Tutorial Article

The current status of antibiotic use in equine reproduction

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Summary

Antibiotics are infused into the uterine lumen, added to semen extenders and given systemically for infections of the reproductive tract of the mare and stallion. Evidence-based guidelines for determining treatment length and route of administration are limited and use is frequently based on convenience or tradition. Current recommended antibiotic use for the treatment of bacterial and fungal endometritis, placentitis and metritis in the mare and genital infections of the stallion are presented. Antibiotic classes used for reproductive problems are also reviewed.

Introduction

Antibiotics are used to treat many infections of the equine reproductive tract including infectious endometritis, placentitis, metritis or retained placenta in the mare and seminal vesiculitis, epididymitis or orchitis in the stallion. Antibiotics may be infused locally, administered parenterally or added to semen extenders. Evidence-based guidelines for the decision on treatment length, the most efficacious route of administration, or the use of intrauterine antibiotics after breeding are limited or nonexistent. Consequently, recommendations are based on clinical experience and tradition. Veterinarians have a responsibility to use antibacterial agents with due care and with appropriate recognition of the wider implications of resistance. Inappropriate courses and doses are often the major instigating factor for antibiotic resistance.

General guidelines

Various factors must be considered in the selection of antimicrobials for treating reproductive conditions including susceptibility of the microorganism, local vs. systemic treatment, concentration of drug attainable at site of infection and the effect of the drug on immediate and future fertility (LeBlanc 2003). Antimicrobial selection should be based on culture and sensitivity results. Unfortunately, in vitro and in vivo efficacy may not always be equivalent. For example, Streptococcus equi ssp. zooepidemicus shows in vitro sensitivity to trimethoprim-sulphonamide combinations but rarely does the drug effect a clinical cure (Ensink et al. 2003, 2005).

Intrauterine antibiotic therapy

Intrauterine (i.u.) infusions need to be administered with sterile equipment and proper aseptic preparation of the mare. Catheters should be passed through the cervix and into the uterine lumen via a speculum or manually to ensure maximal cleanliness. Uterine size, determined by palpation and ultrasonographic examination, can be used to estimate the volume of antibiotic solution to be instilled (Neeley 1983). The objective is to use sufficient volume to achieve uniform distribution in the uterus without excessive backflow through the cervix. Total infusion volumes of 30–200 ml have been recommended (Bedford and Hinrichs 1994; LeBlanc et al. 2003). Volume of infusion may affect rate of drug absorption. Decreasing the volume of β-lactam antibiotic solutions to 100 ml increases the amount and rate of absorption; therefore, to maintain concentrations in the uterus for longer periods, larger diluted volumes of these antibiotics should be infused (Allen 1978; Spensley et al. 1986; van Camp et al. 2000). The frequency of i.u. antimicrobial therapy is usually based on convenience (Bennett 1986; Bretzlaff 1986; Threlfall and Carleton 1986). Mares may be treated for 3–5 days during oestrus, every other day during oestrus or for 1–3 days after ovulation. Intrauterine therapy has been preferred over systemic treatment because bacteria reside within the uterine lumen and antibiotic concentrations tend to be higher in endometrial tissues after i.u. treatment than after systemic treatment (Bennett 1986). Exudate in the uterine lumen may inactivate or dilute an infused antibiotic to a subtherapeutic concentration. Uterine lavage before the infusion of antibiotics is therefore a useful method of increasing the efficacy by removing inflammatory by-products and increasing contact of therapeutic agents with the endometrial surface. Intrauterine infusion of antibiotics should be limited to oestrus when the cervix is dilated. In experimental models of endometritis, progesterone treated mares that received
a uterine inoculation of bacteria followed by infusion of i.u. antibiotics developed either fungal or antibiotic resistant bacterial infections (Hinrichs et al. 1992; McDonnell and Watson 1992). An inability to clear fluids through the cervix and hormonally induced immunological changes probably contributed to the infection after antibiotic administration. In the author’s experience, mares with inadequate cervical dilation at breeding, mares that are manipulated repeatedly to recover embryos on Day 7 of dioestrus and old maiden mares that have received progesterone for long periods are also more prone to develop bacterial or fungal infections.

Drug compatibility is an important principle of therapy. The polypharmacy approach of multiple antibiotics and antiseptics mixed together may be of no therapeutic value and could be harmful. Penicillin, ampicillin or ticarcillin should not be mixed with gentamicin in the same syringe as physical and chemical incompatibilities exist (Paul 1987; Brumbaugh and Langston 2002) and a precipitate may form. Penicillin and ampicillin are inactivated when the pH of a solution is <5.5 or >8, so, they should not be mixed with sodium bicarbonate, gentamicin or sulphonamides. In the UK, an i.u. antibiotic infusion containing 1 g neomycin, 40,000 i.u polymyxin B, 600 mg furaltodone and 3 g crystalline benzylpenicillin is commonly used for bacteria endometritis. It is broad spectrum, having activity against common uterine pathogens of the mare, as well as against *Bacteroides fragilis*, an anaerobe isolated from the *post partum* uterus. It is watersoluble and nonirritating when dissolved in 20 ml of sterile water and infused into the uterus. Pharmacokinetics of this drug combination are not known so it is difficult to predict if incompatibilities exist. Some antibiotics must be diluted or buffered properly to avoid endometrial irritation. Ampicillin and amphotericin B need to be diluted in volumes greater than 100 ml when infused into the uterus to avoid precipitate formation (Paul 1987). Aminoglycosides need to be buffered with an equal volume of bicarbonate as they can irritate the endometrium or induce depigmentation of the vulvar skin. Gentamicin or amikacin is commonly instilled into the uterus of mares and a 2 g dose of either should be buffered with 35 ml of 8.4% bicarbonate.

Complications may arise with i.u. antibiotic treatment. Mares may develop secondary bacterial or fungal infections, exhibit severe endometrial irritation or may fail to resolve an infection. Treatment for one pathogen may result in the proliferation of another that often is more difficult to manage than the original. An example is treatment of a streptococcal infection that, after treatment with the appropriate antibiotic, is followed by development of a yeast or *Pseudomonas* infection. In these cases, a mixed infection may have existed initially and antibiotic use merely allowed proliferation of the other organism. In other cases, a second organism may be introduced accidentally during the course of treatment for the primary infection.

**Systemic antibiotic therapy**

Persistent chronic endometritis, retained placenta and metritis are best treated with systemic antibiotics, uterine irrigation and ecbolics. Systemic administration of antibiotics results in higher minimal inhibitory concentrations (MIC) throughout the genital tract as compared to i.u. therapy. In addition, there is less likelihood of super infections secondary to changes in vaginal flora, the antibiotics are not degraded by conditions in the uterine lumen and parental therapy does not irritate the endometrium (Causey 2007). The length of systemic treatment is not dictated by the oestrous cycle and antibiotics may be given for 10–14 days if deemed necessary. Systemic therapy eliminates the need to invade the vestibule, vaginal canal and cervix. The vestibule and clitoral fossa harbour a vast array of bacteria, even in reproductively normal mares. These organisms might serve as a source of uterine inoculation when the hand or an instrument is passed through the vulva to cannulate the cervix during i.u. infusion (Hinrichs et al. 1988). If metritis is present, systemic antibiotics are indicated because they more easily penetrate the myometrium.

In chronic cases, the uterus should be evaluated on the last day of treatment to determine if therapy should be continued. If there is fluid within the uterine lumen or there is excessive uterine oedema visualised ultrasonographically, i.u. treatment should be continued for 2–3 more days unless the mare has ovulated and the cervix is tightly closed. Treatment of mares during dioestrus should be avoided as it has resulted in fungal endometritis (Hinrichs et al. 1992). The results of therapy should be monitored at the next oestrous. Treatment failure is most common when dealing with fungal or chronic Gram-negative bacterial infections. Failure may be associated with continual contamination of the uterus because of loss of anatomical barriers, inappropriate dosage regimen, drug resistance, inappropriate microenvironment, superinfection, or impaired host’s defence mechanisms. When response to treatment is not as expected, the cause should be sought, and the problem corrected.

**Chronic infectious endometritis**

The 2 bacteria most commonly isolated from the mare’s uterus are *Streptococcus equi* ssp.* zooepidemicus* and *Escherichia coli*. These organisms account for 50–80% of bacterial endometritis cases. Other pathogens recovered include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Cornebacterium* spp., *Actinobacter* spp., *Proteus* spp., *Citrobacter* spp., *Enterobacteria cloaca*, *Serratia* and *α Streptococcus*. (Wingfield Digby and Ricketts 1982; LeBlanc et al. 2007). *Bacillus* and *Micrococcus* have also been isolated from infertile mares, although they are considered to be contaminants. Mixed infections do occur and may be the cause of therapeutifc failure. Chronic and mixed
infections are best identified by small volume uterine lavage or by culture of an endometrial biopsy specimen (Nielsen 2005; LeBlanc et al. 2007). *Bacteroides fragilis* has been isolated from the uterus of post partum mares; however, its contribution to equine endometritis is not well documented because anaerobic uterine cultures are rarely obtained (Ricketts and Mackintosh 1987).

Infectious endometritis is often the result of contamination of the uterus by the mare’s faecal and genital flora in combination with compromised uterine defence. It is most common in aged, pluriparous mares with impaired uterine drainage or degenerative uterine changes such as periglandular fibrosis, glandular dilatation or sclerosis of arterioles in the uterine vascular bed. Treatment of endometritis needs to include removal of the offending organism through uterine lavage, ecboitics and antimicrobial therapy in addition to repair of anatomical defects. Mares with bacterial endometritis should be treated with i.u. antibiotics for 3–7 days. Treatment length depends on chronicity of the infection, bacteria isolated, the mare’s ability to clear uterine fluid and her history. The uterus should be irrigated for the first 2–3 days of treatment prior to infusion of antibiotics to remove inflammatory debris. The status of the reproductive tract should be re-assessed at the next oestrus and a uterine culture obtained. If bacteria are isolated, systemic and local therapy should be considered. *Tables 1* and *2* include dosages of i.u. and systemic antibiotics for treatment of bacterial endometritis. Specific comments about drugs are presented in the section on antibiotic families.

**Fungal endometritis**

Treatment of fungal endometritis is frustrating because affected mares tend to be old and pluriparous with either poor perineal conformation or cervical incompetence. Often, they have been treated repeatedly with i.u. antibiotics. In addition, success rates are poor and relapses are common. Mares with chronic fungal infections may be immunosuppressed or have an endocrine dysfunction such as equine pituitary disorders or

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/infusion</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TABLE 1: Guidelines for administration of intrauterine antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>2 g&lt;sup&gt;a&lt;/sup&gt;</td>
<td>i.v. or i.m.</td>
<td>Buffer with bicarbonate or large volume of saline (200 ml); excellent Gram-negative coverage.</td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>2 g&lt;sup&gt;a&lt;/sup&gt;</td>
<td>i.v. or i.m.</td>
<td>Use only the soluble product; susceptible Gram-positive and E. coli.</td>
</tr>
<tr>
<td>Cefiofur sodium</td>
<td>1 g</td>
<td>i.m.</td>
<td>Resistant to many β-lactamases; broad spectrum; save for resistant organisms.</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1–2 g&lt;sup&gt;a&lt;/sup&gt;</td>
<td>i.v.</td>
<td>Buffer with bicarbonate or large volume of saline (200 ml); some S. zooepidemicus; Enterobacter spp., E.coli, Klebsiella spp., Proteus spp., Serratia spp. P. aeruginosa, S. aureus.</td>
</tr>
<tr>
<td>Penicillin (potassium)</td>
<td>5 x 10&lt;sup&gt;4&lt;/sup&gt; iu</td>
<td>per os</td>
<td>S. zooepidemicus.</td>
</tr>
<tr>
<td>Neomycin</td>
<td>4 g</td>
<td>i.v.</td>
<td>Gram-negative organisms; (some E.coli and some Klebsiella spp.).</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>6 g</td>
<td>i.v.</td>
<td>Anti-pseudomonal penicillin; Gram-positive organisms; infuse with a minimum of 200 ml of saline.</td>
</tr>
<tr>
<td>Ticarcillin-clavulanic acid</td>
<td>3–6 g</td>
<td>i.v.</td>
<td>Beta-lactamase inhibitor confers greater activity against Enterobacter; S. aureus; B. fragilis; infuse with a minimum of 200 ml of saline.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Buffered with equal volume of 7.5% bicarbonate and diluted in saline. <sup>b</sup>Use at high dilutions because it can be irritating.

**TABLE 2: Antibiotics for systemic treatment of bacterial infections of the equine reproductive tract**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin sulphate</td>
<td>10 mg/kg bwt</td>
<td>i.v. or i.m.</td>
<td>24 h</td>
<td>Excellent Gram-negative coverage.</td>
</tr>
<tr>
<td>Ampicillin sodium</td>
<td>29 mg/kg bwt</td>
<td>i.v. or i.m.</td>
<td>12–24 h</td>
<td>Susceptible Gram-positive organisms and E. coli.</td>
</tr>
<tr>
<td>Cefiofur</td>
<td>2.5 mg/kg bwt</td>
<td>i.m.</td>
<td>12–24 h</td>
<td>Broad spectrum Gram-positive and some Gram-negative organisms.</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>10 mg/kg bwt</td>
<td>per os</td>
<td>12 h</td>
<td>Leptospirosis.</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6.6 mg/kg bwt</td>
<td>i.v.</td>
<td>24 h</td>
<td>Slow i.v. infusion; Enterobacter spp., E. coli, Klebsiella spp., Proteus spp., Serratia spp. P. aeruginosa, S. aureus.</td>
</tr>
<tr>
<td>Enrofloxacin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.5 mg/kg bwt</td>
<td>i.v.</td>
<td>24 h</td>
<td>Slow i.v. infusion; Gram-negative infections caused by susceptible bacteria resistant to alternative, first choice drugs; seminal vesiculitis; epididymitis.</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>6.6 mg/kg bwt</td>
<td>i.v.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 h</td>
<td>Leptospirosis.</td>
</tr>
<tr>
<td>Penicillin G (potassium)</td>
<td>25,000 iu/kg bwt</td>
<td>i.v.</td>
<td>6 h</td>
<td>Synergistic with aminoglycosides; do not store mixed in syringe for more than 12 h; do not mix in syringe with gentamicin; S. zooepidemicus, Leptospirosis.</td>
</tr>
<tr>
<td>Penicillin (procaine)</td>
<td>25,000 iu/kg bwt</td>
<td>i.m.</td>
<td>12 h</td>
<td>As above.</td>
</tr>
<tr>
<td>Trimethoprim-sulphonamide</td>
<td>30 mg/kg bwt (combined)</td>
<td>per os</td>
<td>12 h</td>
<td>S. aureus, E. coli, Klebsiella spp., Proteus; some Nocardia spp, Bacteroides fragilis&lt;sup&gt;a&lt;/sup&gt; melitis.</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>15–25 mg/kg bwt</td>
<td>per os</td>
<td>12 h</td>
<td>As above.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Should not be used in pregnant mares or in young growing horses because of the risk of arthropathy. <sup>b</sup>Dilute and give slowly i.v.<sup>c</sup>Clostridium difficile and C. perfringens diarrhoea and death have been reported after use of Metronidazole in western USA.
insulin resistance (Descanio 2007). Prolonged progesterone therapy may also predispose mares to fungal endometritis as cervical drainage is decreased and uterine muscular activity and neutrophil function are altered (Hinrichs et al. 1992). Both yeasts and moulds have been recovered from the uterus of mares (Descanio 2007). Yeast appear as small, round, single cell, brown to black spores on cytological smears obtained from infected mares while moulds have long, filamentous hyphae. In chronic infections, hyphae may form large, tangled masses called mycelia. Mycelia may be visualised ultrasonographically within the uterine lumen as hypechoic, irregular shaped white structures surrounded by fluid. Mycelia recovered in vaginal or uterine fluids have a ‘cotton ball’ appearance. Candida spp. and Aspergillus spp. are the most commonly isolated fungi from the equine uterus. Candida spp., is a normal commensal of the gastrointestinal tract and vagina. Cytological smears obtained from mares with Candida endometritis usually contain spores but hyphae may be seen in chronic infections. Aspergillus is a mould that produces hyphae. Other fungi isolated from the uterus include: Actinomyces spp., Fusarium spp. (filamentous fungi), Mucor (filamentous fungi), Paecilomyces spp., Rhizopus (filamentous fungi), Rhodotorula spp. and Trichosporon spp.

Yeasts tend to proliferate in fluid, whereas hyphae are better adapted for penetrating tissue (Descanio 2007). These characteristics will affect treatment regimens and success. Yeast such as Candida albicans may be treated successfully with uterine irrigation and i.u. infusion of antifungal agents. Fungal infections due to moulds such as Aspergillus, Mucor or Rhizopus may be deep seeded, requiring both systemic and local therapy (Giguère 2006a).

**Treatment**

Development of fungal endometritis is a frequent consequence of repeated i.u. antibiotic treatments (Hinrichs et al. 1992; Descanio 2007). Many of these cases resolve spontaneously if the mare has normal perineal anatomy and adequate uterine clearance. If the infection does not resolve in 1–2 oestrous cycles, the uterus should be irrigated with a disinfectant for 5–7 days. Disinfectant solutions used for fungal infections include 3% (v/v) hydrogen peroxide solution (30 ml hydrogen peroxide in 1 l of 0.9% saline), 2% (v/v) acetic acid (white vinegar: 20 ml of vinegar in 1 l 10.9% saline), 0.1–0.2% (v/v) povidone iodine solution, or 20% DMSO (Ricketts 1999; Descanio 2007). If fungi are isolated after uterine irrigation with a disinfectant for 3–5 days, a uterine culture should be submitted for antibiotic sensitivity. Recalcitrant fungal infections require prolonged therapy, which is costly, and relapses are common. Both local and systemic treatments have been advocated and in some cases, mares are treated with both. Breaches in anatomical barriers must be repaired. Unfortunately, the most difficult fungal infections to resolve, in the author’s opinion, are those in mares with a fibrotic cervix and inadequate uterine clearance and in mares with insulin resistance or Cushing’s disease. In man, a minimum of 10–14 days of treatment is recommended. In horses, i.u. treatment is usually limited to the duration of oestrus or 5–7 days. Mares may require 2–3 treatment sessions conducted during consecutive oestrus periods to resolve an infection. The interval between treatments can be shortened by administration of prostaglandin. The uterus should be re-cultured 2–3 weeks after the second treatment session. If fungi are isolated, the reproductive tract should be re-evaluated for anatomical defects and cervical incompetence and testing should be performed for Cushing’s disease. Systemic therapy for a minimum of 21 days should be considered. Table 3 contains antifungal drugs and dosages for systemic and local infusion.

**Post mating antibiotic infusion for treatment of acute endometritis**

Intrauterine infusion of antibiotics 18–24 h after natural mating of Thoroughbred mares became popular in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Interval (h)</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.3–0.9 mg/kg bwt</td>
<td>i.v.²</td>
<td>24–48</td>
<td>Broad spectrum</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>20 mg/kg bwt (in 0.2 N HCl)</td>
<td>NGT³</td>
<td>12</td>
<td>Yeast³</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Loading dose: 14 mg/kg bwt</td>
<td>per os, i.v.</td>
<td>24</td>
<td>Yeast³</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 5 mg/kg bwt</td>
<td>per os², i.v.</td>
<td>12–24</td>
<td>Broad spectrum⁶</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5 mg/kg bwt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>400–700 mg</td>
<td>i.u.</td>
<td>24 h x 7 days</td>
<td>Broad spectrum</td>
</tr>
<tr>
<td>Miconazole</td>
<td>500–700 mg</td>
<td>i.u.</td>
<td>24 h x 7 days</td>
<td>Broad spectrum</td>
</tr>
<tr>
<td>Nystatin</td>
<td>0.5–2.5 x 10⁶ i.u.²</td>
<td>i.u.</td>
<td>24 h x 7 days</td>
<td>Yeast³</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>100–200 mg</td>
<td>i.u.</td>
<td>24 h x 7 days</td>
<td>Broad spectrum⁶</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100 mg</td>
<td>i.u.</td>
<td>24 h x 7 days</td>
<td>Yeast³</td>
</tr>
</tbody>
</table>

² Diluted to 1 mg/ml in 5% dextrose and administered over 1–2 h. ³ Nasogastric intubation is require to avoid the irritant effect of HCl on the oral cavity and throat. ⁵ The bioavailability of the oral suspension is superior to that of the capsules. ⁶ Yeasts: Candida spp. "Broad spectrum: yeasts, Aspergillus, dimorphic fungi. ⁷ Must be diluted in sterile water (100–200 ml) as it precipitates in saline.
Newmarket and Kentucky about 40 years ago. Various authors have reported that i.u. antibiotic infusion after breeding increases the likelihood of pregnancy in both “problem” and apparently normal mares, even though it is unlikely that normal mares suffer from a post breeding endometritis that cannot be controlled by natural defence mechanisms. Only one clinical field study has substantiated the use of post breeding antibiotics (Pycock 1994). Pregnancy rate/cycle increased by 8–10% in mares treated with i.u. antibiotics and in mares treated with oxytocin after breeding as compared to mares that were not treated (57% no treatment; 67% i.u. infusion of antibiotics; 65% oxytocin). When mares received both treatments, pregnancy rates increased to 77%. Treatment effect was greatest in mares aged >12 years and mares mated at the first oestrus post partum. Unfortunately, the bacterial status of the uterus was not known because uterine cultures were not obtained.

Other studies indicate that administration of ectopic drugs and uterine lavage may be as efficacious as infusion of antibiotics post mating (Troedsson et al. 1995). Saline lavage and PGF2α were equally effective in eliminating bacteria from the uterus as i.u. infusion of penicillin in susceptible mares treated 12 h after they received an i.u. inoculation of Streptococcus equi ssp. zooepidemicus. These results suggest that antibiotics may not be necessary if mares are treated with uterine lavage or ecbolics within 12 h of mating. In a second study, i.u. infusion of ampicillin 24 h after insemination resulted in decreased neutrophils numbers and no detectable bacteria in uterine samples obtained from fertile and subfertile mares 48 h after breeding (Stout et al. 2001). However, unlike fertile mares, subfertile mares accumulated large volumes of fluid within their uterine lumen after insemination irrespective of treatment. This work suggests that antibiotic infusion alone is not sufficient to ensure adequate uterine clearance in problem mares.

Many antibiotics have been used for post breeding uterine infusions, including gentamicin, amikacin, potassium penicillin, ticarcillin, ceftiofur, timentin and commercial antibiotic preparations containing 2 or more drugs. In aged, barren mares, antibiotic therapy after breeding is commonly combined with uterine irrigation, oxytocin or cloprostenol. Treatment length varies among clinicians and may include 1–3 treatments on consecutive days beginning within 4–8 h after breeding or immediately after ovulation. Treatment should be discontinued 48 h after ovulation to avoid iatrogenic inoculation of the uterus with genital bacteria.

**Sexually transmitted endometritis**

Contagious equine metritis is caused by Taylorella equigenitalis. Mares become infected after being mated with an infected stallion. Clinical signs in mares vary from none to severe endometritis with a copious greyish purulent vaginal discharge. Early embryonic death or abortions may occur. Infected mares, either bred by natural cover or artificially inseminated, often have irregular cycles with short luteal phases. Infected stallions are asymptomatic. Treatment of the mare involves thorough cleansing of the clitoris with chlorhexidine surgical scrub for a minimum of 5 days followed by the packing the clitoral sinuses with nitrofurazone ointment (Parlevliet et al. 1997). In some cases the clitoral sinuses or clitoris is removed. The official treatment of the stallion involves daily washing of the penis with 2% chlorhexidine scrub for 5 days followed by packing the urethral fossa with 0.2% nitrofurazone cream and rubbing the antibiotic cream into the shaft of the penis. In countries where nitrofurazone cannot be used, a suitable alternative is to treat the stallion with enrofloxacin.

**Placentitis, retained fetal membranes and metritis**

**Ascending bacterial placentitis**

Placentitis in the mare is a major factor underlying premature deliveries, abortions, stillbirths and perinatal death. Most bacteria gain entry into the uterus by ascending through the vagina and cervix. Infections may be acute or chronic. Because chronically infected mares may deliver precociously mature, viable foals before 320 days of gestation, mares with vaginal discharge or premature udder development are treated empirically with antibiotics, anti-inflammatory drugs and progestins to prolong gestation and the possibility of delivering a viable foal. Recent studies have investigated antibiotic concentrations attained in allantoic fluid of normal and mares experimentally-infected with Streptococcus zooepidemicus after i.v. administration. Drug transfer across the placenta was measured by microdialysis. Intravenous administration of penicillin G and gentamicin resulted in pharmacologically relevant concentrations in allantoic fluid, although active placental infection selectively reduced the concentrations of gentamicin in the allantoic fluid below the MIC for Gram-negative organisms (Murchie et al. 2006). The rate of clearance of penicillin G from allantoic fluid was reduced in comparison to its clearance from serum. Decreased clearance of drugs from allantoic fluid may result in excessively high drug concentrations that may be toxic to the fetus. In a second study, mares were treated with trimethoprim sulphamethoxazole (Table 2) and pentoxyflline (8.5 mg/kg bwt, q. 12 h, per os). Drug transfer across the placenta of normal mares and mares with placentitis were similar and concentrations were sufficient to elicit an antibiotic effect against Streptococcus zooepidemicus for up to 4 h (Rebello et al. 2006). In a third trial, mares with experimentally induced ascending placentitis were administered trimethoprim sulphamethoxazole, pentoxyflline and altrenogest (0.088 mg/kg bwt, q. 24 h, per os) to determine if...
treatment increased the likelihood of delivery of viable foals. More treated mares delivered live foals than control mares (Bailey et al. 2007). Mares with placentitis should be treated cautiously as prolonged therapy has resulted in retention of dead fetuses, metritis and laminitis. Fetal viability should be evaluated weekly by rectal palpation and ultrasonography. Therapy should be discontinued 2–3 days after vaginal discharge has ceased.

Nocardioform-like placentitis

Nocardioform-like placentitis, caused by Amycolatopsis spp. and Cellulosimicrobium cellulans, has resulted in abortions and the premature birth of small, compromised foals (Donahue and Williams 2000). Most cases have originated from central Kentucky; however, it has been reported in Florida, Europe and South Africa. Mares with nocardioform placentitis may develop an udder prematurely but not a vulvar discharge as infections are located in the uterine body and do not extend into the cervical star region. Differential diagnosis is twins, which can be ruled out by transabdominal ultrasonography. Ultrasonographic findings for nocardioform like placentitis include placental thickening or placental detachment in the area of the uterine body or uterine horn, increased amniotic or allantoic fluid cellularity or change in fetal heart rate. Suspect mares are commonly treated with antibiotics, anti-inflammatory drugs and, in some cases, tocolytic drugs until foaling. Trimethoprim sulphonmethoxazole is the antibiotic of choice (Donahue and Williams 2000; Prescott 2006b). Treated mares need to be monitored closely as they may develop enteritis. Drugs should be discontinued immediately if premonitory signs of enteritis develop.

Leptospirosis

Leptospirosis, once considered an infrequent cause of equine abortion, has been increasingly identified as a causative organism in central Kentucky (Donahue and Williams 2000). This may be because of an actual increase in the prevalence of the disease or because of an increased awareness and specific testing for leptospirosis coupled with improved diagnostic techniques. The Leptospira interrogans serovars pomona, Bratislava or grippotyphosa are most commonly isolated from serum of infected horses and from aborted fetuses (Poonacha 1990). Leptospliral abortion is difficult to diagnose because mares rarely exhibit clinical signs of disease. A preliminary diagnosis is based on the post mortem findings in aborted fetuses and placentas. Prolonged treatment with procaine penicillin G (25,000 IU/kg bwt i.m. twice a day), oxytetracycline (5 mg/kg bwt, once daily) or doxycycline (10 mg/kg bwt, q 12 h, per os) may decrease the shedding period. Some clinicians feel antibiotics are useful in preventing fetal infections in mares with high titres during late pregnancy (Bernard 1993).

Retained fetal membranes and metritis

Bacterial endometritis and subsequent development of metritis are commonly associated with prolonged (>6–8 h) retention of the fetal membranes. Coliforms or S. zooepidemicus are most commonly isolated. Drug selection depends on the amount of assistance the mare required, whether she had a fetotomy or caesarean section, cleanliness of the environment, and the general health of the mare. Systemic antibiotic treatment is recommended over i.u. antibiotics as necrotic membranes and lochia inactivates aminoglycosides (Brumbaugh and Langston 2002). Suggested therapy includes broad spectrum antibiotics such as the combination of penicillin or ampicillin with an aminoglycoside or administration of trimethoprim sulphonamide or a third generation cephalosporin such as ceftiofur (Table 2). Metronitazole should be considered because Bacteroides fragilis has been isolated from the uterus of ill mares after foaling. It must be used with caution because there have been reports of horses treated with metronitazole developing severe enteritis in California and resistant strains of Clostridium difficile and C. perfringens have been isolated (Magdesian et al. 2006). The uterus should be irrigated with copious quantities of saline or lactated Ringer’s once or twice daily to remove necrotic membranes and inflammatory by-products in an attempt to prevent metritis, endotoxaemia and laminitis.

Antibiotics used in genital infections of stallions

In the stallion, antibiotics are routinely added to extenders for processing semen (cooled for shipment or for freezing) or for diluting dismount semen samples for reinforcement of natural matings (Varner et al. 1991; Hooper et al. 2002). Genital infections of stallions are uncommon. The stallion’s penis has a normal bacterial flora on its surface and the organisms are generally not pathogenic. Bacterial infections arise when the normal bacterial flora of the penis is altered and colonisation, especially by Gram-negative bacteria such as Pseudomonas aeruginosa or Klebsiella pneumoniae of the skin occurs. To confirm transmission of a pathogen from the stallion to the mare, the same bacterial serotype needs to be isolated from either a uterine or clitoral culture obtained from the mare and from semen, pre-ejaculatory fluid and/or penis of the stallion (Blanchard et al. 1992). Treatment for penile or preputial infections with Pseudomonas aeruginosa or Klebsiella pneumoniae includes daily washing of the genitalia with an iodine-based surgical scrub. The genitals are then rinsed with copious quantities of water with dilute disinfectants added (0.25% solution of 38% hydrochloric acid for Pseudomonas colonisation, or 0.1% solution of 5.25% sodium hypochlorite bleach/litre of water for Klebsiella) until bacteria are no longer recovered (Kenney and Cummings 1990). Systemic treatment with antibiotics
does not seem to be rewarding. If a stallion is shedding *Pseudomonas* and is breeding artificially, semen can be diluted in extenders containing appropriate antibiotics such as amikacin sulphate or gentamicin (Varner et al. 1991). If the mare is bred by natural cover, semen extender can be infused into the mare’s uterus immediately before breeding and the mare’s uterus irrigated 4–8 h after breeding followed by infusion of appropriate antibiotics.

Seminal vesiculitis is extremely rare in stallions. The condition may involve one or both seminal vesicles and the stallion may or may not exhibit clinical signs. In acute manifestations, the vesicles may be enlarged, firm and painful upon palpation. Diagnosis of seminal vesiculitis is made by rectal palpation, observation of large numbers of neutrophils in the semen, bacterial culture of semen and endoscopy of the urethra and seminal vesicles. Treatment is difficult and the prognosis guarded. Treatments include systemic antibiotics based on *in vitro* susceptibility testing or repeated deposition of antibiotics directly into the seminal vesicle after direct lavage using a flexible endoscope (Blanchard et al. 1987; Hooper et al. 2002). Few antibiotics administered parentally diffuse across mucosal cell borders into seminal plasma. Properties of those that do include high lipid solubility, a favourable pKa, low protein binding and a pH that is more basic than the seminal plasma (7.3–7.5). Antibiotics that may prove suitable for treatment of seminal vesiculitis include a basic macrolide such as erythromycin, trimethoprim or enrofloxacin. If infection can not be eradicated, appropriate semen extender must be used for breeding. Doses and antibiotics commonly incorporated in semen extenders are as follows:

- **Penicillin-G** 1000–1500 IU/ml
- **Streptomycin sulphate** 1000–1500 µg/ml
- **Polymyxin-B** 100–1000 IU/ml
- **Gentamicin sulphate** (reagent grade 100–1000 µg/ml)
- **Amikacin sulphate** 100–1000 µg/ml
- **Ticarcillin** 100–1000 µg/ml

Gentamicin sulphate and amikacin sulphate should be buffered with 8.4% sodium bicarbonate solution to adjust pH to approximately neutral before mixing with semen extender (Varner et al. 1991).

Epididymitis is caused by infection or trauma and may occur separately but is commonly secondary to orchitis or infection of the accessory sex glands (Varner et al. 1991). The tail of the epididymis is most often affected. *Streptococcus zooepidemicus* is commonly isolated although a number of other miscellaneous organisms have been incriminated. Diagnosis is based on clinical signs including pain on palpation of the epididymis, irregular swellings or texture of the epididymides, adhesions between the epididymis and scrotal tunic or enlargement of the tail of the epididymis. Infection varies from acute swelling and oedema to chronic abscesses and fibrosis. Inflammatory cells along with abnormal sperm, blood or pus may be present in the ejaculate of affected stallions. Epididymitis is treated with systemic antibiotics selected by *in vitro* sensitivity. Treatment should continue for 1–2 weeks after inflammatory cells, pus and blood disappear.

Orchitis may develop from trauma, haematogenous migration of bacteria, or retrograde movement from an infected epididymis or accessory sex gland. Acutely affected testes are hot, swollen and painful on palpation. Affected stallions may refuse to mate. Ejaculates frequently contain many white blood cells. *Streptococcus equi* ssp. *zooepidemicus* is most commonly isolated. Treatment consists of scrotal cryotherapy (Varner et al. 1991; Hooper et al. 2002) and systemic administration of anti-inflammatory drugs. Bacterial orchitis is treated with antibiotics chosen by semen culture and *in vitro* sensitivity. Antibiotic therapy should continue for 1–2 weeks beyond resolution of testicular swelling and pain. Testicular atrophy and sterility are common sequelae to orchitis.

**Antibiotic classes for use in equine reproduction**

It should be noted that pharmacokinetic data for i.u. infusion of antibiotics or for local infusion of antibiotics for seminal vesiculitis is lacking. Many doses have been chosen empirically and veterinarians rely on resolution of clinical signs as a method for determining antibiotic treatment success. In this section, specific equine literature is noted when available. Data are summarised in Tables 1–3.

**Beta-lactam antibiotics**

The β-lactam antibiotics used in equine reproduction include penicillin, ampicillin, ceftiofur, ticarcillin and the combination of ticarcillin and clavulonic acid. Penicillin G (benzyl penicillin) is the drug of choice for treating infections due to *Streptococcus equi* ssp. *zooepidemicus* and nonresistant staphylococci because of its potent bactericidal activity and its wide margin of safety (Prescott 2006). Activity against Gram-negative bacteria is poor due to inadequate penetration through the lipopolysaccaride outer layer. It may be given either parenterally or locally for infections of the reproductive tract. Potassium penicillin G is synergistic with the aminoglycosides against many Gram-positive bacteria, and is commonly used for retained placenta or metritis (extralabel use). When used concurrently with aminoglycosides, penicillin G should be administered parentally and should not be premixed in a syringe for i.u. infusion as it may precipitate (Paul 1987; Brumbaugh and Langston 2002). Penicillin infused into the uterus has poor penetration of endometrial tissues because it is ionised at physiological pH and has poor lipid solubility, although inflammation does enhance entry across the endometrial surface.

Ampicillin has better penetration through the outer layer of Gram-negative bacteria than penicillin, which
increases its Gram-negative spectrum of activity to include some E. coli and Proteus spp. (Prescott 2006a). When infused into the uterus, the soluble form of ampicillin should be used and it should be diluted to avoid endometrial irritation and to prevent residues from forming on the endometrium (Causey 2007). Intrauterine infusion of 3 g of ampicillin during oestrus and dioestrous resulted in a MIC of ampicillin against bacterial pathogens in endometrial tissue 24 h after infusion. However, more mares in dioestrus had detectable serum concentrations of ampicillin after i.u. infusion than did mares in oestrus (Love et al. 1990).

Ticarcillin has a broad Gram-positive spectrum of activity and has good activity against E. coli, P. aeruginosa and Proteus. Most Klebsiella, Citrobacter and Serratia are resistant. All Enterobacter are resistant. Because of the cost of ticarcillin and the high doses needed, its use is limited to i.u. administration. Ticarcillin is licensed in the US for the treatment of endometritis in mares caused by haemolytic streptococci (6 g in 250–500 ml by i.u. infusion once daily during oestrus for 3 days). Ticarcillin should be diluted with a minimum of 250 ml of saline as fluid volume markedly influences its endometrial concentration (Spensley et al. 1986). Clavulanic acid, a β-lactamase inhibitor added to ticarcillin preparations, has considerably enhanced the activity of ticarcillin against bacteria with acquired plasmid-mediated resistance. In man, the combination has good activity against the majority of ticarcillin-resistant Enterobacteriaceae, S. aureus, anaerobes including B. fragilis and many P. aeruginosa. Ticarcillin in combination with clavulanic acid (Timentin) is used in the USA as an i.u. infusion in mares because ticarcillin alone is not available currently. Intrauterine infusion of ticarcillin and clavulanate at a dose of 12.4 and 0.4 mg/kg bwf, respectively, diluted in 100 ml of saline resulted in poor absorption into plasma and endometrial tissue concentrations declined rapidly. Mares need to be treated frequently (every 4–6 h) in order to maintain drug concentrations above MIC (van Camp et al. 2000). When evaluating sensitivity patterns of pathogens, Timentin should only be chosen if the organism is sensitive to both Timentin and ticarcillin.

Ceftiofur is a third generation cephalosporin that has good spectrum of activity against Gram-positive organisms and some Gram-negative organisms due to increased resistance to Gram-negative β-lactamases. Ceftiofur has been investigated for i.u. infusion in mares with bacterial endometritis. Pregnancy rates were higher and the number of services to conception lower in infected mares that were treated with ceftiofur in the oestrus before breeding as compared to mares treated only with i.u. infusion of saline (Bermudez et al. 1995). A 3 day course of i.u. infusion of ceftiofur (1 g) was also compared to a commonly used commercial preparation of benzyl penicillin, neomycin sulphate, polymixin B and furaltadone hydrochloride in mares with endometritis. Pregnancy rates after treatment were similar in both groups (Ricketts 1997).

### Aminoglycosides

Aminoglycosides are bactericidal, concentration dependent antibiotics that are directed primarily against aerobic, Gram-negative bacteria (Dowling 2006a). High concentrations are needed to effectively kill more resistant bacteria such as Pseudomonas aeruginosa and Proteus mirabilis. They are active against some Gram-positive bacteria such as Staphylococcus spp. and therapy against Streptococci is more effective when they are combined with a β-lactam antibiotic. Aminoglycosides have a significant post antibiotic effect (the period of time where antimicrobial concentrations are below the bacterial MIC, but aminoglycoside damaged bacteria are most susceptible to host defences. The bactericidal action of aminoglycosides on aerobic Gram-negative bacteria is markedly influenced by pH. Aminoglycosides are most active in an alkaline environment. Increased local acidity secondary to tissue damage or bacterial destruction may account for failure of aminoglycosides to kill usually susceptible microorganisms. Purulent debris binds to aminoglycosides and inactivates them (Bretzaf 1986). Therefore, the uterus should be irrigated with saline before i.u. infusion of aminoglycosides.

Amikacin has the broadest spectrum of activity against uterine pathogens. It is also considered the least nephrotoxic. Amikacin is more resistant to bacterial enzymatic inactivation than gentamicin and it has excellent activity against Pseudomonas aeruginosa. It is also effective against Nocardia, S. aureus, gentamicin resistant Enterobacter spp., E. coli, Klebsiella, Proteus and Serratia spp. Streptococci is resistant. Amikacin is licensed for use in the USA and Canada for the treatment of bacterial endometritis. An i.u. infusion of 2 g in 200 ml of saline for 5 days gave highest overall cure rate against Klebsiella endometritis under field conditions (Brooks 1982). Pharmacokinetic studies support the use of 2 g of amikacin i.u. once daily rather than i.m. treatment for bacterial endometritis (Orsini et al. 1996).

Gentamicin has been the mainstay for treating bacterial endometritis since the 1970s. It is effective against Streptococcus equi ssp. zooepidemicus, and many isolates of K. pneumoniae or P. aeruginosa. Treatment success is high when gentamicin is infused into the uterus daily during oestrus for 3–5 days (Houdeshell and Hennessey 1972). Stage of cycle does not appear to affect absorption of gentamicin. Serum and endometrial tissue concentrations of gentamicin are similar in ovariectomised mares that are treated with either oestrogen or progesterone (Pedersoli et al. 1985). Gentamicin needs to be properly buffered with 7.5% bicarbonate as it can adversely affect the endometrial mucosa. Infusion of 2 g of gentamicin mixed with 80 ml of normal saline for 2 consecutive days resulted in perforations of the endometrial epithelium, disruption of ciliated epithelium and shortening of the microvilli.
Gentamicin is commonly administered systemically with a β-lactam drug for placentitis, retained placenta and metritis. Currently, high-dose, once-daily gentamicin therapy for 5–7 days is recommended to maximise antimicrobial efficacy and minimise nephrotoxicity.

Neomycin has been combined with penicillin, polymyxin B and furaltadone hydrochloride in a commercial i.u. preparation for treatment of bacterial endometritis in the UK. Drug absorption is affected by stage of cycle and volume of infusion. Absorption is decreased during oestrus and when neomycin is infused in a large volume, probably due to reflux of the antibiotic through the cervix (Boyd and Allen 1987).

**Fluoroquinolones**

Enrofloxacin is a member of the fluoroquinolone family that is approved for use in dogs and cats and is used extralabel in horses. It has a high potency against many Gram-negative aerobic pathogens and can be administered orally or i.v. Enrofloxacin has widespread distribution throughout the body and has low toxicity. It is rapidly bactericidal, exhibits concentration-dependent killing and it may exhibit a prolonged in vivo post antibiotic effect on certain bacteria. A significant disadvantage of members of the fluoroquinolone family is that there is potential for fairly rapid selection of resistance in some pathogens. Doses need to be determined by the MIC of the organism and reference tables should be consulted (Walker and Dowling 2006).

Enrofloxacin and its metabolite ciprofloxacin both penetrate endometrial tissue adequately after systemic administration and attain concentrations high enough in tissue fluids to treat metritis, endometritis or seminal vesiculitis caused by susceptible bacteria (Papich et al. 2002). Severe uterine and/or vaginal inflammation have been noted by clinicians after i.u. infusion of enrofloxacin. However, one report indicates that i.u. infusion of enrofloxacin (2.5 mg/kg bwt) in genitally healthy mares was associated with a moderate but statistically nonsignificant endometrial inflammatory response following its administration (Fumoso et al. 2002). Enrofloxacin is not recommended for use in pregnant animals. Chronic high doses of enrofloxacin have been associated with articular cartilage lesions in juvenile dogs and morphological changes in equine tendon cell cultures, with more pronounced changes in juvenile tendons (Egerbacher et al. 2001).

**Trimethoprim-sulphonamide combinations**

Trimethoprim-sulphonamide combinations are commonly administered for bacterial placentitis, retained placenta or metritis because it can be administered orally with few side effects (Prescott 2006b). It has good sensitivity against nocardioform like organisms and some isolates of *E. coli* and *Klebsiella* spp. (Prescott 2006b). In recent years resistance has increased in *Streptococcus equi* ssp. *zooepidemicus* isolates and among *Enterobacteriaceae* (Sköld 2001). Trimethoprim sulphonamide was ineffective in eradicating *S. equi* ssp. *zooepidemicus* in a tissue chamber model of infection despite in vitro susceptibility of the isolate and high concentrations of the drugs in the tissue chamber fluid (Ensink et al. 2003). For these reasons, and because it can be partially antagonised by tissue debris such as retained placental tissue or pus, trimethoprim-sulphadiazine is a less desirable choice than procaine penicillin G for treatment of streptococcal infections (Ensink et al. 2005). Clinical response is sometimes lower than expected from in vitro data. Many organisms described as sensitive to the combination of drugs are only sensitive to the trimethoprim component; consequently, there is a lack of synergism between the 2 drugs. In addition, the half life of trimethoprim is short, which can contribute to lack of clinical efficacy (Prescott 2006b). Uterine infusion should be avoided as it results in endometrial inflammation.

**Metronidazole**

Metronidazole has been combined with broad spectrum antibiotics as a treatment for anaerobic infections. It is used to treat reproductive infections due to *Bacteroides fragilis*, an anaerobic organism that has been isolated from uterine fluids of mares with metritis (Ricketts and Mackintosh 1987). Metronidazole is absorbed rapidly and well after oral administration in horses, although, oral administration may cause anorexia. If metronidazole is not tolerated orally, it may be given rectally although bioavailability is decreased by about 50% (Steinman et al. 2000). Since the antibacterial effect of metronidazole is concentration-dependent, twice daily therapy is now recommended over 3 times daily therapy (Dowling 2006b). Administration of metronidazole in the western USA has been associated recently with severe enteritis and, in some cases, death, so it should be used with caution (Magdesian 2006).

**Antimycotic drugs**

The range of antifungal drugs available for systemic or i.u. use in the horse is limited as fungal pathogens have many characteristics that are common with mammalian cells. Few drugs target sites that are unique and important to fungi without also being toxic to man or animals. Drug dosages are not well defined in the horse and minimum inhibitory concentrations for these drugs have not been established for equine uterine infections (Giguère 2006a). Most of the data are extrapolated from man, dogs, cats or animal models. Suggested dosages are presented in Table 3. Treatment of serious uterine infections needs to be prolonged (≥3 weeks) and relapses anticipated.
Polyenes

Polyenes and azoles (imidazoles and triazoles) are the antifungal drugs most commonly used in horses. They are directed against ergosterol a component within the cytoplasmic membrane that is located below the cell wall (Giguère 2006a). The polyene group of antifungal agents includes amphotericin B and nystatin. Amphotericin B is used for systemic administration whereas nystatin is used topically (Table 3). Amphotericin B is the mainstay for systemic treatment of filamentous fungal infections. Amphotericin B binds to ergosterol, the principal sterol of the fungal cell membrane, causing leakage of cell contents. It also binds to cholesterol in mammalian cell membranes, thus making it the most toxic of the clinically useful systemic antifungal drugs. Amphotericin B is not absorbed well orally, and i.v. administration is required. The drug is fairly toxic and renal toxicity is common. Dosing every other day reduces nephrotoxic effects compared to administering the same dose daily. Because of its toxic effects, the drug must be diluted in 20 ml of 5% dextrose and given slowly in the vein (Giguère 2006a). It is not commonly given parentally for uterine infections in mares because of its toxic nature. It has been infused into the uterus, however, it is irritating. Nystatin, a polyene antibiotic, disorganizes the membrane of fungi, occupying ergosterol-binding sites and altering membrane permeability, so that intracellular ions leak from the cell. The drug is effective against Candida albicans, although several other Candida species are resistant (Giguère 2006b).

Azoles

The azoles given systemically for equine fungal endometritis include ketoconazole, itraconazole and fluconazole (Table 3). Azoles are considered fungistatic drugs so treatment needs to be prolonged. Ketoconazole is fungistatic against a wide range of filamentous fungi, including yeasts and dimorphic fungi. It requires an acid pH for dissolution so it must be administered via nasogastric intubation. Ketoconazole may be embryotoxic and teratogenic and should not be given to pregnant animals. It has been reported to suppress plasma cortisol and testosterone concentrations in dogs (Willard et al. 1986). Gynaecomastia, decreased libido and azoospermia have been reported in a small percentage of men but not in dogs or cats. There are no reports in horses. Ketoconazole has been eclipsed in recent years by fluconazole and itraconazole because of their greater activity, lower toxicity and improved pharmacokinetic properties (Giguère 2006a). Itraconazole is a potent inhibitor of most fungal pathogens and has a spectrum that includes Aspergillus, C. albicans and C. tropicalis, but activity against other Candida spp. is variable. Oral or parental itraconazole is well absorbed and widely distributed to tissues where it achieves concentrations several times those found in plasma. Food and an acidic environment significantly enhance absorption. The oral suspension is better absorbed than capsules (Davis et al. 2005). Itraconazole is contraindicated in pregnancy (Giguère 2006a). Fluconazole has marked pharmacokinetic differences from ketoconazole and itraconazole. It is well absorbed after oral or i.v. administration, is minimally protein bound and is distributed widely to tissues. Food does not affect absorption. A loading dose of oral fluconazole (14 mg/kg bwt) followed by 5 mg/kg bwt every 24 h yields plasma and urine fluconazole concentrations above the MIC reported for several equine fungal pathogens (Latimer et al. 2001). Fluconazole, however, has minimal activity against filamentous fungi (Aspergillus spp. and Fusarium spp.).

Clotrimazole, miconazole, fluconazole and itraconazole have been infused into the uterus for fungal endometritis (Table 3); however, there are no reports describing the pharmacokinetics following i.u. use. Clotrimazole is inhibitory in vitro to Aspergillus and Candida and few strains of fungi are resistant. The drug is used to treat human Candida vaginitis. Doses of 400–700 mg diluted in 50–100 ml of saline have been recommended for equine endometritis. Miconazole has similar activity to clotrimazole and has also proven useful for uterine infections due to Candida spp. and Aspergillus spp.

Recently, the chelating agent 8 mM EDTA dehydrate and 20 mM 2-amino-2-hydroxymethyl-1, 3-propanediol has been shown to increase in vitro activity of antifungal drugs (miconazole and itraconazole) against common fungal pathogens isolated from eyes of horses with mycotic keratitis (Weinstein et al. 2006). Tris EDTA has been used to combat uterine infections due to Pseudomonas aeruginosa. In vitro studies have shown that when it was combined with an antibiotic, Tris EDTA increased the cell death rate of Pseudomonas aeruginosa (Kirkland et al. 1983). Chelating agents may be of some benefit in treating fungal endometritis.

Conclusion

When choosing antibiotics for treatment of reproductive diseases, veterinarians should base their decisions on culture and antibiotic sensitivity testing. Although treatment length is frequently empirical, some studies indicate that 3–5 days of i.u. treatment may be adequate for resolving endometritis. As endometritis is frequently due to a breakdown in anatomical barriers and delayed uterine clearance, anatomical barriers should be repaired surgically and ecbolics given to improve uterine clearance. Uterine irrigation with saline or lactated Ringer’s should precede i.u. infusion of antibiotics because many drugs are inactivated by tissue or inflammatory debris. Systemic therapy should be considered in persistent uterine infections, retained placenta, metritis and genital infections of stallions. Antibiotics should be used judiciously as inappropriate course and dose are often the major instigating factor for antibiotic resistance.
Manufacturer’s address

GlaxoSmithKline, London, UK.

References


