

How to Diagnose and Treat Fungal Endometritis

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The diagnosis of fungal endometritis can be made with routine uterine cytology and culture. An antifungal drug sensitivity screen should be performed and intrauterine therapy continued for 7–10 days. Any reservoirs of infection or anatomical defects should be identified and treated. Use minimal contamination breeding techniques and minimal breedings to prevent re-occurrence. Author's addresses: Virginia-Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061 (Dascanio); Oklahoma State University, College of Veterinary Medicine, Stillwater, OK 74078 (Ley); and Cornell University, College of Veterinary Medicine, Ithaca, NY 14853 (Schweizer). © 2000 AAEP.

1. Introduction

The term fungal is a general one referring to both yeast and molds. Yeast are widely distributed in soil, animal excreta, in the vegetative parts of plants, and in substances that contain sugars.¹ Fungal endometritis specifically refers to a yeast infection involving the endometrium. Yeast organisms reported to colonize the equine reproductive tract include *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Candida lusitanae*, *Candida rugosa*, *Cryptococcus neoformans*, *Hansenula anomala*, *Hansenula polymorpha*, *Rhodotorula minuta*, *Rhodotorula rubra*, and *Torulopsis candida*.^{2–4} The purpose of this report is to document our fungal culture results over the last 10 years and to discuss treatment options.

2. Methods

The diagnosis of fungal endometritis can be made with cytological examination of uterine secretions. A Kalayjian® uterine swab or similar methodology can be used to obtain a sample of uterine fluid/cells for microscopic examination.⁵ The swab

contents are placed on a microscope slide, smeared, air dried, and stained using a modified Wright's stain (Diff-Quik®). This staining method allows the identification of cell types, bacteria, and yeast. Yeast often have a clear capsule surrounding them which is visible by altering the focal point when viewing the microscope slide. Yeast are oval to spherical in shape ranging from 3 to 5 μm in diameter.⁶ If a fungal infection is suspected, but culture results are negative or inconclusive, a diagnosis may be made by staining a histopathologic specimen from a uterine biopsy with a silver stain such as Gomori's methenamine silver stain.

3. Results

A retrospective study into the number and type of yeast isolated from uterine cultures submitted over the last ten years (1990–1999) to our bacteriology laboratory indicate that the percent of positive yeast samples calculated from the total number of uterine cultures submitted was 3.08% (22/714). Others have reported that 2.08% (17/816) and 2.05% (28/1365) of uterine cultures submitted to a diagnostic

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laboratory were positive for fungi from April 1994 to March 1995 and from January 1995 to May 1996, respectively.^{7,8} These numbers may include repeat cultures on the same mare; consequently, the numbers are probably slightly elevated. One report involving cervical swabs demonstrated two mares with *Candida albicans* from over 2000 swabs.⁹ Another report involving specifically *Candida* infections demonstrated 2.21% (16/725) positive cervical swabs from mares with cervical discharge or failure to conceive.³ Organisms cultured in our laboratory include: *Candida tropicalis*, *Rhodotorula glutinis*, *Scedosporium apiospermum*, *Fusarium sp.*, *Saccharomyces cerevisiae*, *Rhodotorula glutinis*, *Trichosporon beigeli*, *Rhodotorula glutinis*, *Hansenula anomala*, *Aspergillus sp.*, *Candida lusitanae*, *Rhodotorula glutinis*, *Candida parapsilosis*, *Rhodotorula sp.*, *Candida sp.*, and *Candida zeylanoides*. Anti-fungal sensitivity patterns were not available.

4. Discussion

Once diagnosed, the treatment of fungal endometritis can be unrewarding. Reasons for an unsuccessful course may include: an inappropriate duration of therapy; incorrect selection and/or dosage of anti-fungal medication; failure to treat reservoirs of infection, such as the vagina and clitoral fossa, and failure to correct predisposing conditions such as pneumovagina. Some yeast organisms, such as *Candida albicans*, have been shown to penetrate and grow intracellularly within epithelial cells. Any fungal elements cultured should be sent to a diagnostic laboratory to determine sensitivity patterns to anti-fungal medications. Many laboratories that normally do bacterial sensitivity panels do not offer similar panels for anti-fungal medications and the sample must be sent to a laboratory specializing in such testing.^a

The primary reservoir for infectious agents that colonize the uterus is the caudal reproductive tract including the vagina and external genitalia, although contamination from fecal matter (pneumovagina, poor perineal conformation, etc.) or due to iatrogenic means (after uterine culture/cytology/biopsy or artificial insemination) is also possible. Therefore, it is suggested that, in addition to the uterus, the vagina and external genitalia be cultured when fungal infections are suspected or identified. Although the use of systemic and/or intra-uterine antibiotics is commonly incriminated as predisposing to fungal infections, reports also occur whereby no antibiotic therapy was undertaken.³ Pneumovagina has also been incriminated as predisposing mares to fungal infections,³ supporting the idea of contaminants leading to fungal infections. Other contributing factors to the presence of fungal infections include the presence of a moist environment, exposure to large numbers of fungi, and the presence of a necrotic focus as occurring with trauma, infection or ischemia.⁶ Decreased

uterine defense mechanisms, in the form of delayed uterine clearance or altered immune function may predispose some mares to persistent bacterial and fungal infections. There are no reports of fungal infections occurring as a venereal disease; however, stallion semen has been cultured positive for *Candida sp.*¹⁰

A variety of antimycotic agents have been used to treat fungal infections including the polyene antibiotics (amphotericin B, nystatin, and natamycin).⁶ They exert their effect by altering the permeability of the fungal cytoplasmic membrane. Another class of widely used drugs are the imidazole derivatives (clotrimazole, econazole, ketoconazole, fluconazole, and itraconazole). They cause interference with nutrient exchange across the fungal cell wall and cell membrane. Iodides have also been used, but their mechanism of action is not clearly defined. The duration of intrauterine therapy should be 7–10 days. Longer time frames may be needed for resistant infections. Suggested dosages for daily intra-uterine infusion for antimycotic agents include:^{11,12} clotrimazole, 500–700 mg; nystatin, 0.5–2.5 million units; amphotericin B, 100–200 mg; fluconazole, 100 mg. Oral antimycotics have also been used in conjunction with intrauterine therapy for resistant infections.

Dimethyl sulfoxide (DMSO), in vitro, has been reported at concentrations of 10–20% to decrease growth of *Candida albicans* and at $\geq 30\%$ to inhibit growth.¹³ It appears to be bacteriostatic at lower concentrations (5–10%) and bacteriocidal at higher concentrations. Caution should be used since endometrial cell loss and ulceration occur at higher concentrations with a 10–40% epithelial ulceration occurring with a 25% DMSO intra-uterine infusion.¹⁴ Dilute iodine (0.5%) or white vinegar (1–2%) administered as a lavage or infusion has been anecdotally reported to be effective.^{3,15,16} Lavage of the uterus with sterile saline without additives may decrease the total number of organisms and stimulate an inflammatory response that may assist resolution of the infection.

The reproductive future for mares infected with yeast has been given a poor prognosis.³ Causes of poor reproductive performance may include recurrent infections or cumulative injury to the endometrium. Of 16 mares treated in one report, 6 of 13 treated mares conceived whereas 1 of the remaining 3 untreated mares conceived either during that breeding season or the subsequent breeding season. Treatments consisted of iodine infusions or treatment with nystatin.

To prevent recurrent infections, minimal contamination breeding techniques should be instituted. Mares should be examined via palpation per rectum and by transrectal ultrasonography to determine the best time for breeding, thus limiting the number of times the reproductive tract is entered. Pre- or post-mating antibiotic therapy should likewise be limited to prevent altering normal reproductive

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flora. The selection of good quality semen to increase the likelihood of a successful outcome should be highly recommended to clients.

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