



Therapeutics for Infectious Endometritis: A Clinical Perspective

Opções terapêuticas nas endometrites infecciosas

Dr. Ryan A. Ferris¹

Equine Reproduction Laboratory, Colorado State University, Fort Collins, CO USA.

¹Correspondence: ryan.Ferris@colostate.edu

Abstract

There are multiple options for treatment of infections endometritis. For simple acute cases of bacterial endometritis simple intrauterine antibiotic therapy is often effective. However in chronic cases of bacterial and fungal endometritis the use of both systemic and local therapy can help with clearance of these difficult infections.

Keywords: bacteria, fungal, endometritis, antibiotics, treatments.

Introduction

Mares diagnosed with bacterial endometritis can be divided into acute and chronic infections. While these terms have multiple meanings, for this discussion acute endometritis will describe cases in which mares are exposed to bacterial pathogens and an infection develops. The term chronic endometritis is going to be used in cases where acute bacterial endometritis is detected, appropriate therapy initiated, yet the infection continues persist despite treatment.

Acute Bacterial Endometritis

In cases of acute bacterial endometritis, mares appear systemically healthy, may have intrauterine fluid present on transrectal ultrasound examination, vaginal discharge or fluid in the vaginal vault. On speculum examination, a reddened cervix and cervical discharge can be observed. Normally, the mare's uterus can rapidly clear bacteria or fungi without development of an infection. However, any breakdown in the defense mechanisms of the reproductive tract predisposes a mare to a uterine infection. Increased numbers of bacteria reaching the endometrium due to abnormalities of the perineum, vestibulovaginal seal, or cervix may result in development of infections. A decreased ability of the mare's uterus to contract reduces the clearance of fluid and contaminants from the uterus. Finally, a breakdown in the innate immune system reduces the response toward pathogens in the uterus. All of these factors individually or in combination can contribute to development of bacterial endometritis.

Diagnosis of acute endometritis is usually performed via double-guarded uterine culture swab and cytology brush. This allows for detection, identification, and characterization of microbial organisms and evaluates the uterine lumen for the presence of polymorphic neutrophils (PMNs), which are indicative of active inflammation. The results of the culture and cytology can be interpreted:

- Positive culture result with a positive cytology result is diagnostic of a uterine infection(Riddle et al., 2007).
- Negative culture with a positive cytology result suggests inflammation not caused by an infectious agent (postmating-induced endometritis, pneumovagina, urine pooling). However, intrauterine bacteria are not always cultured using standard techniques and if a significant cause of primary inflammation cannot be identified, further diagnostics such as a low volume lavage(Ball et al., 1988; LeBlanc et al., 2007) or PCR for microbial DNA(Ferris et al., 2014; Ferris et al., 2013) should be performed. In some cases, bacterial and fungal organisms may be seen on a cytology slide, and the uterine culture results are negative.
- Positive culture result with a negative cytology result may be observed with some uterine bacterial infections (eg, *Escherichia coli*); may not always be associated with an inflammatory response(Riddle et al., 2007).

If the culture is from one of the bacterial genus known to be pathogenic in the equine uterus treatment is always warranted (LeBlanc and Causey 2009). However, there is a long list of bacteria with questionable pathogenicity, these organisms may be associated with an infection when in heavy growth, and with evidence of clinical disease (positive cytology, intrauterine fluid, or history of short cycling). The therapeutic plan is to aid the uterus in clearing infectious agents and inflammatory debris (LeBlanc, 2010).

For mares with large volumes of intrauterine fluid a uterine lavage will be performed prior to antibiotic treatment. The goal of the lavage with 0.9% saline or lactated Ringer's solution is to reduce the number of infectious organisms, remove inflammatory debris from the uterus and potentially enhance luminal defense



mechanisms by inducing local irritation and influx of PMNs into the uterine lumen (LeBlanc, 2010). We will typically treat these mares with 3 days of intrauterine therapy based on antimicrobial susceptibility patterns (Dascanio 2011). Ceftiofur sodium (Naxcel[®]) is our antibiotic of choice for empirical therapy, if therapy is initiated before antimicrobial susceptibility is returned. Ecboolics such as oxytocin (5 to 20 IU administered IM or IV) or cloprostenol (250 µg IM) should not be given during the lavage or shortly after the antibiotic infusion as this may cause the majority of the antibiotics to be immediately evacuated from the uterus. We try to collect our culture and cytology samples in early estrus so that if bacterial endometritis is detected therapy can be initiated and the mare still bred on the same estrus cycle.

Antibiotics for Intrauterine Therapy

Medication	Dosage, Route, Frequency	Indications
Amikacin sulfate (Amiglyde-V [®]) (250 mg/ml)	1-2 grams; buffer with 10 to 20 mls sodium bicarbonate (8.4 %) then qs to 60 mls with sterile saline	Antibiotic (gram negative spectrum)
Ampicillin (1 gm vial)	1-2 grams, reconstitute in 60 mls sterile saline	Antibiotic (gram positive spectrum primarily)
Ceftiofur (Naxcel [®])	1 gram, reconstitute with 20 to 60 mls sterile water	Antibiotic (broad spectrum)
Gentamicin (100 mg/ml)	1-2 grams; buffer with 10 to 20 mls of 8.4 % sodium bicarbonate	Antibiotic (gram negative spectrum)
Penicillin (Potassium) (5 million units/vial)	5 million units, reconstitute in 60 mls sterile saline	Antibiotic (gram positive spectrum)
Penicillin (Procaine) (300,000 units per ml)	15 mls, dilute to 60 mls in sterile saline	Antibiotic (gram positive spectrum)
Ticarcillin/Clavulanic acid (Timentin [®]) (3.1 gm per vial)	3.1 grams, reconstitute to 60 mls with sterile saline	Antibiotic combination; clavulanate blocks penicillinase; used for gram positive organisms and <i>Pseudomonas aeruginosa</i>

Part of the treatment plan needs to address issues with perineal conformation. Procedures such as a Caslick, perineal body reconstruction, or cervical laceration. Any mare with less than 2/3 of the vulva below the pelvic brim or >10 degree of angulation of the vulva warrants placement of a Caslick. Severe cases with minimal to no vulva below the pelvic brim or >60° of angulation to the vulva warrant perineal body reconstruction (LeBlanc and Causey 2009). Following treatment, an ultrasound examination should be performed as the mare comes back into estrus for the presence of intrauterine fluid and confirming the uterine environment is free of infection by uterine culture and cytology during the next post treatment estrus.

Chronic Bacterial Endometritis

Chronic cases of bacterial endometritis are those that have been treated traditionally as described for acute infections and are refractory to treatment. Current explanations as to why these cases are refractory to treatment are bacteria are protected by a biofilm from antibiotic exposure; antimicrobial resistance develops during treatment; or the mare become re-infected with the same genus of bacteria. Due to these issues, the management of mares with chronic infections is often much more intense from both a diagnostic and therapeutic perspective.

An option for diagnosing these chronic infections includes a traditional guarded culture swab and cytology brush. However, a more representative sample of the endometrium may be obtained from a small-volume lavage with culture or cytology of the centrifuged pellet (LeBlanc et al., 2007; Ball et al., 1988). Endometrial biopsy for histopathology to evaluate the presence or absence of endometritis can be helpful when clinical and bacteriologic findings are inconclusive (LeBlanc and Causey 2009). Additionally, culture and cytology can be performed on the uterine biopsy sample and has been shown to be more diagnostic than traditional collection from a double guarded device (Nielsen et al., 2010, 2012; Nielsen, 2005).

A further description of therapy for biofilm and latent infections is presented in the proceedings “current understanding of biofilm and latent infections: A clinical perspective”.

Systemic Antibiotic Therapy

An additional consideration is that in many of these mares a 60 ml infusion of antibiotics results in several hundred mLs of fluid in the uterine lumen the next day. For these mares we will often switch to systemic antibiotics if appropriate based on antimicrobial susceptibility. A common antibiotic to use systemically is



Excede[®] to provide 10 days of therapy.

Systemic Antibiotics

Medication	Dosage, Route, Frequency	Indications
Ceftiofur sodium (Naxcel [®]) (50 mg/ml)	1.1 to 2.2 mg/kg, IV or IM, q 12h	Antibiotic (broad spectrum); used in equine reproduction for treatment of bacterial endometritis
Ceftiofur crystalline free acid (Excede [®]) (200 mg/ml)	3.0 mg ceftiofur equivalents/kg, IM; retreat in 4 days if needed	Antibiotic (broad spectrum); used in equine reproduction for systemic treatment of bacterial endometritis
Enrofloxacin (Baytril [®]) (50 or 100 mg/ml)	5 mg/kg, IV, q 24 hours or 7.5 mg/kg, PO, q 24h	Antibiotic (broad spectrum); used in equine reproduction for treatment of bacterial endometritis, specifically for resistant <i>Pseudomonas</i> sp.; Note: intra-uterine therapy of the commercial product is associated with severe necrosis and is not recommended

Treatment of fungal infections

Therapy for fungal endometritis involves treating the active infection via methods such as uterine lavage with dilute acetic acid or dilute povidone-iodine, plus systemic and/or intrauterine infusion of anti-fungal agents, in addition to correction of predisposing factors that could result in treatment failure. Administration of more than one anti-fungal agent may be indicated in refractory or recurrent clinical cases. Uterine lavage is indicated to remove retained fluid, reduce organism load, kill fungal organisms, and remove biofilm. It may also be beneficial to apply topical antifungal medication to the vagina and clitoris as these areas may act as a reservoir or nidus for reinfection.

Ideally, selection of an antifungal agent would be based on results of susceptibility tests for each case of fungal endometritis. Unfortunately, antifungal susceptibility tests are not performed in many diagnostic laboratories and several weeks are often required from sample submission to when results are obtained. Clinicians often rely on empirical choices for initial antifungal therapy drugs based on published susceptibility patterns while awaiting organism identification and susceptibility testing (Tab. 1).

Table 1. Susceptibility patterns of fungi to antifungal drugs commonly used to treat fungal endometritis in mares (from Coutinho and Alvarenga, 2011).

Antifungal Agent	Susceptibility pattern (% of isolates)		
	Susceptible	Intermediate	Resistant
<i>Polyenes</i>			
Amphotericin B	96	0	4
Natamycin	100	0	0
Nystatin	100	0	0
<i>Azoles</i>			
Clotrimazole	80	13	7
Ketoconazole	81	15	4
Miconazole	43	41	16
Itraconazole	62	38	0
Fluconazole	44	14	42
Flurocytosin	83	0	17

Several anti-fungal agents are available for intra-uterine therapy (Table 2). Fluconazole and itraconazole are reported to be absorbed following oral administration, with fluconazole being the most cost effective therapy in the horse. Oral administration of an antifungal agent can provide long term anti-mycotic activity and may be an important component of a multifaceted treatment program for fungal endometritis. Lufenuron has also been reported to be an effective treatment against fungal endometritis by inhibiting chitin synthesis in the cell wall. Lufenuron may not be effective in all cases as not all fungal organisms have chitin in their cell walls.

Tables 2, 3, and 4 list systemic medications and uterine therapies used in the treatment of fungal endometritis.



Table 2. Intrauterine medications used in the treatment of fungal endometritis.

Medication	Dosage, Route, Frequency
Amphotericin B (50 mg/vial)	100 to 200 mg reconstituted in 50 to 100 mls sterile saline
Clotrimazole	500-700 mg in 50 to 100 mls sterile saline
Fluconazole (200 mg/tablet)	100 to 250 mg in 50 to 100 mls sterile water; to reconstitute, add 5 mls DMSO to 1 gram (5 tablets) of fluconazole to dissolve; divide into 4 aliquots of 250 mg each; qs to 50 to 100 mls with sterile water
Lufenuron (Program [®]) (270 mg/packet)	540 mg in uterus suspended in 60 mls sterile saline, 270 mg applied to vaginal vault and clitoral area
Miconazole (1,200 mg insert)	1,200 mg insert deposited into uterus
Nystatin (100,000 IU/gram; 30 gram vial)	5 grams suspended in 50 to 100 mls sterile water; or 0.5 to 2.5 million units

Table 3. Systemic medications that may be used in the treatment of fungal endometritis.

Medication	Dosage, Route, Frequency
Fluconazole (200 mg/tablet)	14 mg/kg, PO, loading dose, followed by 5 mg/kg q 24h
Itraconazole (3 grams/packet)	3 - 5 mg/kg PO q 24h for 2 to 3 weeks or longer

Table 4. Uterine lavage therapies that may be used in the treatment of fungal endometritis.

Medication	Dosage, Route, Frequency
N-Acetylcysteine solution (20 %) (200 mg/ml)	30 mls (6 grams) diluted into 150 mls sterile saline infused into uterus
Dimethyl sulfoxide (DMSO) (99%)	50 ml DMSO per liter saline; may repeat as needed; follow with lavage with 1 liter saline or LRS
Hydrogen Peroxide (3 %)	60 to 120 mls infused into uterus; follow the next day with lavage using sterile saline or lactated Ringer's solution (LRS)
Lactated Ringer's Solution (LRS)	1 to 4+ liters; repeat lavage until effluent fluid is clear
Povidone-Iodine (Betadine [®] Solution) (1 %)	10 -15 mls added to 1 liter sterile saline
Saline (0.9 %)	1 to 4+ liters; repeat lavage until effluent fluid is clear
Tris-EDTA (Tricide [®])	250 to 500 mls infused into uterus; followed by uterine lavage with lactated Ringer's solution (LRS)
Acetic Acid (Distilled White Vinegar) (2 %)	20 – 100 mls added to 1 liter sterile saline

Mares are often treated empirically while awaiting results of antifungal susceptibility tests. A combination of two antifungal agents may be warranted in the event that the fungal organism is resistant to one of the agents. A potential protocol for treatment of a mare with fungal endometritis is presented below:

1. Uterine lavage during early estrus with sterile saline (plus acetic acid or other agent) and administer oxytocin (20 units, IM or IV) to promote evacuation of uterine fluid. May be repeated daily as needed.
2. Administer systemic fluconazole therapy (14 mg/kg loading dose PO, once; followed by 5 mg/kg maintenance dose PO q 24h for 2 to 3 weeks) (Scofield et al. 2013)
3. Administer intrauterine antifungal therapy using either nystatin (500,000 IU in 50 mls saline, IU q 24h x 5 days) or one miconazole pod (1,200 mg IU; once) as indicated by organism and antimicrobial sensitivity tests
4. Lavage uterus (\pm oxytocin) at conclusion of intrauterine therapy
5. Short-cycle mare with prostaglandins
6. Re-culture when back in estrus
7. Anticipate treatment for secondary bacterial infection (esp. *S. equi* subsp. *zooepidemicus*)

It is common for a moderate to heavy growth of a bacterial organism such as *Streptococcus equi* subsp. *zooepidemicus* to be detected in mares following treatment of fungal endometritis. Consequently, it is often necessary to treat for bacterial endometritis along with or after treatment for fungal endometritis.



Conclusion

Treatment of infectious endometritis due to latent bacteria, biofilm, or fungal organisms can be difficult. However, an understanding of the pathophysiology of the organisms in their current states can help when selecting treatment protocols.

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