INTRODUCTION

Despite significant research and study, endometritis continues to be a major clinical problem in broodmare practice, and a major source of sub-fertility. Appropriate diagnosis and treatment are imperative when attempting to get these mares in foal. In general, persistent endometritis can be divided into two generalized categories: chronic infectious endometritis and persistent mating-induced endometritis. After mating, there is a physiologic inflammatory reaction to semen that serves to assist in the elimination of spermatozoa from the reproductive tract. When this reaction persists beyond 36 hours it is considered abnormal. In these cases, endometritis occurs in the absence of true infection. The key to successful management of these mares is to identify them prior to or shortly after breeding and manage them appropriately. Treatment generally consists of a combination of uterine lavage and ecbolic administration to enhance uterine clearance as well as administration of intruterine antibiotics.

Chronic infectious endometritis is more common in older, pluiparous mares with poor perineal conformation. This predisposes them to repeated self contamination resulting in chronic infection. Other factors predisposing mares to chronic infections include abnormal cervical function (cervical fibrosis, cervical tears or adhesions, and/or “older maiden mare” syndrome) and mares in which the uterus sags well below the pelvic brim. The organisms most frequently isolated in cases of infectious endometritis include: Streptococcus zooepidemicus, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, and various yeast (most commonly Candida or Aspergillus). Long term chronic, refractory infections typically involve yeast and/or gram negative bacteria.

DIAGNOSIS OF CHRONIC INFECTIOUS ENDOMETRITIS

A thorough reproductive history and a complete physical/reproductive exam generally provide the most productive information for determining the cause of endometritis. Mares are most commonly older and can be multiparous or nulliparous. Modalities available for diagnosis include: physical examination, rectal palpation and ultrasound, vaginal speculum examination, uterine culture, cytology, and uterine biopsy. Frequently a combination of these modalities is utilized in making a diagnosis. Careful examination of the reproductive tract via rectal ultrasound can provide indications of chronic inflammation/infection. Fluid accumulation within the uterine lumen, excessive or inappropriate endometrial edema, the presence of hyperechoic spots within the uterine lumen, and even potentially an increased thickness of the uterine wall can all be indications of chronic infection. A vaginal speculum examination will typically show evidence of inflammation and also allows for the competency of the vestibule-vaginal sphincter to be evaluated. The presence or absence of bacteria via uterine culture unfortunately does not always definitively diagnosis clinical endometritis (Kenney, 1978; Knudsen, 1964; Nielsen, 2005).

Obtaining an endometrial cytology sample along with culture has been promoted to increase the accuracy of diagnosis by providing clear evidence of inflammation in conjunction with a positive culture. Mares with chronic infections typically have long-standing inflammatory changes. The author typically obtains cytology at the time of culture via the cap of a Kalajian swab or via cytology brush. An alternative method for culture and cytology is the use of a low-volume uterine flush in which a small volume of sterile saline (60-mL) is instilled into the uterus and re-collected via a 10-12-cm catheter. The fluid is then centrifuged and the resulting pellet is sampled for culture and cytology (LeBlanc et al, 2007). This method can be especially helpful for isolation in cases of focal infections.
TREATMENT

Treatment protocols should be designed around a specific diagnosis and pharmaceuticals should not be used indiscriminately. Any anatomical defect that contributes to re-infection must be addressed. The importance of this cannot be understated. The perineal conformation of a mare with a history of subfertility should be carefully evaluated and corrected if needed via a Caslick’s and/or episiotomy. Additional traditional treatment protocols in cases of chronic infectious endometritis include uterine lavage, treatment with ecbolics, and antimicrobial therapy.

Uterine lavage allows for mechanical removal of the offending pathogen along with inflammatory debris. Depending on the case and the inciting cause of endometritis, daily lavage can be performed prior to breeding and up to 2-3 days after ovulation without affecting pregnancy rates. For post-breeding endometritis, lavage as soon as four hours post-breeding has been shown to not interfere with conception rates (Brinsko et al, 1991). The lavage solution of choice varies depending on practitioner preference, but is commonly either saline or lactated ringer’s solution. In cases of fungal endometritis dilute antiseptic solutions of betadine (0.01-0.05%) and acidic solutions of vinegar (20-mL white vinegar per liter of saline) have been recommended.

Ecbolics allow for increased uterine clearance, but are generally ineffective in cases where the cervix fails to dilate normally. Topical application of the prostaglandin E1 analog misoprostol to the cervix prior to breeding can be extremely useful in facilitating uterine drainage in mares with failure of appropriate cervical relaxation during estrus. Oxytocin is the most common ecbolic in use in the United States. Generally 10-20 IU IM or IV are given. Due to the drug’s very short half-life, repeated dosages may increase effectiveness (Paccamonti et al, 1999). Data suggests that lower doses of oxytocin may be more effective than higher doses at promoting uterine clearance as larger boluses tend to produce tetanic contractions. Cloprostenol (250-µg IM), a synthetic prostaglandin, can be given as an alternative to oxytocin to aid in fluid evacuation. The mechanism of drug action allows for a more sustained, low-amplitude uterine contraction and is potentially more effective than oxytocin. However, there is evidence of decreased progesterone production from the CL associated with administration of this drug when given after ovulation (Troedsson et al, 2001; Nie et al, 2003; Brendemuehl, 2002). Therefore, cloprostenol use may be best served prior to ovulation or in case of post-ovulation use (within 12 hours of ovulation), progesterone supplementation should be considered.

Antimicrobial therapy is typically a key component in the treatment of chronic infectious endometritis. Due to increased resistance and the risk of inducing fungal infections, judicious use of antimicrobials should always be practiced and the choice of antibiotic should be based on culture and sensitivity results whenever possible. Intra-uterine antibiotics in general should be used during estrus as their use during diestrus has been associated with increased incidence of fungal infections (Hinrichs et al, 1992; McDonnell & Watson, 1992). Lists of common intrauterine antimicrobials are listed in tables 1 and 2. In cases of deep seated, refractory infections, systemic antimicrobial treatments can also be used with success. The advantage of systemic treatment is that it does not induce further contamination of the uterus and allows for less fluctuation in antibiotic levels. This treatment approach can be used alone or in combination with intrauterine therapy.

RECENT TREATMENT UPDATES

As traditional treatment protocols have not always been successful in treating long-standing infections, adjunctive therapies have been suggested to improve success rates. These additional therapies include intrauterine (buffered chelators and mucolytics) and systemic (corticosteroids and immunomodulators) modalities. In recent critical evaluation, these treatments have shown potential as effective therapies.
Recently, the role of mucus in the pathophysiology of endometritis and uterine clearance has been highlighted (Causey 2007). The endometrium alternates between ciliated cells and mucus-secreting cells that support a mucopolysaccharide blanket on its surface. This mucous blanket, in combination with endometrial folds, appears to have an important role in uterine clearance. Inflammation within the uterus leads to increased mucus production (Freeman et al 1990). This is a protective mechanism meant to trap the source of inflammation and protect the exposed endometrium. However, when in excess, mucus can lead to increased inflammation, and ultimately lead to a vicious cycle of irritation and inflammation. In cases of excessive mucus production, uterine lavage alone may not be sufficient for removal.

In cases of mares with excessive mucus, irrigation with solvents or mucolytic agents is recommended prior to antibiotic treatment. These treatments are also recommended for mares infected with a pathogen known to produce a biofilm. The biofilm provides a secure environment for pathogen growth that helps protect it from antibiotic penetration and mechanical removal with uterine lavage. These organisms include *Pseudomonas* spp., *Escherichia coli*, *Klebsiella* spp., and yeast organisms. The treatment is generally repeated for 2-3 days prior to the addition of intrauterine antibiotics. Solvents that have been used include DMSO (50-mL per liter of saline or LRS), and kerosene (50-mL directly instilled). Intra-uterine treatment with kerosene has been shown to cause severe inflammation and necrosis of the endometrium. However, this is also associated with removal of the infectious agent and its offending products and one study showed a surprising 50% pregnancy rate post-treatment (Bracher et al 1991). More recently, there has been an increased interest in the use of mucolytic agents in the treatment of mares with long-term infections. N-acetylcysteine, a mucolytic agent, decreases the viscosity of mucus by disrupting disulphide bonds. It has been recently reported to be nonharmful to the equine endometrium and possibly beneficial (LeBlanc, 2009). A solution of 30-mL of 20% N-acetylcysteine in 150-mL of saline is infused into the uterus 24 to 48 hours prior to breeding. Buffered chelating agents have also been utilized in cases of endometritis associated with a biofilm-producing pathogen. Tris-EDTA, is a first-generation chelator that is reported to enhance the effectiveness of antimicrobials (Wooley & Jones 1983). Recently, Tricide® (Medial Molecular Therapeutics, LLC, Athens, GA), a third-generation chelator, has been evaluated for its ability to enhance antimicrobial effectiveness (Weinstein et al, 2006 and LeBlanc, 2009). These agents are speculated to chelate calcium and/or magnesium within the bacterial cell wall, which alters the integrity of the organism allowing for increased antimicrobial effectiveness.

The use of corticosteroids around the time of breeding has been shown to help modulate the post-breeding inflammatory reaction. By reducing pro-inflammatory cytokines, judicious use can potentially increase pregnancy rates. A single dose of dexamethasone (50-mg IV) at the time of mating has been shown to improve pregnancy rates in mares with a history of incompetent cervical function and retention of fluid post-breeding (Bucca et al, 2008). Appropriate mares should have three or more of the following risk factors for endometritis: abnormal reproductive history, abnormal perineal conformation, cervical incompetence, positive endometrial culture, ≥2-cm intrauterine fluid prior to breeding, significant endometrial fluid present post mating, and/or post-mating intrauterine fluid that persisted for 36 hours. While initial results are promising that the use of dexamethasone in appropriate cases can improve pregnancy rates, a large study found that its use after breeding did not improve pregnancy rates (Vandaele et al, 2008). Alternatively, oral prednisolone (0.1 mg/kg BID for two days prior to and two days after breeding) has also been shown to increase pregnancy rates in mares bred with frozen-thawed semen that had a history of endometrial fluid retention (Papa et al, 2008).

Some research has shown that immunomodulators may improve pregnancy rates in mares with post-breeding endometritis. The theory is to induce a nonspecific cell-mediated immune response to increase overall immune system activity. Settle ® (Bioniche Animal Health, Bogard, GA) is approved as an aid in the treatment of mares infected with *Streptococcus zooepidemicus*. EqStim ® (Neogen Corp, Lexington, KY) is approved as an aid in the treatment of horses with equine respiratory disease complex and has been studied as an adjunct treatment for chronic endometritis.
Finally, in recent years there has been increased interest in the use of acupuncture as an adjunct to traditional medicine. A small number of studies have shown it to have an effect on circulating reproductive hormones in some species (Zhao et al, 2003; Zhaohui et al, 2007; Lin et al, 1998). It seems to be used most commonly in the treatment of delayed uterine clearance post-breeding. Currently, there is a very limited body of clinical data in the horse, although research is on-going.

CONCLUSION

Successful treatment of chronic infectious endometritis requires a lot of work and diligence on the parts of the veterinarian and owner. Mares with long standing infections frequently require repeated treatments over multiple cycles. Unfortunately due to the wide variety of variables associated with endometritis, blanket treatment recommendations are not practical. However, successful pregnancies can be achieved with a thorough, individually-based treatment approach.

FURTHER READING


### Table 1: Commonly Used Intrauterine Antibiotics

<table>
<thead>
<tr>
<th>Drug - Antibiotics</th>
<th>Dose per Treatment</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>1-2 grams</td>
<td>Requires buffering due to acidic nature; gram negative coverage</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1-3 grams</td>
<td>Only the soluble product should be used and should be diluted to decrease irritation; gram positive and <em>E. coli</em> coverage</td>
</tr>
<tr>
<td>Ceftiofur sodium</td>
<td>1 gram</td>
<td>Gram positive and gram negative coverage</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1-2 grams</td>
<td>Requires buffering due to acidic nature; gram negative coverage</td>
</tr>
<tr>
<td>Potassium penicillin</td>
<td>5 million IU</td>
<td>Gram positive coverage (<em>Strep zooepidemicus</em>)</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>6 grams</td>
<td>Should be infused in a 200-ml solution; gram positive coverage with some <em>Pseudomonas spp.</em></td>
</tr>
<tr>
<td>Ticarcillin with clavulanic acid</td>
<td>3-6 grams</td>
<td>Should be infused in a 200-ml solution; greater gram positive coverage than ticarcillin alone</td>
</tr>
</tbody>
</table>

*Table adapted from LeBlanc, 2008*

### Table 2: Commonly Used Intrauterine Antifungal Agents

<table>
<thead>
<tr>
<th>Drug – Antifungal</th>
<th>Dose per Treatment</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>100-200 mg</td>
<td>Dilute in greater than 100-mL solution; <em>Candida</em> spp., <em>Aspergillus</em>, and dimorphic fungi coverage</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>400-700 mg</td>
<td><em>Candida</em> spp., <em>Aspergillus</em>, and dimorphic fungi coverage</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100 mg</td>
<td>Acidic – may need to adjust pH; <em>Candida</em> spp. coverage</td>
</tr>
<tr>
<td>Miconazole</td>
<td>500-700 mg</td>
<td><em>Candida</em> spp., <em>Aspergillus</em>, and dimorphic fungi coverage</td>
</tr>
<tr>
<td>Nystatin</td>
<td>0.5-2.5 million IU</td>
<td>Dilute in sterile water; <em>Candida</em> spp. coverage</td>
</tr>
</tbody>
</table>

*Table adapted from LeBlanc, 2008*