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Nonantibiotic therapies for endometritis: what, when, and why

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Abstract

Endometritis, inflammation of the inner lining of uterus, can be caused by several insults. The simplicity of this definition belies the havoc it can wreak on a mare's reproductive efficiency. Potential inciting causes include a physiologic response to foreign invasion (breeding-induced endometritis), bacterial infection, fungal infection, and an iatrogenic interference in uterus. Regardless of its source, inflammation creates an inhospitable embryonic environment.

Keywords: Equine endometritis, mare, antibiotics

Introduction

Antibiotic use in human and animal medicines has rapidly accelerated since the discovery of penicillin in 1928. Consequently, microorganisms resistant to particular antimicrobials or classes of antibiotics have emerged. Growing trends in antimicrobial resistance underscore the urgency of directed, rational, and prudent antibiotic usage. Antibiotics are indispensable in treating endometritis. However, not all causes of uterine inflammation call for antibiotics, and many other therapeutic approaches can be used to decrease reliance only on antibiotics. Endometritis is not a foe that will be conquered by an ever-escalating arms race of antibiotics and chemical infusions. Rather, endometritis should be respected as a condition with which every reproductive clinician must coexist, and only through appreciating its origins and accordingly modifying its natural course success (pregnancy) can be achieved. At the forefront of this approach is a focus on diagnostic precision to ensure that all underlying and contributing causes are addressed.

Endometrial resistance has historically been attributed to physical clearance of irritants in response to appropriate local inflammation. Physical clearance requires an appropriate disposition of the genital tract,[1] competence and function of anatomical barriers,[2,3] myometrial contractility,[4,5,6] lymphatic drainage,[7]and mucociliary clearance.[8,9] Additionally, local cellular and humoral aspects of the immune system are important.[5]

Treatment of persistent endometritis includes restoration of appropriate external genital anatomy,[2] augmentation of uterine clearance,[4] and overcoming deficiencies in function of humoral and cellular immune response to endometrial contamination.[10] Excellent reviews discussing alternatives to primary antimicrobials for treatment of endometritis are available.[11,12]

Since reproductive efficiency declines in the face of poor systemic health, general physical examination and establishing an overall health are important components of initial approaches to treat endometritis. Age and immunosuppressive diseases (e.g. pituitary pars intermedia dysfunction) have potential impacts on body's resistance to infection and endometrial resistance to disease.[13,14]

Anatomic considerations

A mare's uterus is protected from external environment by 3 distinct caudal to cranial anatomic barriers: vulva, vestibulovaginal fold, and cervix. A compromise of 1 or more of these barriers will predispose a mare to uterine contamination and to subsequent endometritis. Any amount or type of antibiotic cannot effectively resolve this type of endometritis unless the anatomical cause is rectified.

Importance of mare's vulva, as the frontline barricade between environmental contaminants and reproductive tract, cannot be overemphasized. Functionality is compromised when vulva deviates from its ideal position of being vertically oriented, in the same plane as anus with > 70% positioned below the pelvic brim. Caslick's vulvoplasty is commonly performed to correct imperfect vulvar anatomy. Mares with more severe anatomical deficits may be good candidates for perineal body reconstruction (common approaches include the Gadd and Pouret techniques).

Moving inward, the next anatomical barrier is the vestibulovaginal fold. Assessment of vestibulovaginal fold can be made by parting the vulvar labia. Mares with an incompetent

vestibulovaginal fold will aspirate air that causes audible 'windsucking' and pneumovagina.

Cervix is the most cranial anatomical defense for the uterus. Longitudinal folds of cervix are contiguous with endometrial folds, thereby providing direct access from vagina to uterus. Cervix is dynamic throughout a mare's reproductive career. Its elasticity is illustrated by its ability to stretch to accommodate 50+ kg of foal at parturition and constrict to a neck that can sometimes be difficult to navigate even a small diameter instrument during diestrus. This plasticity is not to be taken for granted, as each extreme can pose challenges for managing endometritis. Cervix that is damaged during foaling trauma is vulnerable to lose its function to serve as a barrier to opportunistic ascending infections. In contrast, cervix that fails to appropriately dilate during estrus promotes debris accumulation within the uterus and exacerbates endometritis.

Beyond these major anatomic defenses of the uterus, description of endometritis would be incomplete if additional anatomic concerns were not discussed. Uterus that is substantially pendulous over the pelvic brim is prone to poor uterine clearance and subsequent accumulation of fluid and debris that will hamper efforts to achieve pregnancy. Mares that had trauma to the reproductive tract (e.g. dystocia), surgery (e.g. Cesarean section or mass removal), or iatrogenic exposure to irritating substances may be affected by adhesion formation or other mechanical disruption within the uterus and/or in caudal reproductive tract. Vesicovaginal reflux ('urine pooling') can have many contributing causes, including anatomic variables. Downstream effects of urine pooling include the potential for direct transport of pathogens into uterus, and for generalized vaginitis and endometritis.

Uterine lavage

Uterine lavage is the keystone of endometritis treatment. Uterine lavage provides a method of removing detritus and inflammatory products from the uterus and rinsing away planktonic bacteria. Uterine irrigation should be considered fundamental in treating endometritis without disregarding its inherent inflammatory effects. Autologous plasma, potassium penicillin, prostaglandin $F_{2\alpha}$ treatments reduced uterine neutrophils and cleared *Streptococcus equi* subspecies *zooepidemicus*; however, large volume lavage alone had similar effects.[15] Postbreeding uterine lavage 4 - 6 hours after breeding can be useful in managing postbreeding inflammation and to increase pregnancy rates.[16-18] Effective management of postbreeding inflammation may mitigate progression to chronic endometritis.[11]

Ecbolic therapy

Endometritis is classically (but not necessarily) accompanied by fluid accumulation within the uterine lumen. Evacuation of this fluid is the goal in therapeutic approaches. Ecbolic therapy can take on several forms that may be also used in combination. These include oxytocin, carbetocin, cloprostenol, acupuncture, and exercise. Small, frequent doses of oxytocin have substantial impact whereas larger doses can lead to tetanic uterine contractions that are ineffective. Hormonal status of the mare influences the recommended dose of oxytocin required to have a desired effect. Smaller doses of oxytocin (10 IU) are effective prior to ovulation, whereas after ovulation, larger doses (25 IU) may be necessary.[19] Carbetocin, a synthetic analog of oxytocin, has prolonged half-life (17.2 versus 6.8 minutes) and requires a smaller dose (1 mg carbetocin equivalent to 50 IU oxytocin).[20]

Cloprostenol, a synthetic analog of prostaglandin $F_{2\alpha}$ is an effective ecbolic agent for clearing intrauterine fluid.[21] Concern regarding its postovulation use is warranted; however, cloprostenol could be used until the second day after ovulation without negatively impacting pregnancy rates, despite having lower serum progesterone concentrations in mares receiving cloprostenol versus oxytocin.[22]

Acupuncture is an attractive adjunct therapy to increase uterine contractility and fluid clearance in mares.[23,24] Lastly, exercise represents extreme value in promoting fluid clearance, is economical, effective,[25] and easy to use.

Intrauterine treatments

Several nonantibiotic intrauterine therapies are available and considerable variation exists among clinicians regarding preferred treatment regimens. Commonly employed nonantibiotic intrauterine products include tris-EDTA, Tricide™ (Molecular Therapies, LLC, Athens, GA), dimethyl sulfoxide (DMSO), hydrogen peroxide, N-acetylcysteine, kerosene, Ceragyn® (CSA Biotech, Spanish Fork, UT), and bActivate™ (Bojesen and Petersen Biotech Aps, Copenhagen, Denmark). Recent and ongoing research has suggested amniotic microvesicle infusion,[26] lactoferrin,[27] and stem cells[28] as potential aids in combating endometritis, although these are not yet as widespread in clinical use as those mentioned above.

Tris-EDTA and its third-generation cousin Tricide® are chelators that presumably act to destabilize bacterial structural integrity, especially useful for those bacteria existing in a biofilm mass.[29] Tris-EDTA is safe in an equine uterus[30] and its activity against bacterial biofilms has been demonstrated in vitro.[31] Chelators are often instilled into the uterus following lavage and in conjunction with antimicrobials to potentiate their action.[32]

Despite a dearth of peer-reviewed resources to support its use in treating endometritis in mares, DMSO is utilized widely for this purpose. At increasing concentrations, DMSO induces membrane thinning, followed by transient membrane water pores, and then disintegration of membrane bilayer structure.[33] It is recognized as an antiinflammatory agent and has the ability to reduce biofilm biomass in vitro.[34] Intrauterine use of solutions containing up to 30% DMSO was safe.[35] Its economy, accessibility, and versatility of use make it an

attractive option for approaching endometritis.

Hydrogen peroxide, the household and medicine cabinet staple, exerts its antibacterial effects through free radical generation and subsequent oxidation. As with DMSO, controlled studies evaluating its use in the equine uterus are lacking; however, in vitro work suggests that it is an effective antibiofilm disrupting agent.[31] Anecdotally, 3 - 5% hydrogen peroxide infusion can induce palpable adhesions and serosanguineous discharge in some mares.

Povidone iodine is an antimicrobial commonly added to lavage fluids. After disassociation, iodine penetrates microbial cell membranes to oxidize proteins, nucleotides and fatty acids. Dilute preparations may be more rapidly bactericidal than full strength solutions.[36] Uterine lavage with 0.05% povidone iodine (5 ml of 10% betadine solution in a liter) was not associated with deleterious effects; however, infusion of 1% povidone iodine caused chronic endometrial inflammatory changes.[16,37]

The mucolytic N-acetylcysteine improved reproductive performance in mares and resulted in decreased COX-2 presence in endometrial biopsy samples.[38,39] We have observed enhanced sensitivity in diagnosis of bacterial endometritis when performing uterine lavage for culture and cytology following N-acetylcysteine infusion (Lu et al: unpublished data).

The proprietary commercial products Ceragyn® and bActivate™ are labeled for use in managing subfertility in mares. Ceragyn® mimics antimicrobial peptide, is intended to penetrate and destroy biofilms, and is available in both lavage and as infusion formulations for use within the equine uterus. bActivateTM is not a treatment for endometritis per se, but rather a method to complement diagnosis of subclinical endometritis due to dormant beta *Streptococcus* sp.[40]

Intrauterine infusion of kerosene is intended as a chemical curettage of the endometrium. Anecdotes attributed to success of kerosene are abundant; however, practitioners are cautioned that kerosene is not a panacea it may seem to be, and that inherent risks to mare and personnel exist with its use.[41] Case selection and client communication are important when using kerosene and for treatments that have no peer-reviewed clinical trials.

The idea that the equine endometrium has the ability to support a robust mucus layer that can aid and abet nefarious microorganisms is not new. However, the past decade's work[42] has promoted a resurgence of discussion regarding the potential for bacterial biofilm formation in the equine uterus and what can be done to diagnose and address this condition. It is challenging to definitively diagnose and characterize bacterial biofilm in vivo, leaving extrapolation from in vitro work as our current best resource for combating tenacious bacterial endometritis due to suspected biofilm presence. A project has evaluated 3.3% N-acetylcysteine, EDTA, and hydrogen peroxide as antibiofilm treatments against isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Of treatments evaluated, no single treatment was active against all bacterial isolates, highlighting an important point about the individuality of bacterial isolates.[31] This challenge has been addressed by the development of an in vitro biofilm assay that is currently available in clinical practice to target bacteria in a more bespoke fashion than empiric treatment selection.

Immune modulation and antiinflammatories

Use of glucocorticoids prednisolone acetate and dexamethasone around breeding in mares have been described to control inflammation. Oral prednisolone acetate (0.1 mg/kg, every 12 hours) improved pregnancy rates in a limited group of mares bred with frozen semen.[43] Similarly, intravenous dexamethasone (0.1 mg/kg) at breeding improved pregnancy rates in mares classified as at-risk for susceptibility to persistent mating induced endometritis.[44] Furthermore, in mares challenged by intrauterine inoculation of a known quantity of *Escherichia coli*, intravenous dexamethasone (0.1 mg/kg) resulted in modulation of the innate uterine immune response.[45]

Potential interactions between systemic corticosteroid treatment and pituitary/ovarian function should not be overlooked. Quarter Horse mares (n = 18) received either placebo, intravenous dexamethasone (0.05 mg/kg, twice a day) or oral prednisolone (0.5 mg/kg, twice a day) for 5 days in early estrus. Mares treated with dexamethasone had a 40% ovulation rate (2/5 mares), those treated with prednisolone had 83% ovulation rate (5/6 mares) and those receiving placebo had 100% ovulation rate (6/6 mares).[46] These results suggest case selection for using glucocorticoids should carefully weigh risks and benefits, and the lowest doses and length of therapy should be prescribed.

Nonsteroidal antiinflammatories can also be harnessed to control endometrial inflammation. Caution is necessary since a substantial increase in anovulatory follicle development was observed in mares treated with flunixin meglumine (2 mg/kg, twice a day, a supratherapeutic dose for standard antiinflammatory purposes),[47] and at therapeutic doses of meloxicam (0.6 mg/kg, once a day) and phenylbutazone (4.4 mg/kg, once a day).[48] In contrast, other projects involving flunixin meglumine at therapeutic doses (1.1 mg/kg, once a day)[49] and phenylbutazone (4.4 mg/kg, once a day)[50] observed substantial differences in ovulation rates compared to placebo treated mares. The cyclooxygenase-2 (COX-2) inhibitor firocoxib is an attractive choice given its more selective systemic effects and reduced postbreeding uterine inflammation (as assessed by polymorphonuclear cell presence on cytology and biopsy as well as endometrial COX-2 expression) while not negatively impacting ovulation.[51] Similar promising work from Europe has provided support for the use of the COX-2 inhibitor vedaprofen to improve pregnancy rates in mares.[52]

Although platelet rich plasma (PRP) has been considered as a more recent therapy in equine reproductive medicine, the

concept originated from a 1940 study with frog legs and it was observed that some unknown property of platelets controlled the formation of edema.[53] From these beginnings, PRP has evolved, and used widely in human and veterinary medicine for a wide range of purposes, from musculoskeletal and wound healing to dentistry and reproduction. Intrauterine infusion of PRP has modulated the immune response in mares previously diagnosed with chronic degenerative endometritis[54] and improved pregnancy rates in mares classified as susceptible to persistent mating induced endometritis.[55]

Measured exposure to emasculated bacterial products has been demonstrated to have positive immune effects. Immune stimulation through systemic treatment of *Propionibacterium acnes* (EqStim®, ImmunoVet, Inc., Tampa, FL) improved endometrial cytology scores and pregnancy rates in barren mares.[56,57] Recently, mares were inseminated and treated intravenously with either dexamethasone (50 mg at insemination) or mycobacterial cell wall extract (MCWE, Settle®, NovaVive, Ontario, Canada, 1.5 mg, at 24 hours prior to insemination). Nitric oxide concentrations in uterine secretions and inflammatory cytokine presence in uterine biopsy samples (collected 6 hours after insemination) were used as end points for assessing uterine inflammatory response. Mares treated with MCWE had lower nitric oxide concentrations in uterine secretions than untreated mares or mares treated with dexamethasone.[58]

Conclusion

Historical and ongoing research have identified several products and techniques that have the potential to aid in the resolution of endometritis. When approaching this ever-expanding 'pantry of options', a strategic approach rooted in fundamentals is advised. Critical consideration of why a mare is 'dirty' or 'problematic' will provide a blueprint for addressing underlying factors and primary endometritis.

Conflict of interest

There are no conflicts of interest to declare.

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