Antibiotics in mare reproduction

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Abstract

Antibiotics are used to treat a variety of reproductive tract infections in the mare. The results of an on-line survey of veterinarians concerning the use of antibiotics in mare reproduction are presented. Listservs were used to acquire the data. Most veterinarians follow the recommendations in the literature for treating mares with reproductive tract infections. However, some veterinarians may mix antibiotics inappropriately, treat mares too soon after breeding, use inappropriate mixed lavage solutions, or use antibiotics in cases that do not warrant their use.

Keywords: Mare, antibiotic, reproduction, uterine, systemic, fungal

Introduction

Antibiotics are used in the mare to treat potential or realized reproductive tract infections including vaginitis, cervicitis, endometritis, metritis, pyometra, and placentitis. Alternatively, infections may be associated with or classified as sexually transmitted diseases, post-mating induced endometritis, acute or chronic endometritis, abortion related, and/or bacterial and fungal infections.[1] Antibiotics are administered either through intravenous/intramuscular routes or directly into the reproductive tract lumen. Antibiotics are naturally occurring or synthetic substances that inhibit the growth of or kill microorganisms. The definition may be limited to substances affecting bacteria or may also include fungi and protozoa. In this paper antifungals will be considered part of the antibiotic class.

There are a few reviews of the use of antibiotics in mare reproduction.[2-4] The choice of antibiotic should be based on culture and sensitivity patterns when possible or based on the most likely organism when not possible. The most common bacteria isolated from the mare's reproductive tract are *Streptococcus equi* subspecies *zooepidemicus* (Gram positive), *Escherichia coli* (Gram negative), *Klebsiella pneumonia* (Gram negative), *Pseudomonas aeruginosa* (Gram negative), *Staphylococcus aureus* (Gram positive), and *Bacteroides* (Gram negative, anaerobe).[5-10] *Streptococcus equi* subspecies *zooepidemicus* and *Escherichia coli* are the number one and two isolates in almost all reports. The most common fungi isolated from the mare's reproductive tract are *Candida* spp and *Aspergillus* spp.[11]

There are many factors that may affect antibiotic effectiveness/clearance such as overwhelming microorganism numbers, presence of uterine fluid/debris, lack of uterine contractility, use of ecbolics, normality of uterine mucocilliary clearance mechanisms, cervical dilation, and dependency of the uterine horns.[12-15] Disruptions of natural barriers to infection, such as previous cervical trauma/scarring, vestibulovaginal fold incompetence (windsucker), and poor vulvar conformation, may also contribute to continued bacterial/fungal contamination.[16]

Intrauterine antibiotic therapy appears to have decreased in use, most likely due to concerns about inducing secondary fungal infections and/or antibiotic resistance and due to new information on the effectiveness of uterine lavage and the use of ecbolics, such as oxytocin and prostaglandin. Antibiotic therapies are now more targeted at specific organisms, are used with more specific disease processes or are used in conjunction with methods to disrupt biofilms or after decreasing bacterial numbers with lavage techniques. This manuscript will describe the results of an on-line survey of veterinarians concerning antibiotic use in mare reproduction and correlate the results to the literature.

Survey on antibiotic usage

Two surveys were conducted with regards to the use of antibiotics in equine reproduction. The surveys were initiated to see what is commonly used in practice vs. what is recommended in the literature. Both surveys were sent to the Equine Clinicians Network listserv (ecn@listserv.vetmed.wsu.edu), the American Association of Equine Practitioner's listserv (aaep_discussion@list.aaep.org), the Equine Reproduction listserv (eqrepro-l@po.missouri.edu) and the American College of Theriogenologists listserv (ACTList@lists.theriogenology.org). The first was initiated in September 2008 (190 respondents) and the second was initiated in March 2009 (109 respondents). The second survey was performed to augment the first survey results. Sixty-one percent of participants in the second survey partook in the first survey.

Approximately 69% of survey participants stated that the primary way that mares are bred in their practice is by the use of fresh cooled semen, 27% are bred primarily by natural cover, 3% primarily with frozen semen and 2% did not provide an answer. The number of years in practice was: <5 years – 7%, 5 to 10 years – 20%, 11 to 15 years – 13%, 16 to 20 years – 18%, >20 years – 39%, no answer – 2%. The percentage of their practice that was devoted to equine reproduction was: <10% - 11%, 10 to 25% - 21%, 25 to 50% - 18%, 50 to 75% - 15%, >75% - 34%, no answer – 1%. The larger number of practitioners in the >75% category most likely reflects the distribution of the survey to two predominately reproductively oriented listservs (ACT and EqRepro). Veterinarians from 14 countries participated in the survey, with 70% of respondents practicing in the United States.

When asked which bacterial and fungal organisms they encountered most frequently, the overwhelming answers for bacterial isolates were *Streptococcus zooepidemicus* followed by *Escherichia coli*. One practice stated that they had 80% beta-hemolytic Streptococcus isolated

from 1400 uterine cultures in their clinic. An antibiotic with both Gram positive and Gram negative properties may be appropriate for the treatment of uterine infections in those cases without culture. Fungal cultures, according to survey results, yielded primarily *Candida* spp followed secondarily by *Aspergillus* spp.

Intrauterine usage of antibiotics.

Antibiotics may be placed into the uterus prior to or after breeding or in association with treatment of suspected or known uterine infections. Dosages for antibiotics commonly used for intrauterine infusion are presented in Table 1. Practitioners responding to the survey stated that antibiotics administered prior to breeding were used for mares that were known to be problem breeders, mares that were repeat breeders, mares with uterine fluid pre-breeding, mares with excessive uterine edema, mares suspected of having an infection (awaiting culture/cytology results), mares suspected of having an infection (owners decline culture/cytology) or strictly at the owner's request.

Survey participants stated that they used post-breeding antibiotics in situations where they knew the mare had previous problems, in mares with uterine fluid, in those mares susceptible to post-mating induced endometritis, in mares bred late in the breeding season, in mares with previous pregnancy loss or as a routine procedure with a single dose of antibiotics, especially in natural cover situations. A study by Pycock found that pregnancy rates were better after a single dose of antibiotics (± oxytocin) post-breeding, especially in older mares (>12 years) and mares mated at the first estrus post-partum.[17] Some Thoroughbred farms may routinely use a single post-breeding antibiotic to limit bacterial contamination from natural cover.[18]

When asked how many days mares were commonly treated with intrauterine antibiotics, the responses were: one day (12%), two days (7%), three days (50%), four days (5%), five days (7%), one week (1%), other (13%), and no answer (5%). Those answering "other" may treat for 1 to 3 days, 3 to 5 days, number of days would depend on bacteria isolated, number of days would depend on presence of fluid, or would never treat a mare with intrauterine antibiotics. It has been recommended, based on endometrial biopsy, that treatment for mild intrauterine infections be performed for 3 days, moderate infections for 5 days, and severe infections for 7 days.[12] The determination of how mares fit into these categories may not be clear in practice and would need to be subjectively based on clinical signs and possible cytologic examination as biopsy results may not be returned for a number of days. It has also been suggested that mares not be treated for more than 2 or 3 days post-ovulation so as to decrease possible negative effects on corpus luteum progesterone secretion from prostaglandin released in response to endometrial irritation caused by the antibiotic or vehicle.[12] Antibiotics should also not be used immediately pre-breeding as high concentrations of antibiotics may negatively affect sperm function.[12]

Forty-three percent of practitioners would increase the volume of antibiotic solution infused to between 50 to 100 ml prior to infusion. Eight percent used the antibiotic without dilution; 19% added extra volume, but kept the total less than 50 ml; 11% added extra liquid so that the final volume was >100 ml; 7% added the antibiotic to the lavage solution; 6% did not answer the question; and 8% provided an alternative answer of "other" which included leaving some lavage solution in the uterus and adding the antibiotic to that fluid, using a 250 ml bottle of fluid for infusion with antibiotics added, or using a 10 ml or 20 ml total volume. The literature has suggested intrauterine infusion volumes ranging from 30 to 200 ml to achieve distribution throughout the uterine lumen.[2] Six grams of ticarcillin, for instance, has a higher intrauterine

concentration over time when a 250 ml volume is infused rather than a 60 ml volume.[19] With large volumes, however, reflux of fluid back through the cervix could occur, diminishing the overall dose. A more appropriate recommendation may be to maximize the volume of an antibiotic solution while considering the relative size and position of the uterus. Multiparous mares would naturally require a larger volume, while nulliparous mares should require less. With a dependant uterus, infused fluids tend to pool in the base of the uterine horns making it difficult to achieve uniform coverage of the endometrium; consequently, systemic antimicrobials may be a good choice in these mares.

The most common antibiotic used for intrauterine treatment prior to receiving culture/antibiotic sensitivity results by veterinarians who participated in the survey was ceftiofur (21%), followed by gentamicin (19%), ticarcillin with clavulanic acid (13%), ampicillin (12%), other (12%), procaine penicillin (5%), amikacin (5%), potassium penicillin (3%), and ticarcillin (3%). Nine percent of survey participants did not answer this question. The category "other" included combination of penicillin and gentamicin (2%), penicillin and neomycin (2%), ampicillin and gentamicin (1%), oxytetracycline, framomycin, framycetin, cefquinome, cefazolin, or chloramphenicol. Interestingly, procaine penicillin was used even though there are no dosages reported in most published reviews. Some practitioners had concern about residues that may be left within the uterus with the use of the procaine penicillin suspension. Enrofloxacin has been administered by intrauterine infusion without causing more than a moderate inflammatory response,[20] but there are other reports that the basic pH of enrofloxacin is very irritating to the endometrium.[12] Differences among reports may be due to the formulation studied in various countries and dosage, thus caution should be exerted when considering intrauterine enrofloxacin or, alternatively, enrofloxacin should be used systemically.

If we examine some of the more common antibiotics used in practice, one study found that 19% of beta-hemolytic Streptococcus isolates (includes *Streptococcus zooepidemicus*) were susceptible to gentamicin, whereas 96% of *Escherichia coli* isolates were susceptible.[10] In that study, 100% of the beta-hemolytic Streptococcal isolates were susceptible to ampicillin and penicillin G, whereas 86% of *Escherichia coli* isolates were susceptible to ampicillin. Another study evaluated intrauterine ceftiofur in mares and found that the drug had good antimicrobial activity and caused no increase in uterine inflammation when compared to controls.[21] Ticarcillin with clavulanic acid has been evaluated for intrauterine use and it was found that adequate intrauterine concentrations of the clavulanic acid portion are not maintained. Thus, this formulation may be questionable for intrauterine use.[22] These authors also reported that concentrations of ticarcillin declined rapidly after intrauterine administration, and multiple daily doses would be required.

Aminoglycosides have an acid pH that will irritate the endometrium.[3] It is suggested that aminoglycosides be buffered to a neutral pH with an equal volume of 7.5% sodium bicarbonate. Forty-three percent of practitioners added sodium bicarbonate, while 38% increased the volume of infusion as a means to moderate the acidic effects, and 10% did not add anything to the aminoglycoside. If saline is used to increase the volume of infusion to reduce the effect of low pH, it should be noted that saline has a pH of ≈5.5. A more suitable diluent may be lactated Ringer's solution which has a neutral pH.

Aminoglycosides should not be mixed with beta-lactam antibiotics. Precipitates may form when they are combined or, more importantly, aminoglycosides may cause a nucleophilic opening of the beta-lactam ring which then combines with an amino group from the aminoglycoside, resulting in a biologically inactive amide.[23,24] While the two drugs are

synergistic in controlling Gram positive (beta-lactams) and Gram negative (aminoglycosides) infections when given systemically, it is not completely understood how effective they are when placed together into the uterine lumen. In addition, penicillin G (potassium or procaine) is inactivated by acids, so if penicillin and an aminoglycoside are used together in an unbuffered form, the penicillin may be less effective because of the low pH environment caused by the aminoglycoside. From survey results it appears that quite a few practitioners (34%) mix the two classes of drugs together either in the same syringe (20%) or the drugs are infused into the uterus at the same time (14%). For maximum effectiveness, mixing these drugs within the uterus should be discontinued and the drugs should be given either systemically or their administration separated in time by an unknown number of hours if given by intrauterine infusion. It is also not recommended to mix the two classes of drugs in lavage solutions. Interestingly, there are many semen extenders that combine potassium penicillin and amikacin. This practice may diminish the effectiveness of the antibiotics. Conversely, gentamicin has a high rate of inactivation when mixed with certain beta-lactams, while amikacin is only slightly inactivated.[25]

When asked about which antifungal intrauterine drug they used prior to receiving culture results, the majority of practitioners (32%) would not use an antifungal drug, but instead opted for either a povidone-iodine solution lavage, lufenuron or, less commonly, a dilute vinegar lavage. If an antifungal drug were used, then the most common responses included clotrimazole (17%), nystatin (11%), miconazole (10%), fluconazole (8%) and amphotericin B (3%). No answer was provided by 19% of the respondents. Only 53% of practitioners submitted fungal cultures for sensitivity assay. Lack of antibiotic sensitivity patterns to determine the most appropriate therapy may explain, in part, why fungal uterine infections are difficult to treat. The reasons stated for not submitting fungal cultures for a sensitivity are: length of time to receive

results; had success with povidone-iodine lavage; all seem sensitive to amphotericin B; inability to obtain fungal sensitivities from the laboratory; the relative infrequency with which fungal infections were encountered precluded sensitivity testing; just treated *Candida* infection with nystatin; or treating seems to work just fine. There are a number of laboratories that offer fungal sensitivity patterns including the laboratory at Cornell University. There was also concern from practitioners that in vitro sensitivity patterns may not correlate with in vivo effectiveness. It would appear that within the group of polyene antifungal antibiotics, amphotericin B (96% susceptibility of all fungal organisms) and nystatin (100% susceptibility) are good choices, where as clotrimazole (80% susceptibility) or ketoconazole (81% susceptibility) are good choices when using azole antifungal antibiotics. (personal communication, Marco Coutinho da Silva, Cornell University) Polyene antibiotics are generally considered fungicidal, whereas azole antibiotics are fungistatic, except at higher doses. Some practitioners try to avoid intrauterine antifungal treatments with the concern that repeated intrauterine treatment may make the mare more susceptible to re-infection or prolonged inflammation. An alternative would be oral antifungal drugs which may be expensive.

Lufenuron is a chitin inhibitor which has been used in an extra-label manner for treatment of fungal uterine infections.[26] It should be noted that lufenuron affects the wall of growing fungi and may not be appropriate for treatment of mature infections. A better approach may be to treat with an antifungal antibiotic and then at the end of treatment, place lufenuron in the uterus to prevent new growth. The effectiveness of lufenuron still remains in question.[27,28]

Uterine lavage with either iodine or vinegar is a component of therapy for many veterinarians when treating fungal infections. Forty percent of veterinarians used a dilute iodine solution for lavage (24% added iodine to saline, 16% added iodine to lactated Ringer's solution).

The percent iodine in lavage solutions in the survey range from 0.02% (2 ml of 10% iodine per liter) to 0.5% (50 ml of 10% iodine per liter). A 0.2% solution of iodine infused into the uterus has been associated with endometrial inflammation and fibrosis.[29] A 0.01% to 0.05% solution of iodine maintains antimicrobial activity[30] without causing inflammation and fibrosis.[31] Practitioners should be cautious of the higher concentrations of iodine in intrauterine infusions. Twenty-two percent of veterinarians used a dilute vinegar solution (15% of practitioners added vinegar to saline, 7% added it to lactated Ringer's solution). When using vinegar, saline would be a more appropriate lavage solution, if the desire is to lavage with a lower pH solution. Addition of 20 ml of white vinegar to 1000 ml of saline (2% v:v solution) will reduce the pH from ≈5.5 to ≈3, whereas it has little effect on the pH of lactated Ringer's solution.

Intrauterine antibiotics and lavage should be avoided within 4 hours of breeding[12] so that spermatozoa are not negatively affected by the drugs or the vehicles in which they are delivered. After 4 hours post-insemination, spermatozoa are located in the oviduct and intrauterine treatment at this time does not have a negative effect on fertility.[32] Most practitioners who participated in the survey appeared to be aware of this, with only 16% of them infusing antibiotics within 4 hours post-insemination. Most practitioners (37%) withheld treatment for more 4 hours post-breeding, because the next examination, and thus treatment of the mare, did not occur until the day following insemination.

Systemic antibiotics

The decision to use systemic antibiotics either in combination with intrauterine infusion, after intrauterine infusion or instead of intrauterine infusion of antibiotics may be due to personal preference, a desire to prolong the treatment period, because the organism is not susceptible to non-irritating drugs, or to avoid manual manipulation of the reproductive tract. Results of the

on-line survey indicated that systemic antibiotics are chosen when intrauterine treatments extend beyond 3 to 5 days, when treating mares with metritis, when treating mares with contaminated caudal reproductive tracts, when treating mares with anatomical defects of the caudal reproductive tract or occasionally when treating mares with fungal infections. Respondents felt that systemic antibiotics negate the need to invade the uterus, possibly avoiding the chances of iatrogenically placed bacteria or fungi. The disadvantages of using systemic antibiotics are increased costs and inconvenience from having to dose at the animal's full body weight and possibly the need to treat multiple times per day. A very small number of practitioners felt that it was not good veterinary practice to place antibiotics directly into the uterus, since systemic antibiotics work well, do not cause endometrial irritation, and do not lead to further contamination.

Dosages for antibiotics commonly used systemically are presented in Table 2. Trimethoprim sulfadiazine, ceftiofur, and a combination of penicillin and gentamicin were the most common antibiotics administered by practitioners who participate in the survey. Trimethoprim sulfamethoxazole (30 mg/kg, per os, q12h) was found to provide adequate antibiotic concentrations in fetal tissues in mares with placentitis.[33] In a separate study, ceftiofur dosed at 2 mg/kg q12h intramuscularly, did not result in adequate endometrial tissue levels;[34] however, it has been suggested as a potential treatment for mares with placentitis.[35] Higher dosage concentrations (recommended up to 4.4 mg/kg) and/or intravenous treatment could perhaps result in adequate endometrial levels. In cattle, minimal inhibitory concentrations of ceftiofur are achieved in endometrial tissue after subcutaneous administration.[36] A study by Murchie, et al., found that intravenous administration of penicillin G potassium and gentamicin sulfate resulted in adequate allantoic fluid concentrations in pregnant pony mares.[37]

Enrofloxacin has also been used in mares with more resistant bacteria.[20,38,39] Enrofloxacin should not be used in pregnant mares due to its effects on developing cartilage.[40] Doxycycline has also been demonstrated to reach endometrial concentrations above the minimum inhibitory concentration for *Streptococcus equi* subspecies *zooepidemicus*.[41]

Antifungal antibiotics may be administered systemically. Amphotericin B is fairly caustic due to a low pH and needs to be given via nasogastric intubation or diluted and given slowly intravenously. Oral fluconazole has been recommended for treatment of *Candida* spp. while oral itraconazole has been suggested for treatment of *Aspergillus* spp. (personal communication, Marco Coutinho da Silva, Cornell University).

Uterine Cytology

Uterine cytology was performed in conjunction with 67% of uterine cultures. This is a relatively easy procedure to perform and interpret.[42] Sixty-four percent of practitioners either read their own (56%) or had someone in their practice (8%) read cytologies. By performing this examination "in-house" results may be interpreted and therapy instituted without the delay of sending the slides to an outside laboratory. Only 9% of practitioners, however, used Gram stain to distinguish Gram negative from Gram positive bacteria in order to institute appropriate antimicrobial therapy.

Treatments to augment antimicrobial therapy

Uterine lavage is recommended to remove uterine debris, bacteria and fungi and to enhance uterine contractility. DMSO lavages may be useful to augment tissue penetration and to disrupt microbial biofilms.[43] Acetylcysteine and kerosene have also been suggested as possible mucolytic agents. Biofilms are aggregates of bacteria and/or fungi encased in an adherent polymeric matrix which may inhibit antibiotic penetration.[44-46] Biofilms have been known to

form with *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Candida* spp.[47]

Tris-EDTA has been demonstrated to act synergistically with antimicrobials by increasing the membrane permeability of bacteria to these drugs.[48] Uterine lavage with tris-EDTA, either alone or in combination with antibiotics, should be considered with resilient infections or in cases with antibiotic-resistant organisms.

New intrauterine therapies

Intrauterine foam (Fatroximin®; Fatro, Bologna, Italy) containing the antibiotic rifaximin, a synthetic derivative of rifamycin, has been developed for use in cattle and horses.[49] It has a spectrum of activity that includes Gram negative, Gram positive and anaerobic bacteria. The drug, in the foam vehicle, has a 72+ hour residual effect and expands to cover the entire uterine lumen. A single treatment is recommended for treatment of endometritis or the product may be administered for two consecutive days for treatment of vulvovaginitis. This drug is currently available in Europe.

Conclusions.

Veterinarians should base antibiotic therapy on sensitivity tests. Consideration should be given to antibiotic therapy alternatives such as proper breeding management, use of uterine lavage and oxytocin or prostaglandin treatment. Biofilm formation should be appropriately treated to enable antibiotics to access bacteria and fungi. With a plan, antibiotic usage can be minimized and treatment success optimized. The main issues of concern identified from the on-line survey of veterinarians are: mixing beta-lactam and aminoglycoside antibiotics for intrauterine infusion, intrauterine infusion of high concentrations of iodine solutions, use of

lactated Ringer's solution with vinegar for uterine lavage, and treatment of mares less than 4 hours post-breeding with intrauterine antibiotics.

Table 1. Intrauterine antibiotic dosages.

Intrauterine antibiotics			
Antibacterial antibiotics			
Antibiotic	**Dosage**	**Comments**	**Major bacterial susceptibility**
Amikacin	1 to 2 grams	Buffer with sodium bicarbonate or 150 to 200 ml solution	Gram negative
Ampicillin	1 to 3 grams	Use soluble product, may be irritating when concentrated	Gram positive and *E.coli*
Ceftiofur sodium	1 gram		Gram positive and Gram negative
Chloramphenicol	2 to 3 grams	Can be irritating	Gram positive and Gram negative
Gentamicin	1 to 3 grams	Acidic – need to dilute and/or buffer	Gram negative
Neomycin	2 to 4 grams		Gram negative
Potassium penicillin	5 million		Gram positive

	international units		
Procaine penicillin	4.5 to 6 million international units	Concern about residue left in uterus	Gram positive
Ticarcillin	3 to 6 grams	Infuse with 150-200 ml solution	Gram positive, *Pseudomonas*
Ticarcillin with clavulanic acid	3 to 6 grams	Beta-lactamase inhibitor, infuse with 150-200 ml solution	Same as ticarcillin plus more Gram positive (*Staph, Bacillus, Enterobacter*)
Antifungal antibiotics q24h for 7 days			
Drug	**Dosage**	**Comment**	
Amphotericin B	100-200 mg	Polyene, dilute in >100 ml solution, mix well	
Clotrimazole	400 to 700 mg	Azole, tablets usually crushed and mixed with solution	
Fluconazole	100 mg	Azole, may need to adjust pH to avoid acidic nature	
Miconazole	500-700 mg	Azole	
Nystatin	0.5 to 2.5 million international units	Polyene, Dilute in sterile water, not saline to avoid precipitates, mix well	

Table 2. Systemic antibiotic dosages. (IV-intravenous, IM-intramuscular, PO-per os, q-every, h-hour, IU-international units, kg-kilogram)

Systemic Antibiotics			
Antibacterial antibiotics			
Drug	**Dosage**	**Route, Comment**	
Amikacin	10 mg/kg q24h	IV or IM	
Ampicillin	29 mg/kg q12-24h	IV or IM	
Ceftiofur	2 to 4 mg/kg q12h	IV or IM	
Doxycyline	10 mg/kg q12h	PO	
Enrofloxacin	5.5 mg/kg q24h	IV	
	7.5 mg/kg q24h	Per os	
	4.0 mg/kg q12h	Per os	
Gentamicin	6.6 mg/kg q24h	IV or IM	
Metronidazole	15 to 25 mg/kg	PO	
Oxytetracycline	6.6 mg/kg q12h	IV, dilute and give slowly	
Potassium Penicillin	22,000 IU/kg q6h	IV	
Procaine Penicillin	22,000 IU/kg q12h	IM, only 10 ml per injection site	
Trimethoprim Sulfa	30 mg/kg q12h	PO	
Antifungal antibiotics			
Drug	**Dosage**	**Route**	**Comments**
Amphotericin B	0.3 to 0.9 mg/kg q24-48h	IV	Polyene, dilute and give slowly
Fluconazole	14 mg/kg loading,	IV or per os	Azole

	then 5mg/kg q24h; alternatively, 2 grams q24h		
Itraconazole	5 mg/kg q12-24h	IV or per os	Azole, oral suspension more bioavailable than capsules
Ketoconazole	20 mg/kg q12h in 0.2 N HCl	Per nasogastric intubation	Azole, irritant if given per os due to low pH – need to place into stomach

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