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Immunology and immunomodulation of the reproductive tract
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Introduction
Persistent endometritis is a major cause of reproductive wastage and hence economic loss to the equine breeding industry. The endometrium of the mare is periodically exposed to numerous irritants and potentially infectious agents during breeding, iatrogenically during veterinary procedures, and when normal defense mechanisms become incompetent.

Multiple physical and functional barriers exist to prevent or minimize contamination between episodes of breeding and during pregnancy. Once introduced to the endometrium infectious agents encounter both innate and adaptive immune defenses consisting of both cellular and humoral factors. Components include the epithelial mucus barrier, resident innate immune cells, and their pro-inflammatory secretions that minimize the risk of infection. Acting in concert with the innate immune system, the adaptive immune system includes both cell-mediated and humoral responses generated towards specific pathogens. Cells of the innate and adaptive immune systems are influenced by the ovarian sex hormones, local growth factors, and the commensal genital tract flora. Much of what is known has been determined from laboratory species, humans and production animals. In the current review, this will be extrapolated to the horse where applicable.

Background
The reproductive tract of the mare is a dynamic organ system, rhythmically changing under the influence of estrogen and progesterone of ovarian origin. While providing protection against sexually transmitted pathogens and environmental contaminants, it must tolerate commensal flora present in the lower reproductive tract. The endometrium must also allow for tolerance of sperm, develop an appropriate and limited inflammatory response following mating to initiate uterine clearance and increase chances for conception, provide an environment for fertilization and implantation of the conceptus, and facilitate growth of the genetically distinct fetus.

The tubular female reproductive tract can be divided into a number of regions with differing structure and function. These include the oviducts, uterus, cervix, vagina and vestibule. The mucosal lining varies between these regions, but all consist of an epithelial lining with underlying stroma which display a cycle-dependent structure composed of mucous glands, vascular tissue, and cellular components. This mucosal barrier to infection is not merely physical, but instead consists of innate cellular and chemical responses to the invasion of potential pathogens. These responses vary with the region of the tract involved. During natural mating, stallions ejaculate into the uterus, thus placing the burden of immunological response post-breeding on the endometrium.

Resistance of the mare endometrium to the establishment of persistent endometritis has historically been considered the result of physical clearance of irritants and an appropriate local inflammatory response. Physical clearance requires an appropriate disposition of the genital tract competence and function of anatomical barriers,myometrial contractility,lymphatic drainage, and mucociliary clearance. Local cellular and humoral aspects of the immune system have been widely investigated. These include immunoglobulin and complement concentrations and polymorphonuclear neutrophil function.

Treatment of persistent endometritis has sought to overcome deficiencies in the immune response of the uterus as a whole, and has varied over time as more has become known about the factors operating. Restoration of appropriate external genital anatomy, augmentation of uterine clearance, and treatment of specific infections with antimicrobials and/or chelating agents have become the mainstays of current treatment, although for some time deficiencies in function of both the humoral and cellular immune response to endometrial contamination were thought responsible for the persistence of endometritis. However, impaired uterine defenses were shown not due to a local immunoglobulin deficiency.
Responses to endometrial challenges

Local innate immune responses

Mucosal epithelial cells form a physical and immunological barrier, initiate signaling of the underlying immune system, are involved in production of cytokines and chemokines, participate in apoptosis and phagocytosis of infected cells, enable activation of the adaptive immune response, and initiate an acute inflammatory reaction in response to irritation or infection.17 The mucosal epithelial barrier is affected by cytokines, ovarian hormones, Toll-like receptor (TLR) agonists, and the presence of pathogens.18 In addition to the epithelial cells themselves, the mucosal barrier is augmented by a mucus layer preventing direct contact with potential pathogens.19 Mucus consists of water and mucin, a high-molecular-weight glycoprotein that can trap microorganisms.20 Amount of mucus and its properties vary depending on sex hormones. Estrogen dominance leads to mucus that is less viscous and more favorable for sperm migration, whereas mucus during progesterone dominance is comparatively thick, sticky, and hostile to the passage of sperm into the uterus.21

During the initial stages of the immune response, antigen presenting cells (APC) which include dendritic cells and macrophages express a multitude of surface molecules which non-specifically recognize pathogen-derived molecules or pathogen-associated molecular patterns (PAMPs). The best known of these surface molecules are a family of transmembrane proteins known as the Toll-like receptors (TLRs), however a number of other surface molecules performing a similar function have been elucidated.22 Exogenous molecules recognized include bacterial lipopolysaccharides (LPS), lipoproteins and peptidoglycans, and viral RNA and DNA. The TLRs are able to respond to a diverse array of structures, however they may require simultaneous binding to other endogenous cell surface receptors (e.g. in the case of TLR4 binding to CD14 is necessary to bind LPS) to respond. Once engaged, the TLRs initiate downstream signaling by recruitment of one or more adaptor proteins, the MyD88-dependent cascade which leads to secretion of pro-inflammatory cytokines, or the TRIF-dependent cascade which results in production of type 1 interferon (IFN) in addition to inflammatory cytokines and chemokines. These in turn promote genomic protein transcription by NF-κB and initiation of a non-specific immune response.1 TLR4 is involved in the recognition of lipopolysaccharide on the surface of Escherichia coli, commonly isolated from mare endometritis cases.23 Response to bacterial pathogen invasion may be different however as TLR4 expression by the endometrium in one equine study was not altered by insemination with live sperm.24

Toll-like receptors and antimicrobial peptides have been demonstrated in the bovine endometrium.25 The response of the endometrium to bacteria and their purified PAMPs has been investigated using ex vivo bovine endometrial explants, with IL-6, IL-1β and IL-8 produced with the inflammatory response dependent on the stage of the estrous cycle.26 In the equine, endometrial mRNA expression of pro-inflammatory cytokines (IL1-β, IL-6, TNF-α and IL-8) increases and anti-inflammatory IL-10 decreases after insemination with killed sperm.27,28 Neutrophil chemotaxis requires IL-8 which is expressed in higher levels in mares susceptible to endometritis compared to those resistant during estrus.28

Complement cleavage factor C3b has been demonstrated in mare uterine secretions during infection.16,29,30 In one study complement was shown to be an important contributor to opsonization activity in uterine secretions preceding an inflammatory response.31 The complement system may directly lyse the infectious agent. Other inflammatory products include PGF₂α, secreted in response to uterine inflammation and correlated to neutrophil numbers.32,33 Acute phase proteins are also present, with α1-antitrypsin recovered from uterine flushings however this was not increased following induction of bacterial endometritis, and was instead related to cycle stage with levels in estrus greater than diestrus.34 As levels were correlated to albumin present in uterine fluid, a systemic origin of α1-antitrypsin was determined.

Antimicrobial peptides have also been demonstrated in the reproductive tract, and are considered an ancient mechanism of the innate response.35 In addition to microbiocidal activity they affect cytokine induction, chemotaxis, cell proliferation, and modulate both innate and acquired immunity.36 These
compounds act synergistically and have redundancy of function enhancing protection over any single factor. \(^{37}\) Members include lactoferrin, the defensins, elafin, cathelicidin, and lysozyme, being produced by both epithelial cells and neutrophils\(^ {35}\) with regulation by bacterial activity, hormonal status and inflammation. \(^ {38}\)

Epithelial cells, macrophages, natural killer cells, and neutrophils produce cytokines and chemokines. Chemokines are cytokines with potent local chemotactic properties, recruiting leukocytes to site of inflammation. \(^ {39}\) Subsequent to this, local cytokines enable the differentiation and activation of the attracted leukocytes. \(^ {40}\) Secretion has been shown experimentally in other species to be preferentially to the cell apex or uterine lumen creating a gradient along which to attract cells to the endometrium. \(^ {41}\) Additionally, bactericidal and virucidal agents are enhanced, these providing a system of defense during times the adaptive immune response is downregulated, particularly by sex hormones during pregnancy.

Innate cellular responses are provided by dendritic cells (DC), macrophages, and natural killer (NK) cells. Dendritic cells are essential for induction of the immune response, prevent infection by direct inactivation, and as the major APC of the reproductive tract provide a link between innate and adaptive immunity. Location is variable, being the subepithelial stroma of the endometrium and epithelium of the vagina. \(^ {42}\) Exposure to pathogens and inflammatory stimuli, such as lipopolysaccharide (LPS), leads to maturation of DC which can then enable the development of T-helper 1 (Th1) cells. \(^ {42}\) Function and differentiation of DC is the result of local cytokines, chemokines and ovarian steroids. \(^ {43}\) In addition to induction of a protective immune response, DC are also integral in the induction of immunological tolerance essential for the maintenance of pregnancy. \(^ {44}\) Macrophages are involved in inflammatory responses, removal of debris, pathogen recognition, and stimulus of the immune system via production of cytokines and chemokines. Widely distributed throughout the reproductive tract, migration into the endometrium is influenced by estradiol and progesterone. \(^ {45-47}\) Macrophage proliferation and function is influenced by estrogen, \(^ {48}\) while phenotype reflects the local environment. \(^ {40}\) Natural killer cells are key innate immune cells, both promoting the immune response and by secretion of cytotoxic compounds eliminating virus-infected and neoplastic cells. \(^ {49}\) The inflammatory response is amplified, macrophage activation promoted, cytotoxic T cells are generated, and cytokines produced. \(^ {50}\) Within the uterus, specialized uterine NK cells (uNKs) express multiple TLR and produce cytokines in response to TLR agonists further activating of innate immunity. \(^ {49,50}\) Eosinophils are occasionally seen within the endometrium and have been associated with failure of anatomical barriers and thus pneumometra. \(^ {51}\) Eosinophils have also been associated with fungal infection. \(^ {52}\)

Local adaptive immune responses

The adaptive immune response is initiated by specific pathogens. Following pathogen capture and processing of antigens (innate immune response) APCs present the non-self ligands in conjunction with MHC class 1 and 2 molecules. The APC themselves are highly secretory promoting both local and systemic inflammatory and immune responses. With the benefit of expression of costimulatory molecules also induced by the non-self antigens, APCs are involved in the activation of both specific B and T lymphocyte function (adaptive immune response). Lymphocytes in turn crosstalk with activated macrophages to promote efficient phagocytosis. Adaptive immunity includes Th1 (cell-mediated), Th2 (humoral), and T regulatory responses. Th1 based immunity is driven primarily by T lymphocytes and results in destruction of intracellular pathogens. The CD8+ cytotoxic T cells target infected cells via MHC class I molecules on the cell surface, inducing apoptosis and cytolysis. \(^ {53}\) High levels of IFN-\(\gamma\) are secreted by CD4+ T cells which regulates cytotoxic T cells while also blocking viral replication. \(^ {54}\)

Humoral immunity is based on the production of specific antibodies that bind antigens (cell-associated or free) interfering with cellular invasion or directly neutralizing the pathogen. Phagocytosis by macrophages is enhanced. The transformation of B cells to plasma cells is facilitated by the CD4+ helper T cells. \(^ {55}\) Antibody production in the genital tract is influenced by ovarian activity. In the uterus, IgA and IgG are experimentally elevated in rats by estradiol. \(^ {56}\) In contrast, vaginal antibody levels are decreased. \(^ {57,58}\) In response to estrogen, IgG moves down a concentration gradient from blood to tissue.
before entering the luminal fluid, either by paracellular diffusion or receptor facilitated means. In contrast, IgA travels against a concentration gradient as in the male.\textsuperscript{59} Difference in class, anatomical distribution, and antibody level implies compartmentalization in the immune function throughout the female reproductive tract, with modifying hormonal influences. Furthermore, these responses must be tailored to provide specific pathogen protection while allowing maintenance of the fetal allograft.

Antibodies, IgA and protein levels were investigated in mares categorized as infected by bacteriology and supportive cytological findings.\textsuperscript{60} Infected mares were found more likely to have elevated levels of IgA and protein, while levels of IgG were not increased. Progesterone treated acyclic mares were found to have higher numbers of bacteria and IgA compared to control mares, further supporting the finding of increased IgA in infected mares.\textsuperscript{7}

Systemic inflammatory and immune responses

Serum amyloid A (SAA) concentration has been widely investigated as a systemic marker of inflammation in the horse.\textsuperscript{61-63} Uterine inflammation is a normal post-breeding event in the mare.\textsuperscript{4} Histologically normal endometrium of the mare has been shown to constitutively express mRNA for SAA in moderate levels.\textsuperscript{64} Conflicting information exists regarding a detectable systemic SAA response to endometritis as in one study a systemic increase in levels was not found\textsuperscript{24} however in another plasma SAA levels were found significantly correlated with endometrial SAA gene expression.\textsuperscript{65} In experimentally induced placenitis, SAA was found to be elevated within 96 hours after intra-cervical inoculation of \textit{Streptococcus zooepidemicus}.\textsuperscript{66}

Response to breeding

Spermatozoa in the uterus induce rapid chemotaxis of polymorphonuclear cells that are detectable in the uterus as soon as 0.5 hours after AI and peak at 4-8 hours after AI.\textsuperscript{67} Endometrial mRNA expression of pro-inflammatory cytokines (IL1-β, IL-6, TNF-α and IL-8) increases and anti-inflammatory IL-10 decreases after insemination with killed sperm.\textsuperscript{27,28} In a study comparing the inflammatory response to frozen semen and extender alone, the luminal neutrophil response was found to be greater in mares inseminated with the frozen semen, while macrophages, lymphocytes and plasma cells did not differ between the groups.\textsuperscript{24} Concentrations of prostaglandin (PG) F2α increased 16 hours after both frozen semen and extender treatments, SAA did not change with treatment, and IL-8 and TLR4 (the key receptor of pathogen associated molecular patterns) had no changes in expression.\textsuperscript{24}

Mares susceptible to post-breeding inflammation have higher basal levels of mRNA expression of proinflammatory cytokines compared to normal mares.\textsuperscript{27} At 24 hours after insemination, susceptible mares also have increased mRNA expression of IL8, a neutrophil chemoattractant, and lower expression of IL10, an inflammation modulating cytokine.\textsuperscript{25,68} In another study evaluating endometrial inflammatory markers within the first 24 hours after breeding, differences were detected between susceptible and resistant mares 6 hours after insemination. Resistant mares had higher mRNA expression of IL-6, IL-1 receptor antagonist and IL-10 compared to susceptible mares, while susceptible mares had an increased numbers of polymorphonuclear cells 2 and 12 hours after insemination when compared to resistant mares.\textsuperscript{69} This suggests a deficiency in the immunomodulatory response in mares susceptible to post breeding endometritis.

Additional studies have evaluated uterine nitric oxide (NO) production associated with breeding induced endometritis.\textsuperscript{70} During inflammation, nitric oxide is produced by inducible nitric oxide synthase (iNOS), a calcium independent mechanism of producing large amounts of nitric oxide. Inflammatory signals such as IL-1 and IFN-γ lead to transcription of iNOS. Effects of NO include removal of pathogens and smooth muscle relaxation. These studies revealed differences in intrauterine NO between mares that are sensitive to or resistant to breeding induced endometritis however it remains unclear whether this difference is a cause or an effect of endometritis.
Treatments to modulate the immune response in the non-pregnant mare

Glucocorticoids

Glucocorticoid use has been reported as a successful method of controlling post-breeding endometritis. Compounds investigated include prednisolone acetate (0.1 mg/kg) and dexamethasone (50 mg IV per horse). In a fertility trial evaluating the use of prednisolone, thirty cycles of fifteen mares were evaluated comparing frozen semen insemination without immunomodulatory treatment followed by insemination with corticosteroid therapy. Corticosteroid therapy consisted of 0.1 mg/kg prednisolone acetate administered when a 35 mm follicle and endometrial edema were present, followed by repeat administration every 12 hours until ovulation was detected. In this trial, none of the mares achieved pregnancy without prednisolone treatment and 64.5% achieved pregnancy with prednisolone treatment. Dexamethasone (0.1 mg/kg IV) administered once at the time of breeding was evaluated for efficacy in reducing breeding induced inflammation and increasing pregnancy rates in susceptible mares. Dexamethasone decreased post-breeding small volume lavage efflux turbidity and endometrial edema. Dexamethasone did not alter the pregnancy per cycle rate, however in mares that were determined to be at high risk of developing post-breeding endometritis with at least three of the study’s risk factors, pregnancy rates were significantly improved. Risk factors included: abnormal reproductive history, positive endometrial culture, at least 2 cm endometrial fluid prior to breeding, abnormal perineal conformation or unrepaird Caslick’s surgery after foaling, abnormal cervix, greater than 1.5 cm post-breeding fluid, post-breeding fluid persisting beyond 36h, and abnormalities of the reproductive tract. A recent study evaluated use of 0.1 mg/kg IV dexamethasone with intrauterine infusion of 10^5 CFU of E. coli to assess changes in pro- and anti-inflammatory cytokine expression. Treatment with dexamethasone caused a significant effect on endometrial expression of cytokines and SAA in susceptible mares. Of the pro-inflammatory cytokines, decreased expression of IL-1β was observed, an increased expression of IL-6 was noted immediately after dexamethasone administration, and IL-8 (a potent chemoattractant for transepithelial migration of PMNs into tissue) expression was decreased. The anti-inflammatory cytokines IL-10 and IL-1ra had increased expression following dexamethasone administration.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in clinical practice to manage inflammation associated with breeding, embryo transfer, and placentitis. In a study evaluating the COX-2 inhibitor vedaprofen, barren mares (n=8) with a history of post-breeding endometritis were treated (2 mg/kg PO initial dose, 1 mg/kg PO BID) beginning the day before artificial insemination and continuing until 1 day after ovulation. These mares were compared to an untreated group though all mares received oxytocin. This study found a significantly improved pregnancy rate among mares treated with the COX-2 inhibitor around the time of breeding.

Immunostimulants

Mycobacterium phlei cell wall extract (MCWE) is available as Settle (Bioniche Animal Health, Athens, GA) with the licensed indication as an aid in the treatment of equine endometritis caused by Streptococcus zooepidemicus by enhancing the innate humoral immune response. In a study assessing the endometrial mRNA expression of the proinflammatory cytokines IL-1β, IL-6, and TNF-α in mares resistant and susceptible to post-breeding endometritis, intravenous MCWE treatment at the time of artificial insemination modulated mRNA expression of cytokines such that no differences between the two groups was found. A recent study evaluated use of 1.5 mg Settle with intrauterine infusion of 10^5 CFU of E. coli to assess changes in pro- and anti-inflammatory cytokine expression. This study did not find MCWE to significantly modulate the endometrial inflammatory response in contrast to previous studies. Immunostimulants containing Propionibacterium acnes (EqStim, Neogen Corp, Lexington, KY) has been shown to induce a non-specific cell-mediated response predominantly by macrophage activation.

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and cytokine release. In a study evaluating its efficacy in a clinical setting, 95 mares with cytologic evidence of endometritis were randomly administered *P. acnes* or placebo additional to other veterinary treatments. This study found improved pregnancy and live foal rates.75

**Plasma**

Autologous intrauterine plasma infusion reportedly provides serum-derived opsonins to enhance phagocytic function. One study describes the intrauterine infusion of 100 mL frozen-thawed autologous plasma either as part of active endometritis therapy in conjunction with uterine lavage (n=24) or as a post-breeding infusion in mares with subclinical endometritis (n=3). Pregnancies were achieved in 62.5% of the first group and 100% of the second group.76 In a subsequent study, mares with induced mild to moderate lymphocytic endometritis were treated with 100 mL intrauterine plasma daily for 5 days similar to the above report (n=16) or received no intrauterine treatment (n=10). This study revealed no significant differences between treatment and control groups.77

A variation of autologous plasma is infusion of platelet-rich plasma (PRP). The use of PRP is widely practiced in orthopedic cases in an attempt to expedite healing with growth factors and inflammatory modulators. Recently, practitioners have described its use in the uterus for treatment of post-breeding endometritis. One study evaluated the efficacy of infusion of 20 mL autologous PRP (containing on average 257,000 platelets per microliter) 4 hours after insemination in 15 mares resistant to post-breeding endometritis and 8 mares susceptible to post-breeding endometritis. Parameters evaluated included nitric oxide concentration in uterine fluid, percent neutrophils in uterine cytology, and uterine fluid quantity 24 hours after insemination. In resistant mares, the only significant difference was in percent neutrophils in cytology. In susceptible mares, a significant difference was seen in percent neutrophils, nitric oxide quantity and uterine fluid leading the group to conclude that PRP reduced the inflammatory response after breeding.78 Another study described improved pregnancy and decreased post-breeding fluid in mares susceptible to post-breeding endometritis following PRP infusion.79

**Pregnancy**

Pregnancy maintenance requires the maternal immune system to tolerate the antigenically different fetal and placental tissue. Mechanisms to achieve this have been divided into three categories: 1) suppression of paternally inherited alloantigens such as MHC antigens; 2) altered maternal immune response during pregnancy; and 3) local immune modulation at the interface between uterus and placenta.80

The majority of the allantochorionic trophoblast cells suppress the expression of major histocompatibility class (MHC) II genes that are involved in the activation of CD4+ helper T lymphocytes. Allantochorionic trophoblasts of the horse also fail to express MHC class I molecules that are targeted by alloantibodies and CD8+ cytotoxic T cells. Equine chorionic girdle and early endometrial cup trophoblast cells do express MHC class I molecules, similar to other species in which the most invasive trophoblast cells express MHC class I molecules for reasons that are not completely understood. These MHC class I antigens induce strong maternal antibody responses in early gestation.80

While the mare may mount a systemic humoral immune response to paternal MHC class I antigens, the cell-mediated immune response appears to be suppressed. During pregnancy, mare peripheral blood lymphocytes are less able to develop into cytotoxic T lymphocytes.81 Though this may be advantageous to spare the fetus, there is potential that this may make the mare more vulnerable to certain types of infection. Progesterone also seems to modulate the immune response in the uterus. In experiments in sheep, progesterone supplementation prolonged survival of allografts in the endometrium compared to controls without progesterone supplementation.82

The mare exhibits a local immune response in the form of CD4+ and CD8+ T cells surrounding the endometrial cups. Trophoblast cells produce factors that appear to locally modulate the immune response by limiting T cell function or inducing apoptosis.83 In the majority of mares, endometrial cups have a lifespan of approximately 60 to 80 days, forming at approximately 40 days gestation and persisting until around 120 days gestation. In a recent study investigating the role the immune system surrounding
the endometrial cups plays in their degradation of the cups, equine chorial girdle trophoblast tissue was transplanted into severe combined immunodeficient (SCID) mice that would be unable to mount an immune response to the transplanted tissue. In these animals, the trophoblast lifespan was approximately the same duration as expected in the pregnant mare, suggesting that the maternal immune response does not play the largest role in elimination of endometrial cups.84

In later gestation, placentitis is of significant concern as a cause of fetal loss. In an experimental placentitis model, infection was associated with high concentrations of PGE₂ and PGF₂α in the allantoic fluid and elevated mRNA expression for IL-8, TNF-α, IL-6, and IL-1β in the chorioallantois.85

**Treatments to modulate inflammation in placentitis**

Pentoxifylline is a theobromine derivative, non-selective phosphodiesterase inhibitor. Phosphodiesterase inhibitors can decrease uterine activity by increasing intracellular c-AMP concentrations and thus lowering Ca++ concentration. Pentoxifylline down-regulates pro-inflammatory cytokines such as TNF-α, IL-6 and IFN-γ. This drug also increases erythrocyte flexibility, fibrinolytic and tissue plasminogen activator activity and inhibits platelet adhesion.86

In mares, pentoxifylline has been shown to reach the allantoic fluid in normal pregnancy and in experimental placentitis models.87 Pentoxifylline has been detected in placental and fetal tissues at foaling, confirming its ability to cross the placenta and reach the foal.88 Additionally, a combination of altronegost, antimicrobials and pentoxifylline (8.5 mg/kg PO BID) resulted in increased number of live foals in an induced placentitis study.89

Non-steroidal anti-inflammatory agents such as flunixin meglumine (1.1 mg/kg) are commonly used as part of pregnancy maintenance therapy. Support for this modality can be found in the finding of high concentrations of PGE₂ and PGF₂α in the allantoic fluid as described above.85

**Conclusion**

For the practitioner, having a basic understanding of the immunology of the reproductive tract can guide the choice and application of treatments to stimulate or suppress the immune system in attempt to establish pregnancy or coax a pregnancy to term. Optimizing immunological function can only occur once anatomical defects are corrected, uterine clearance is enhanced, and specific infections have been addressed.

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