The “problem mare” has been defined as 1) any mare that despite breeding to a fertile stallion and timely ovulation fails to conceive after three consecutive breedings, 2) a mare that cannot carry a pregnancy successfully to term, or 3) a mare with known reproductive or overall health issues which prevents conception, maintenance of pregnancy, and normal parturition. There is an extensive list of causes for why a mare is identified as a “problem mare,” but the most common causes that are identified include: bacterial endometritis, persistent mating-induced endometritis, cervical pathology (failure to relax, failure of cervical competency), failure of uterine clearance, and ovulation abnormalities (anovulatory follicles, hemorrhagic follicles, irregular cycles). Management of these mares requires identification of the cause for infertility and should include an intense investigation of the mare’s history, systemic health and condition, conformation (overall and perineal), a thorough reproductive examination (character of the reproductive tract, aerobic culture and cytology of the mare’s endometrium, uterine biopsy) and identifying any anatomical defects that require surgery or more intense management.

<table>
<thead>
<tr>
<th>Common Causes of Infertility</th>
<th>Less Common Causes of Infertility</th>
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<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
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<tr>
<td>Illness, laminitis, abnormal condition (obesity or cachexia)</td>
<td>Chromosomal abnormalities, PPID?, Metabolic syndrome?</td>
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<tr>
<td><strong>Ovarian</strong></td>
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<tr>
<td>Anovulatory follicles, hemorrhagic follicles, irregular ovulation/estrus, failure to develop dominant follicle or follicular waves, shortened luteal phase or luteal insufficiency (often associated with endometritis)</td>
<td>Neoplasia, cysts(ovarian, fossa cysts)</td>
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<tr>
<td><strong>Oviduct</strong></td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td>Occluded oviducts, parovarian cysts</td>
</tr>
<tr>
<td><strong>Uterus</strong></td>
<td></td>
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<tr>
<td>Bacterial endometritis, Persistent mating-induced endometritis (PMIE), cysts, periglandular fibrosis (associated with IIB-III endometrial biopsy grade)</td>
<td>Fungal endometritis, persistent endometrial cups, foreign body (marbles, fetal remnants), neoplasia</td>
</tr>
<tr>
<td><strong>Cervix</strong></td>
<td></td>
</tr>
<tr>
<td>Failure to dilate (fibrosis, maiden, breed).cervical</td>
<td>Minor cervical defects, neoplasia</td>
</tr>
</tbody>
</table>
In the last few years there have been several new treatments, management schemes, and advances in our arsenal of tools that we can reach for in managing the problem mare. Reproductive management of the problem mare is complex, and multiple opinions and treatment plans are usually effective, making it difficult to determine which treatment is “best.” Below is a summary of new, published findings and treatments that I have found useful in my management of the problem mare and I hope this information is helpful or may give you some new options.

Systemic Health
1) Omega-3 (N-3) fatty acids, specifically docosahexaenoic acid (DHA), have been shown to confer anti-inflammatory properties in many species by inhibiting the production of cytokines involved in acute and chronic inflammation. Reproductive benefits of supplementation are now being published, including positive effects for mares and stallions. In mares it has been shown that daily supplementation with an algal N-3 fatty acid (14,400mg of N-3 fatty acids, 4,000mg DHA from micro-algal source) resulted in reduced post-breeding inflammation (reduced uterine fluid and neutrophils in the uterine lumen after 63 days of supplementation) in both susceptible and resistant mares.1
   a. Recommended treatment:
      Administer omega-3 fatty acids (15,000 mg N-3 fatty acids) daily, beginning approximately 2 months prior to the breeding season and maintain through gestation. Reliable products include KER (EO-3, dose: 1.5 ounces daily (35% omega-3) and Wellpride.

Oviduct Treatments
   The incidence of true oviductal blockage as a cause for infertility has not definitively been proven. That being said, there is a body of research showing that oviductal flushing (antegrade and normograde) and topical application of PGE₂ (to facilitate oviductal plug expulsion) by various surgical techniques has improved fertility in a very specific subset of mares. A new technique described by Dr. Inoue in 2013 that does not require surgery and can be achieved by hysteroscopic catheterization and antegrade flushing of the oviduct. This procedure is less invasive, has decreased risk with regard to surgery and potential rupture of the oviduct, and has been shown to be effective in a small group of infertile mares. Mares to consider treatment for oviductal blockage should be mares that all other causes of infertility have been ruled out (stallion, full breeding soundness exam reveals no abnormalities, no chromosomal abnormalities).

Uterine Treatments
   Broad-spectrum anti-microbials/mucolytics
   1) Acetylcysteine (NAC) is the N-acetyl derivative of the amino acid L-cysteine, a precursor in the formation of the antioxidant glutathione in the body. It has anti-inflammatory effects (antioxidant and reduces free radicals) and mucolytic effects. It is
useful in removing mucus that may be abnormal in mares with PMIE, or infused prior to antimicrobial use for bacterial or fungal endometritis to remove mucinous debris and facilitate antimicrobial penetration and efficacy. It has been demonstrated that NAC decreased biofilm produced by certain gram-negative bacteria (E.Coli)\(^2\).

a. Pre-breeding recommendation: Infuse NAC (33% solution, dilute 30 mL 20% solution into 150 mL sterile saline) 24-48 hours prior to breeding. Administer ecbolic agents (oxytocin 20IU IM every 6-8 hours but not within 4 hours of breeding), or uterine irrigation with sterile lactated ringers prior to breeding if debris is excessive. Studies have shown pre-breeding NAC infusion increased the per-cycle pregnancy rate in a group of barren mares\(^3\) and had no significant effect on sperm motility at concentrations of 0.5% or 1% when directly added to cooled extended semen and frozen semen\(^4\).

b. Pre-antimicrobial recommendation: Infuse 33% solution (150 mL volume) into the uterus 24 hours prior to antimicrobial treatment, and lavage prior to antimicrobial treatment. If the efflux is cloudy, it is recommended to repeat treatment prior to antimicrobial infusion. NAC has been shown to reduce antibacterial activity of aminoglycosides, fluoroquinolones & erythromycin and enhances efficacy of β-lactams against several bacterial strains.

2) **Tricide/ (EDTA-tris)**

EDTA-Tris (ethylene diamine tetra-acetic acid-tromethamine) is an agent that chelates calcium and magnesium, components of the cell wall of bacteria and fungi. EDTA-Tris has been shown to have broad-spectrum, anti-microbial and anti-biofilm properties and can even have synergistic effects when combined with certain antimicrobials. Its use has been adapted to the mare from use in cases of chronic canine otitis externa, dermatitis, and fungal keratitis. Its anti-biofilm properties have been demonstrated, and it appears to be most effective against biofilm produced by *P.aeruginosa* & *E. coli*\(^5\).

a. **Recommended use**: Infuse Tricide (8mM disodium EDTA dehydrate and 20mM 2-amino-2-hydroxymethyl-1,2propanediol 500-750 ml\(^6\). Must lavage uterus 6-24 hrs post infusion. Repeat 2-3 days until efflux is clear/free of debris. Can be added to amikacin, gentamicin or clotrimazole (decreases the MIC 90 of some bacteria). Decreases MIC 90 of penicillin based drugs. Do not add to ceftiofur, K Pen or Timentin\(^6\).

3) **Cationic Steroid Antimicrobial (CSA)**

CSA is a class of peptides that are now being synthesized which have demonstrated broad spectrum antibacterial, anti-vial, and some anti-fungal properties. They cause depolarization of bacterial cell membranes and activate apoptotic pathways leading to cell death. These peptides have been used in human medicine as anti-biofilm peptides that are incorporated into catheters to prevent biofilm formation, used for treatment of chronic wounds and valued for their broad-spectrum, anti-biofilm, anti-microbial properties. They also have the benefit of having a decreased risk of bacterial resistance. There is currently a product on the market (Ceragyn uterine infusion) that has been shown to be no more irritating than saline when infused into the uterus of mares and contains a mimic CSA-13 to these antimicrobial peptides.

a) **Recommended use for Ceragyn product:**
1) Uterine lavage: Mix 60 ml with sterile saline or LRS and use as a pre- or post-breeding lavage.
2) Uterine infusion: Administer 60 ml as a uterine infusion to treat bacterial or fungal endometritis

References