Pyometra, Are There New Treatment Options for This Old Reproductive Problem?
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OBJECTIVES OF THE PRESENTATION
Pyometra is the accumulation of pus into the uterus while under the influence of progesterone. Nevertheless, not all accumulation of uterine fluid is septic. There are other pathological conditions that can cause the uterus to accumulate sterile fluid. The condition is believed to be initiated by an interaction of hormonal influences and uterine bacteria. This accumulation of fluid can be life threatening. In closed pyometra fluid drainage is impaired, leading to uterine distention to the point of rupture. This review will examine tools available to diagnose and treat this deadly disease.

GENERAL KEY POINTS
Canine pyometra is the accumulation of purulent material in the uterus of a bitch during diestrus or shortly after. Diestrus is characterized by a closed cervix and high levels of progesterone, conditions required to maintain pregnancy. Growth of contaminant bacteria is possible due to the endometrial proliferation, increased glandular secretion ("uterine milk") and reduced uterine clearance mechanism induced by the elevated levels of progesterone.

The source of uterine bacteria is probably vaginal although a hematogenous route is also a possibility. *E. coli* is the most common bacterial pathogen followed *Staphylococcus, Streptococcus* and *Pseudomonas*. Intra uterine deposition of *E. coli* into the uterus during diestrus will readily induce pyometra. The vagina is not a sterile compartment. Bacterial populations of the anterior vagina of healthy bitches are similar to those of bitches with pyometra making the interpretation of vagina cultures difficult without other clinical signs of the disease.

The terminology used to describe pyometra as open or closed, depending on the presence of vulvar discharge, is questionable despite of being terms widely used. Several closed pyometras have visible purulent discharge from the cervix on vaginoscopy. Even in the presence of a small drainage, closed pyometras are characterized by the accumulation of large volume of uterine pus, leading to the clinical disease.

KEY CLINICAL DIAGNOSTIC POINTS
There are typically two types of history associated with bitches with pyometra. The first is the presence of vulvar discharge, reduced appetite, PU, PD, depression, vomiting dehydration, coma and shock. The second is characterized by the lack of clinical signs with the diagnosis made at the pregnancy examination or for failing to whelp. Differentiation of pyometra, from other intra uterine fluid accumulation, e.g., mucometra, may explain the lack of clinical signs in some bitches.
Pyometra is usually a disease of the old bitch (> 7 years old) but has also been reported in animals as young as 4 months old. There appears to be an increase in incidence of pyometra in nulliparous bitches and bitches older than 4 years old.4,5

Most bitches show clinical signs within 12 weeks after the onset of the previous estrus with an average of 5 weeks. However, pyometra can occur at any stage of the estrous cycle or pregnancy with some breeds showing predisposition to the disease.6,7 No association has been found between false pregnancy and pyometra.8,9

The total WBC count in dogs with pyometra can be quite variable. Increase in total WBC count is identified in a slight majority of bitches with open cervix pyometra but normal or even decreased WBC count may be observed. Various forms of anemia are also reported in animals with pyometra.

Dog with pyometra should have their kidney function examined. Bacterial endotoxins can interfere with sodium and chloride resorption by the kidney leading to hyposthenuria and PU/PD. Endotoxins may also interfere with the antidiuretic hormone function further reducing the capacity of the kidney to conserve water. The possibility of primary kidney damage should always be considered before and after pyometra.

Vaginal cytology is useful in indicating genital tract infection, not specifically uterine disease, and it can confirm the site of infection evidenced by the elevated WBC count. Cytology may also help in differentiating pyometra from mucometra or hematometra.

Cultures are most useful for the determination of antibiotic sensitivity for proper antibiotic selection.

Ultrasonography is the best tool to diagnose pyometra with findings including enlarged uterus with tubular horns filled with anechoic to hypoechoic fluid. The contents are usually homogeneous but can be echodense with slow, swirling movements. The endometrium may be thick and cystic in the presence of Cystic endometrial hyperplasia (CEH).10

Radiography may also be used as an aid in the diagnostic of pyometra. However, this condition cannot be differentiated from a pregnancy until fetal calcification begins around day 45.

**Key Etiologic and Pathophysiologic Points**

Pyometra, as mostly a diestrous disease, indicates that progesterone is a major physiologic component of the disease. Pyometra has been produced experimentally by prolonged progesterone administration, through induction of artificial estrus with estrogen and by the administration of both hormones at the same time.11,12

Cystic endometrial hyperplasia the most common uterine disease in the bitch has been associated with pyometra and other uterine diseases that cause abnormal accumulation of fluid in the uterus, namely hematometra, mucometra and hydrometra. However, CEH does not always precede pyometra. Histological classification of pyometra divides the disease in four categories. Uncomplicated CEH/pyometra is graded type I with few clinical signs and a mucoid vaginal discharge may be present. Type II pyometra consists of CEH plus a diffuse plasma cell infiltrate with possible vulvar discharge. In pyometra type III the animal has a
uterus with acute endometritis and CEH, is clinically ill and uterus is distended with fluid. Pyometra type IV is characterized by chronic endometritis and systemic illness.13

Unilateral horn pyometra has been reported in association with uterine lumen occlusion preventing fluid from draining from a portion of the uterus. Possible causes of blockage include but are not limited to neoplasia, hyperplasia, stenosis, torsion.

**KEY THERAPEUTIC POINTS**

Correction of dehydration and antibiotic therapy should be started as soon as possible. Stabilization of the patient before surgery greatly decreases mortality.

Bitches not intended for breeding should be ovariohysterectomized.

Removal of the effects of progesterone in the uterus is critical for the success of medical therapy. Progesterone is produced by the ovary, more specifically the Corpus Luteum (CL) during diestrus. Blockage of progesterone effects can be achieved by blockage of progesterone production or by preventing progesterone from attaching to its receptors in the uterus.

Concomitantly with the removal of progesterone, medical treatment should focus on the elimination of bacterial infection, if present, and stimulating physical clearance of the uterus. This can be achieved with proper antibiotic therapy and by terminating the luteal phase with the use of prostaglandins, dopamine agonists or progesterone receptor antagonist. Prostaglandins cause myometrial contraction helping in the physical emptying of the uterus.

Surgical drainage and lavage of the uterus was used to salvage reproduction of valuable females before the introduction of prostaglandins. The recent development of transcervical catheters for artificial insemination has given a new life for intra uterine therapy. These devices are being used to empty the uterine contents and to inject therapeutic infusions into the uterus.

Antibiotic therapy should be based on culture and sensitivity. A broad spectrum antibiotic can be used initially.

Prostaglandins have multiple functions on the treatment of pyometra. They cause relaxation of the cervix, lyse the CL and cause uterine contractions.

Misoprostol (PGE) can be deposited locally, at the cervix, to cause relaxation for the treatment of closed pyometra. This is followed (after 2–3 hours) by the use of PGF2α to lyse the CL and to contract the uterus. Natural prostaglandin is used at 0.1 mg/k SQ every 12 hours for 48 hours and then at 0.2 mg/kg SQ every 12 hours until effect. Cloprostenol is administered at 1–3 mcg/kg at 48-hour intervals until effect. Higher doses of prostaglandins are not necessarily better as the increase in contractility is short lived. Multiple treatments per day are more effective. Since prostaglandins are not approved for use in small animals in the United States, it is prudent to have the owner sign an informed consent form prior to the initiation of treatment. Prostaglandins should not be dispensed for client administration as it can cause asthmatic attacks and pregnancy loss in humans.
The addition of dopamine agonist Bromocriptine or Cabergoline after day 25 of diestrus is recommended to achieve rapid and permanent reduction in blood levels of progesterone. The combination of prostaglandins and dopamine agonists has additive effect for cervical relaxation. It also induces a speedier reduction in progesterone levels.

Antiprogestins can also be used for the treatment of pyometra, and pregnancy termination. No drugs in this class are commercially available in the United States. Administration of Aglepristone at 10 mg/kg on days 1, 2, 8 and then also 15 and 28 as needed successfully treated bitches with both open and closed-cervix pyometra. Aglepristone can be associated with PGF2α provided that cervical opening has occurred. In bitches with closed cervix pyometra, administration of Aglepristone is often followed by cervical opening within 24 to 48 hrs. The addition of prostaglandin to Aglepristone provides faster emptying of the uterus and the luteolytic activity of the prostaglandin will strengthen the effect of Aglepristone.

**KEY PROGNOSTIC POINTS**

Early detection and diagnosis is central for successful treatment of pyometra. Early detection is also associated with short treatment protocols. The fewer the number of prostaglandin treatments necessary, the higher the chances for full return to reproduction.

Correction of dehydration and reestablishment of renal function should be addressed before medical or surgical treatment.

Broad spectrum antibiotics should be used while waiting for bacterial culture and sensitivity.

To improve chances of successful treatment, blockage of progesterone effects into the uterus should be done by using a combination of different drugs, i.e., dopamine agonist and prostaglandins or aiplepristone and prostaglandin.

Progesterone should be measured 7 to 14 days after the last prostaglandin treatment to confirm complete removal of the CL and progesterone production. Shortened interestrous interval is common after treatment for pyometra.

Vaginal culture of the bitch at the following estrus and treating with appropriate antibiotic prior to breeding may be necessary, mainly if pure, overgrown colonies are observed. Success is relative to the goal, i.e., elimination of the pyometra vs. restoring reproductive function. If the target is return to fertility, one should expect 50 to 65% conception rate after medical treatment. Presence of CEH can negatively affect post treatment success.

Recurrence is variable depending on the presence and severity of CEH. Bitches with advanced CEH have a higher incidence of recurrence and treatment failure. Treated bitches that fail to conceive or complete a cycle can have a high incidence of recurrence of pyometra.

**KEY DRUGS, DOSAGES AND INDICATIONS**
<table>
<thead>
<tr>
<th>Key drug</th>
<th>Drug class</th>
<th>Dose range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline</td>
<td>Prolactin inhibitor</td>
<td>5 mcg/kg/day</td>
<td>Day 1 and 3</td>
<td>PO</td>
<td>Remove support for CL function</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>PGE</td>
<td>1-3 mcg/kg</td>
<td>BID or SID</td>
<td>Intravaginal</td>
<td>Cervical relaxation</td>
</tr>
<tr>
<td>Dinoprost</td>
<td>PGF2α</td>
<td>0.1 to 0.2 mg/kg</td>
<td>BID</td>
<td>SQ or IM</td>
<td>Uterine contraction, CL lysis, cervical relaxation</td>
</tr>
<tr>
<td>Cloprostenol</td>
<td>PGF2α</td>
<td>1 to 3.0 mcg/Kg</td>
<td>SID or every 3rd day</td>
<td>SQ or IM</td>
<td>Uterine contraction, CL lysis, cervical relaxation</td>
</tr>
<tr>
<td>Aglepristone</td>
<td>Progesterone blocker</td>
<td>10 mg/kg</td>
<td>Days 1, 2 and 8</td>
<td>SQ</td>
<td>Block effect of progesterone</td>
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**Summary**

Pyometra is a medical emergency that happens usually during diestrus, under elevated levels of progesterone. Removal of progesterone influence in the uterus is essential for success. The presence of cystic endometrial hyperplasia can negatively influence treatment and future reproductive performance. The novelty in the treatment of pyometra comes from the better understanding of the pathophysiology of the disease and the smart use of drugs available. The outlook is favorable for the medical treatment of pyometra as new effective drugs may become available.

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