need for continued supportive care and antimicrobial therapy is evaluated several times daily on a case-by-case basis.[49] Antimicrobial therapy is discontinued as soon as possible. The overall health status and most laboratory abnormalities improve rapidly after surgery and often normalize within 2 weeks.[56,66]
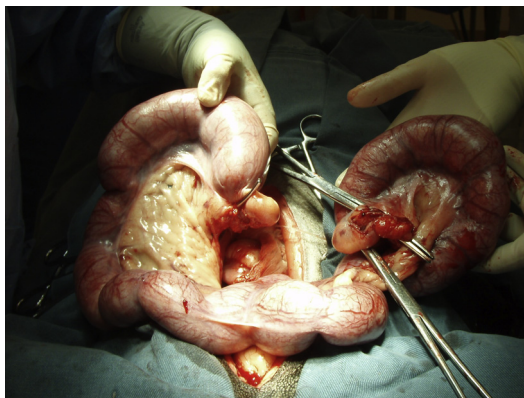

Fig. 5. Canine pyometra uterus.

Fig. 6. Canine pyometra uterus.

Considering the seriousness of pyometra, the prognosis for survival is good and mortality rates relatively low, 3% to 20%.[1,9,49,67] If more severe systemic illness or complications, such as uterine rupture, peritonitis, or septic shock, develop, however, mortality rates can be considerably higher.[9,62,68] In queens with pyometra and uterine
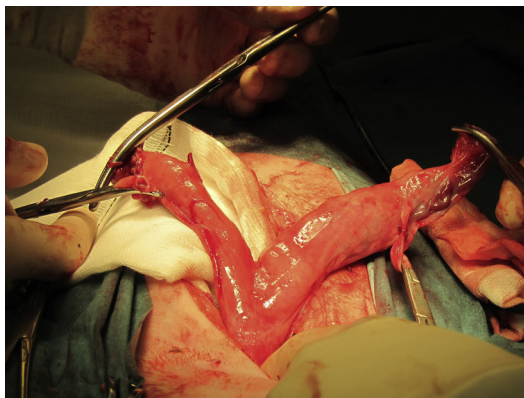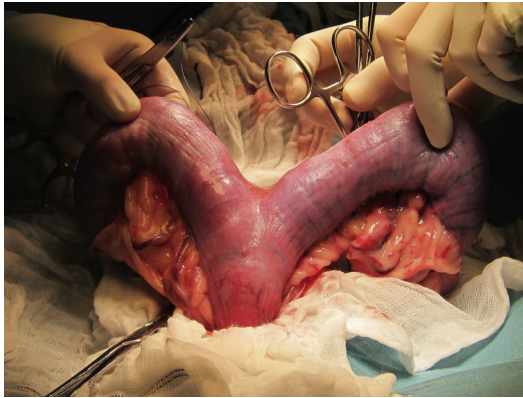

Fig. 7. Feline pyometra uterus.

Fig. 8. Canine pyometra uterus.

rupture, a mortality rate of 57% has been reported.[8] Complications develop in approximately 20% of pyometra patients, the most common peritonitis, in 12%.[9,43,44,49,69] Other reported complications include uveitis, urinary tract infection, intracranial thromboemboli, bacterial osteomyelitis, pericarditis, myocarditis, septic arthritis, incisional swelling, dehiscence, urethral trauma, recurrent estrus, uterine stump pyometra, fistulous tracts, and urinary incontinence.[43,44,54]

MEDICAL (NONSURGICAL) TREATMENT

For purely medical management, careful patient selection is central to ensure the best possible outcome (ie, resolution of clinical illness and maintained fertility). Suitable candidates are young and otherwise healthy breeding bitches and queens with open cervix and that have no ovarian cysts. It is important that the patients are stable and not critically ill, because it may take up to 48 hours until treatment effect for some drugs used.[70] Contraindications include systemic illness, fever or hypothermia, intrauterine fetal remains, organ dysfunctions, or complications, such as peritonitis or sepsis. Adverse drug effects may occur, and endotoxemia and sepsis can quickly transform a clinically stable pyometra to an emergency. Hospitalization is, therefore,
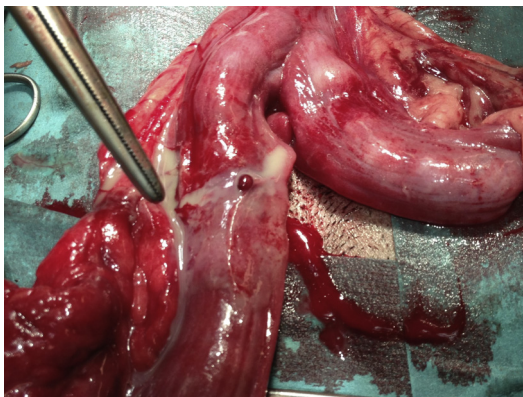

Fig. 9. Canine pyometra uterus with rupture and leakage of pus showing at the tip of the clamp.

recommended to allow close monitoring, supportive treatments, and rapid intervention. Clinical signs, reduction, and clearing of the vaginal discharge, the uterine size, and laboratory abnormalities gradually normalize in 1 week to 3 weeks.[71] OHE may be necessary without delay if complications arise or the general health status deteriorates and in refractory cases. Antimicrobials alone for treatment of pyometra may reduce the disease and prevent its progression but does not result in uterine healing.

The strategies of medical treatment are to minimize effects of progesterone by preventing its production and/or action, eliminate the uterine infection, promote relaxation of the cervix and expulsion of the intraluminal pus, and facilitate uterine healing. Commonly used drugs are natural prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or its synthetic analog cloprostenol, dopamine agonists (cabergoline and bromocriptine), or progesterone-receptor blockers (aglepristone)[72] (**Tables 4** and **5**). The available protocols include systemic antimicrobial therapy, often recommended for 2 weeks or more.[73] The shortest effective duration of adjunctive antimicrobial therapy, however, has not been determined, and 5 days and 6 days were sufficient in 2 studies using aglepristone.[70,74] The antimicrobial drug and administration protocol should be based on bacterial culturing, sensitivity tests, and pharmacokinetics/pharmacodynamics for achieving optimal effect. Additional supportive treatment, including intravenous fluids and electrolyte supplementation, is provided depending on physical examinations and laboratory tests results.

$PGF_{2\alpha}$ is luteolytic and uterotonic and stimulates smooth musculature. Side effects, such as hypothermia, frequent defecation, diarrhea, salivation, vomiting, restlessness, shivering, and depression, are common and dose dependent and may last for approximately 1 hour after administration.[75] $PGF_{2\alpha}$ should be administrated far from feeding to reduce the risk of vomiting. Treatment with metoclopramide or walking the bitch for 15 minutes to 20 minutes after administration has been suggested to lessen nausea and vomiting.[72,76] Serious adverse effects of the drug ($PGF_{2\alpha}$), such as death, shock, and ventricular tachycardia, have been reported and the therapeutic window is narrow, which is why dosage calculations should be done meticulously. It is therefore very important to chose the lowest possible effective dose and hospitalize patients during treatment for monitoring and immediate intervention if severe side-effects develop. Brachycephalic breeds may be predisposed to bronchospasm, making $PGF_{2\alpha}$ contraindicated.[73,76] Owner consent, with information of potential risks, is necessary to obtain prior to extra-label drug usage. Several protocols are still considered experimental, because efficiency and optimal dosages have not yet been established. For natural $PGF_{2\alpha}$, ie, dinoprost tromethamine, subcutaneous administration of 0.1 mg/kg every 12 hours to 24 hours until resolution is the dose generally recommended in bitches and queens. Despite at the lower end of the recommended range and administered once daily, this dose is associated with many undesired side effects (the recommended range includes higher doses, following evaluation of the effect of a lower dose), which is why other lower dose alternatives and drug combinations are becoming more commonly used.[75,77] Other authors suggest starting by giving 10 μg/kg subcutaneously 5 times on the first day, gradually increasing the dose to 25 μg/kg 5 times on the second day, and reaching 50 μg/kg by day 3. Doses of 50 μg/kg were then given 3 times to 5 times daily from day 3 and onward over the treatment period, a regime resulting in side effects in 15% of treated bitches.[72] A dose of 100 μg/kg natural $PGF_{2\alpha}$ administered subcutaneously once daily for 7 days resulted in recovery in 7 bitches, but many side-effects were observed and lower doses are preferable.[78] Natural $PGF_{2\alpha}$, 20 μg/kg, was given intramuscularly 3 times daily on up to 8 consecutive days in 1 study, and 30 μg/kg was given subcutaneously twice daily for 8 days in another study, resulting in resolution of the illness in 70% of 10 bitches and in 100% of 7 bitches, respectively, and no side effects.[79,80] More recent low dose protocols, recommend subcutaneous administration of natural $PGF_{2\alpha}$ at a dose of 10-50μg/

Table 4
Examples of studies of medical treatment protocols for open cervix pyometra in dogs

Drug	N	Protocol and Dosage	Outcome and Side Effects	Reference
Aglepristone	24	Aglepristone 10 mg/kg SC q 24 h on day 2, 7 and 14	Recovery in 100%; recurrence after up to 54 months 12%; fertility in 12% of 17 bitches mated	Jurka et al,[84] 2010
Aglepristone	28	Aglepristone 10 mg/kg SC q 24 h on days 1, 2, 7, 15, and 23, 29 if not cured	Recovery in 75% (resolution of clinical signs); recurrence: 48% after up to 6 y; fertility in 69% of 13 mated bitches	Ros et al,[85] 2014
Aglepristone	52	Aglepristone 10 mg/kg SC q 24 h on days 1, 2, and 7	Recovery in 92%; recurrence: 10% after 3 months, 19% in 37 bitches followed up to 1 y; fertility in 83% (5/6 mated bitches)	Trasch et al,[83] 2003
Aglepristone	13	Aglepristone 10 mg/kg SC q 24 h on days 1, 2, 7, and 14	Recovery in 46%	Gurbulak et al,[82] 2005
Aglepristone	20	Aglepristone 10 mg/kg SC q 24 h on days 1, 2, and 8 and if not cured on day 15	Recovery in 60%	Fieni,[70] 2006
Aglepristone + cloprostenol	32	Aglepristone 10 mg/kg SC q 24 h on days 1, 2, and 8 and if not cured on days 14 and 28 + cloprostenol: 1 μg/kg SC q 24 h on days 3–7	Recovery in 84%; no side effect of cloprostenol in 45% of the bitches; in 56% some side effects were noted: loss of appetite, lethargy, vomiting, nausea; 19% recurrence; in closed cervix pyometra cases: recovery in 76.5%, in open cervix pyometra recovery in 74.3%; 1 euthanasia due to declining health, 1 death; Follow-up time: 90 d and up to 2 y in 23 bitches; fertility in 80% (4/5 mated bitches)	Fieni,[70] 2006

Table 4
(continued)

Drug	N	Protocol and Dosage	Outcome and Side Effects	Reference
Aglepristone	73	Traditional protocol: aglepristone 10 mg/kg SC q 24 h on days 1, 2, and 7 (26 bitches) Modified protocol: aglepristone 10 mg/kg SC q 24 h on days 1, 3, 6, and 9 (47 bitches)	Recovery with traditional protocol in 88%; recurrence: 17%; fertility in 86% Resolution of clinical signs of pyometra with modified protocol, in 100%; recurrence: 0%; fertility in 78% Follow-up after 2 y	Contri et al,[74] 2015
Aglepristone + cloprostenol	15	Aglepristone 10 mg/kg SC q 24 h on days 1, 3, 8, and 15 (if not cured) + cloprostenol: a. 1 µg/kg SC q 24 h on days 3 and 8 (N = 8) b. 1 µg/kg, SC q 24 h on days 3, 5, 8 10, 12, and 15 (N = 7)	Recovery in 100%, recurrence: 20% by the next estrus cycle (in all 15 bitches); fertility in 100% (1 bitch mated); no side effects reported	Gobello et al,[91] 2003
Cabergoline + cloprostenol	29	Cabergoline 5 µg/kg PO q 24 h + cloprostenol 1 µg/kg SC q 24 h for 7–14 d	Recovery in 83% by day 14, recurrence: 21%; fertility in 1/2 mated bitches. Mild side effects noted.	Corrada et al,[81] 2006
Cabergoline + cloprostenol	22	Cabergoline 5 µg/kg PO q 24 h + cloprostenol 5 µg/kg every third day SC for 7–13 d	Recovery in 90.5% by day 13; recurrence: 20%; fertility in 64% of 11 bitches mated; side effects: retching, vomiting, mild abdominal straining, diarrhea, and panting up to 60 min after administration	England et al,[71] 2007

All protocols combined with and systemic antimicrobial therapy. See the original reference for the most accurate information and more details.

Abbreviations: N, number of bitches; PO, per os; PG, prostaglandin; recovery, resolution of pyometra; SC, subcutaneous.

Table 5
Selected studies of medical treatment protocols for open cervix pyometra in cats

Drug	N	Protocol and Dosage	Outcome and Side Effects	Reference
PGF$_{2\alpha}$ (natural)	21	0.1 mg/kg SC q 12–24 h for 3–5 d (6 queens); 0.25 mg/kg was used in 15 queens but was not more effective	Resolution of signs of pyometra and return to cyclicity in 95%; treatment was repeated in 1 queen; fertility in 81%; no difference between the 2 different dosages (ie, the lower dosage recommended); transient side effects observed in 76%: vocalization, panting, restlessness, grooming, tenesmus, salivation, diarrhea, kneading, mydriasis, emesis, urination, and lordosis lasting up to 60 min. Recurrence of pyometra in 14% (3 cats)	Davidson et al,[8] 1992
Prostaglandin F$_{2\alpha}$ (synthetic analog cloprostenol)	5	5 μg/kg SC q 24 h for 3 consecutive days	Resolution of signs of pyometra in 100%; no recurrence after 1 y; fertility in 40%; transient side effects: diarrhea, vomiting, vocalization	Garcia Mitacek et al,[92] 2014
Progesterone receptor blocker (aglepristone)	10	10 mg/kg SC q 24 h on days 1, 2, and 7 and on day 14 (if not cured)	Resolution of signs of pyometra in 90%; no recurrence after 2-y follow-up; no side effects observed	Nak et al,[87] 2009

See the original reference for the most accurate information and more details.
 Abbreviations: IM, intramuscular administration; q, every; N, number of cats; PO, oral administration; SC, subcutaneous administration.

kg every 4-6 hours.[73] The synthetic PGF$_{2\alpha}$ analog cloprostenol is administered at a notably lower dose than for natural PGF$_{2\alpha}$,[78] and accurate calculations are crucial to avoid serious side-effects or fatalities. For cloprostenol, subcutaneous administration of 1 μg/kg to 3 μg/kg every 12 hours to 24 hours to resolution/effect is the recommended dose for bitches and queens.[75] Subcutaneous administration of low-dose cloprostenol, 1 μg/kg, once daily was effective in 100% of 7 bitches in 1 study but with a high recurrence rate, 85%, and subsequent fertility rate of 14%.[78]

The dopamine agonists cabergoline and bromocriptine are effectively luteolytic from day 25 after estrus because of their antiprolactin effects and have been used together with PGF$_{2\alpha}$ for augmented treatment of pyometra.[71,72] Cabergoline usually causes less vomiting than bromocriptine, which is an advantage.[72,73,76] Cabergoline combined with a low dose of cloprostenol led to resolution of the illness in 90.5% of 22 treated bitches with pyometra in 1 study.[71] In another study using cabergoline and cloprostenol, 83% of 29 bitches recovered from the illness.[81] This combination was also shown the most effective compared with only low-dose cloprostenol or natural PGF$_{2\alpha}$.[78] For treatment

of pyometra in cats, no clinical studies have been published on cabergoline and bromo-criptine, but similar doses and regimes as for dogs have been suggested.[16]

The progesterone blocker aglepristone is commonly used in Europe for treatment of pyometra (see **Tables 4** and **5**) but is not currently approved for use in North America. Aglepristone binds to progesterone receptors effectively and competitively and without stimulating any of the hormone's effects. Side effects are usually rare and not severe, and cervical relaxation induced within 48 hours.[70,74,82–85] According to the recommended protocol, 10 mg/kg aglepristone is administered subcutaneously once daily on days 1, 2, and 7 or 8 and on days 14 and 28 if not cured. This protocol results in success rates of 46% to 100%, recurrence rates 0% to 48% and subsequent fertility rates of 69% to 85%.[86] Aglepristone was administered more frequently (on days 1, 3, 6, and 9) in a modified protocol, which resulted in resolution of the illness in all 47 treated bitches and with no reported recurrence for up to 2 years.[74] Treatment with aglepristone resulted in resolution of pyometra in 9 of 10 queens, with no recurrence reported after 2 years and no side effects observed (see **Table 5**).[87]

Local treatment methods of pyometra have been shown effective but are not yet commonly used in clinical practice in bitches and have not been reported in cats.[88] Intravaginal infusion of prostaglandins and antimicrobials yielded successful result in 15 of 17 treated bitches, without side effects or recurrence after 12 months.[89] Aglepristone in combination with intrauterine antimicrobials was successful in 9 of 11 bitches.[82] Intrauterine drainage through transcervical catheters may facilitate recovery in refractory cases.[88] Surgical drainage and intrauterine lavage resulted in fertility in 100% of 8 treated bitches.[90] Whether prostaglandin E_2, administered intravaginally or orally, gives a cervical relaxation that is beneficial in medical treatment protocols remains to be studied.[73,76]

PROGNOSIS AFTER MEDICAL TREATMENT

The prognosis for survival and fertility is considered guarded to good. Breeding on the subsequent estrus cycle is consistently recommended after medical treatment, to avoid recurrence. The mean reported long-term success (resolution of clinical illness) of medical treatment is approximately 86% (range 46%–100%) in dogs[67,70,71,74,78,81–83,85,91] and in cats 95% (range 90%–100%)[8,87,92] (see **Tables 4** and **5**). The prognosis for fertility after medical treatment is generally considered good, with a mean fertility rate of 70% (range 14%–100%) reported in dogs and of 60% in cats. The mean recurrence rate reported in dogs is 29% (range 0%–85%), and 0% to 14% in cats. Fertility rates after aglepristone treatment are higher in younger (<5 years) bitches and those that have no other uterine or ovarian pathology.[84,85]

PREDICTIVE MARKERS

Of clinical and laboratory parameters investigated, leukopenia has been associated with both presence of peritonitis and increased postoperative hospitalization in surgically treated bitches with pyometra.[49] Concentrations of the acute-phase proteins, C-reactive protein and serum amyloid A, are increased in sepsis.[69,93] Concentrations of C-reactive protein and $PGF_{2\alpha}$ have been linked with length of postoperative hospitalization.[25,69] Acute-phase proteins concentrations decrease gradually during postoperative recovery, and maintained or increased concentrations may indicate complications.[56] Persistent proteinuria and urinary protein-creatinine indicate renal disease that requires special attention.[54] Central venous oxygen saturation and base-deficit and lactate levels were valuable for determining outcome in bitches with pyometra and sepsis.[94] Band neutrophil concentrations, lymphopenia and monocytosis, blood urea nitrogen greater than 30 mg/dL, and creatinine concentrations

greater than 1.5 mg/dL have been associated with death.[95] Certain inflammatory variables may be clinically useful for prognostication if cageside tests become available.[96] In queens, white blood cell counts, neutrophils, band neutrophils, monocytes, and the percentage band neutrophils were positively, and albumin concentrations negatively, associated with postoperative hospitalization.[10]

DIFFERENTIATION OF PYOMETRA AND MUCOMETRA OR HYDROMETRA

Fluid in the uterine lumen is present in both pyometra and mucometra/hydrometra, and their clinical manifestations can be similar. In pyometra, however, life-threatening complications may develop because of the bacterial infection, and differentiation of these disorders is thus important to optimize treatments. Ultrasonographic examination of the uterus illustrating the fluid echogenicity and hemodynamic parameters may be helpful in some cases but is not diagnostic.[51] The health status is more depressed and lethargy and gastrointestinal disturbances more frequently observed in pyometra. More than 3 clinical signs of illness and a more pronounced inflammatory response are also indicative of pyometra as opposed to mucometra/hydrometra.[24,25]

PREVENTION

To diagnose and treat CEH and pyometra early is favorable, and noninvasive diagnostic methods are warranted.[97,98] Elective OHE has the advantage of being performed in a healthy animal and preventing pyometra and other uterine diseases. Because there are many negative side effects of spaying, all pros and cons of such intervention, need to be thoroughly evaluated in each individual.[99] If breeding on the first estrus after medical treatment is not possible, close monitoring is advisable to rule out abnormalities that may emerge during the luteal phase. Progesterone receptor blockers or prostaglandins may prevent the development of pyometra in high-risk patients.[97] Some investigators recommend postponing the subsequent estrus after medical treatment of pyometra, to promote uterine healing.[72]

STUMP PYOMETRA

A stump pyometra is when pyometra develops in residual uterine tissue in incompletely spayed bitches and queens, most often because of hormone-producing ovarian remnants.[100] The clinical presentation is similar, except for a history of previous spay. Ultrasonography usually shows areas of local fluid accumulation at the tissue stump, but it may be difficult to localize the ovarian remnant tissue unless follicles are present (Fig. 10). Incomplete resection is the leading cause, but ectopic or revascularized
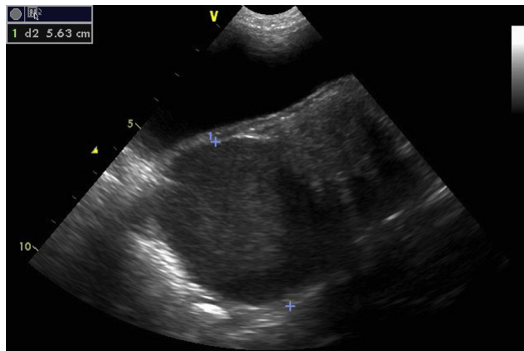

Fig. 10. Stump pyometra due to ovarian remnant.

ovarian tissue separated from the ovary during surgery have also been proposed.[100] Treatment includes surgical resection of remaining uterine and ovarian tissue, in combination with supportive treatments and antimicrobials, if indicated.

Pyometra has been described in many other small animals, such as rabbits (see Fig. 3), rodents, guinea pigs, hamsters, gerbils, ferrets, and chipmunks.[101–104] The causative microbes often differ from isolates in dogs and cats with the disease. Ultrasonography and cytology are helpful to confirm a presumptive diagnosis based on clinical signs and physical examination, and the preferred treatment is OHE. Aglepristone combined with antibiotics has been used successfully for medical treatment in a golden hamster and a guinea pig.[105,106]

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SUPPLEMENTARY DATA

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