Therapy of Postpartum Uterine Infections

Jerry D. Olson, *D.V.M., M.S.*
Leslie Ball, *D.V.M., M.S.*
Robert G. Mortimer, *M.S., D.V.M.*
Department of Clinical Sciences
Colorado State University
Fort Collins, Colorado 80523

Postpartum uterine infections are a common occurrence in cows in intensively managed dairy operations. The literature contains numerous reports of therapies for postpartum uterine infection but a paucity on the effects of these therapies upon subsequent fertility. If the pathology, endocrinology, and bacteriology of the peripartum period are understood, then a more rational therapeutic approach to management of postpartum uterine infections can be derived. In selecting therapies, the objective of restoring reproductive performance to normal should never be lost from sight.

The therapies for postpartum uterine infections can be classified into two general areas; hormonal and antimicrobial. In the selection of antimicrobial therapy, several factors should be considered. The first consideration should be whether or not information exists on the effect of the therapeutic agent upon subsequent fertility. A second consideration in selection of antimicrobial agents is an appreciation of which bacteria are significant pathogens in the mixed bacterial population of the postpartum uterus. Studies using concurrent biopsy and aerobic culture techniques have demonstrated that *C. pyogenes* should be considered a primary uterine pathogen. Any time *C. pyogenes* has been recovered from the uterus for more than a week, a severe metritis has also been present. More recent work has identified gram negative anaerobes as concurrent isolates with *C. pyogenes.* This work is significant because experimental models have demonstrated a pathological synergism between *C. pyogenes* and certain gram negative anaerobes. The role of other bacteria in the very early postpartum period is less clear but *Clostridium spp* contribute to severe puerperal metritis. With an appreciation for the significant pathogens in a disease process, antimicrobial selection can be based upon culture and antimicrobial susceptibility testing or upon previously reported susceptibility patterns.

Another consideration in the selection of antimicrobial therapy is the oxygen tension and the tissue debris in the bacterial enviroment. The isolation of fastidious obligate anaerobes from the lumen of the postpartum uterus indicates that the uterus is an anaerobic environment. An anaerobic environment precludes the effective use of antibiotics such as the aminoglycosides because their antibacterial activity is markedly reduced under anaerobic conditions. Likewise, the effectiveness of other antimicrobial agents such as sulfonamides and nitrofurans is markedly reduced by the presence of blood, pus, and tissue debris, products common to the early postpartum uterus. A last consideration is that of the pharmacokinetics of the antimicrobial agent per se. It is important to have an appreciation for the concentrations of an antimicrobial agent that can be attained at the site of an infection and the length of time effective concentrations can be maintained following treatment. With these guidelines for selection of an antimicrobial agent in mind, individual antimicrobial agents will be reviewed and evaluated as therapeutic agents for post partum uterine infections.

Penicillin

Penicillin is a fermentation product of *Penicillium spp.* It derives its antimicrobial activity by inhibiting the transpeptidase reaction thus interfering with cell wall synthesis and making the bacteria more susceptible to lysis. The primary mechanism of bacterial resistance to penicillin is mediated through bacterial production of the enzyme penicillinase which inactivates penicillin by splitting its beta-lactam ring. An important feature to appreciate is that resistant bacteria must release penicillinase into the environment to destroy penicillin before it can bind to the enzymes of cell wall synthesis. Thus the release of penicillinase into the resistant bacterias' environment not only affords protection for the resistant bacteria but for other susceptible bacteria as well. This mechanism of resistance created problems in treating mixed infections with penicillin when part of the population is resistant. This is the case in early postpartum uterine infections. However, as the postpartum period progresses in cows with metritis, the bacterial population of the uterus changes from a mixed population to a population composed predominately of *Corynebacterium pyogenes, Fusobacterium necrophorum,* and *Bacteroides spp.* All three of these bacteria are generally susceptible to penicillin. Thus, penicillin would not be a good choice for local intrauterine therapy in the early postpartum uterus because the population of bacteria is mixed. However, systemic penicillin therapy is a sound choice at this time because the bacteria likely to invade the endometrium from the uterine lumen are usually susceptible to penicillin. Systemic dosages of 5-10,000 IU/kg provide serum concentrations of greater than 1 ug/ml for 6-12 hours.

Although the ratio of penicillin concentration between serum and genital tissue has not been determined experimentally, it is likely that this level is high enough to be effective for *Clostridium, C. pyogenes,* and gram negative anaerobes. Later in the postpartum period when the bacterial population has been reduced predominately to *C. pyogenes* and gram negative anaerobes, intrauterine infusion of penicillin is probably a good choice. One million units of procaine penicillin infused into the involuted uterus provides therapeutic levels in both the lumen and endometrium for 30 hours.

In summary, intrauterine infusion of penicillin may not be effective in the early postpartum period because resistant bacteria are likely to be present in the mixed bacterial population but as the mixed population changes with time to a selective susceptible population, penicillin is more likely to become an effective choice for intrauterine therapy.

Tetracyclines

Oxytetracycline will serve as a type for the commonly used tetracycline antibiotics. It derives its broad spectrum antibacterial activity by binding to the 30 S ribosomes and inhibiting protein synthesis. The tetracyclines gain access to the bacterial cell by a two stage process. The first stage is passive diffusion through the outer cell membrane; the second is an active, energy-dependent transport across the inner cell membrane which may require a specific carrier protein. The mechanism for resistance centers around blockage of tetracycline entrance into the cell by interference with the energy dependent transport system. There is an important consideration relative to the effect of bacterial resistance to tetracyclines in the therapy of mixed bacterial infections. The production of proteins which prevent tetracycline transport is an internal process occurring within individual bacteria. These protective proteins are not released into the immediate enviromnent and thus do not confer protection to neighboring cells. Thus there is a greater probability of at least partial success in treatment of a mixed infection in which both susceptible and resistant bacteria are present. In addition, the activity of tetracyclines is only slightly reduced by tissue debris, purulent exudate, and lowered oxygen tension. There are both mixed bacterial infections and purulent exudate in an anaerobic enviroment in the early postpartum uterus. These conditions make oxytetracycline a desirable choice for intrauterine therapy during this period.

However, recent studies into the pharmacokinetics of oxytetracyclines in the genital tissues have given insight into its lack of therapeutic value following parenteral administration. The serum to tissue ratio for oxytetracycline in the genital tissue of both healthy and diseased cows ranges from 1:1 to 1.5:1. It is necessary to treat cattle twice daily with 11 mg of oxytetracycline kg of body weight to acheive and maintain a minimal serum concentration of 5 ug/ml. This would result in a concentration of about 5-8 ug of oxytetracycline ml of uterine tissue. However, the average MIC for isolates of *C. pyogenes* from the uterus is 20 ug/ml. These MICs are much higher than the antibiotic concentration in genital tissue following intravenous therapy at 11 mg/kg. Thus systemic dosages large enough to obtain effective tissue levels against *C. pyogenes* would be nephrotoxic; consequently, parenteral therapy using oxytetracycline for metritis cannot be recommended.

Aminoglycoside Antibiotics

The aminoglycoside antibiotics which include streptomycin, neomycin, gentamicin, kanamycin, and amikacin are highly polar polycations. The bactericidal activity of the aminoglycoside antibiotics depends on inhibition of protein synthesis at the level of the bacterial ribosome. Since the aminoglycoside antibiotics are highly polar, they must be actively transported across cell membranes. Transport is an active process requiring energy derived from oxidative phosophorylation. Consequently transport of animoglycosides can be significantly decreased by a lowered oxygen tension in the bacterial environment. Thus, the antimicrobial activity of the aminoglycosides can be markedly reduced in an anaerobic environment like the postpartum uterus. Ziv compared the minimal inhibitory concentrations (MIC) of the aminoglycoside antibiotics under aerobic and anaerobic test conditions using postpartum uterine secretions as a fluid media. The MIC of neomycin, dihydrostreptomycin, and gentamicin for *Corynebacterium pyogenes* increased 64, 32, and 128 fold, respectively, from aerobic to anaerobic conditions. Fuquay, in a field trial comparing postpartum uterine treatments, found that cows treated with neomycin boluses were less fertile than nontreated controls. Since recent work strongly indicates that the postpartum bovine uterus is an anaerobic environment, the aminoglycoside antibiotics are probably a poor choice for either systemic or intrauterine therapy of metritis.

Nitrofurazone

Nitrofurazone is a furan derivative which possesses bacteriostatic to bactericidal activity depending upon its concentration. However, neither the mechanisms of antibacterial action or bacterial resistance as well understood. Nitrofurazone has been available in several forms for intrauterine therapy but the most common is a 0.2% nitrofurazone solution which is equivalent to 2000 ug/ml. In a recent survey, isolates of *C pyogenes* from the bovine uterus had an average MIC in excess of 590 ug/ml for nitrofurazone. This MIC is very close to the concentration of commercially available nitrofurazone solution without the dilution effect of uterine fluids. Furthermore, the antibacterial activity of nitrofurazone is markedly reduced by plasma, blood and dense bacterial populations. Nitrofurazone is also irritating to the endometrium and causes a shortened inter-estrous interval when it is infused

into the diestral uterus. Cows in which nitrofurazone solution was infused following evacuation of pus were significantly less fertile than noninfused contemporaries. We conclude that nitrofurazone is contraindicated in the treatment of uterine infections.

Sulfonamides

The sulfonamides obtain their antibacterial capability by competitively inhibiting the enzymatic incorporation of paraaminobenzoic acid into the immediate precursor of folic acid. The antibacterial activity of sulfonamides is markedly reduced in an environment containing blood, pus, and tissue breakdown products. This is a result of a reduced bacterial requirement for folic acid in an environment that contains purines and thymidine released from necrotic cells. In the postpartum uterus, necrotic tissue debris and dead leukocytes furnish metabolites necessary for bacterial growth. Consequently, sulfonamides have minimal antibacterial activity in the postpartum uterus.

Hormonal Therapy

Estrogens, luteolytic prostaglandins, and gonadotropin releasing hormone (GnRH) have been used in the postpartum period alone or in conjunction with other agents to treat retained fetal membranes (RFM), metritis, and pyometra. Estrogens have not been effective in the treatment of RFMs or metritis and some studies indicate they may actually be detrimental to fertility. Estrogens are effective in the treatment of pyometra but do not perform as well as prostaglandins. GnRH has been used in the postpartum period. However, three criteria must be met for GnRH to improve fertility. It must be given between days 12 and 18 postpartum. If given earlier, the pituitary is unresponsive and if given later a prolonged luteal phase results without improvement in fertility. To show a benefit from GnRH, the cow must have had an abnormal peripartum period, i.e. RFM, metritis, abnormal uterine involution. Lastly, the cow must be serviced before 60 days post partum to show benefit. In a recent report, cows treated with SnRH in the early postpartum period had a marked increase in the incidence of pyometra. Further work is needed to clarify the role of GnRH as a hormonal treatment for restoration of normal fertility.

Prostaglandin F_2 alpha and its analogs are potent luteolytic agents. This attribute has made the luteolytic prostaglandins the treatment of choice for pyometra. The luteolytic prostaglandins are also the treatment of choice for behavioral anestrus. Hormonal therapy, when indicated has the distinct advantage that milk withdrawal is not required as with antibiotic therapy.

Application of Specific Treatments

The early postpartum period is defined as the period from parturition to 8-14 days post partum when the pituitary becomes sensitive to GnRH.

Retained fetal membranes are important because they are associated with an increased risk of metritis-pyometra complex. The degree of risk and the severity of metritis seem to be associated with animal density, frequency of use of maternity pens, and immunity of dam. For this reason, minimal treatment of cows with RFMs should be intrauterine infusion of tetracyclines. If cows with RFMs frequently develop systemic involvement following local therapy only, penicillin should also be administered parenterally. Treatment should begin immediately if fetal membranes are retained more than 12 hours post partum and be continued daily until the membranes are expelled. Attempts to remove the membranes should be limited to gentle traction; anything more is detrimental to fertility.

Cows with puerperal metritis can be divided into two categories, those with and those without systemic involvement. Within each category there is a gradation of severity. If a cow has only local signs such as a fetid vaginal discharge of uterine origin, the uterus should be treated locally. If the cow is febrile, anorexic, depressed or has decreased milk production, she should be treated systemically. Since pathogenic clostridial organisms have been isolated from uterine tissues and secretions of cows that have died from puerperal metritis, clostridial organisms probably play a significant role in the pathogenesis of puerperal metritis with systemic involvement. The potential pathogens of the early postpartum period, *Clostridium spp, C. pyogenes,* and gram negative anaerobes, are usually susceptible to penicillin. Therefore, penicillin is the antibiotic of choice for systemic therapy of cows having puerperal metritis with systemic involvement. In addition, the uterus of cows with septic puerperal metritis, either with or without RFM, should also be treated locally with tetracyclines as previously discussed. In cows with puerperal metritis without systemic involvement, local therapy with tetracyclines alone is usually effective. In all cases of puerperal metritis, cows should be re-examined 20-30 days after calving to evaluate uterine involution.

The intermediate postpartum period is defined as the period from 8-14 days post partum to the first ovulation.

Uterine infections in the intermediate period are primarily localized to the uterus. The predominant discharge, if observed, is purulent. A common problem of this period is identification of the cow with the uterine infection by the herdsman. Deposits of purulent discharge are often left on the ground when a diseased cow lies down. She may have few external signs although caking or exudate on the buttocks and tail can be seen on close inspection of most infected cows. Once identified, intrauterine infusion of a tetracycline is indicated because the uterus may still contain a mixed population of bacteria. Therapy should be continued for a minimum of three days. Recently workers have presented conflicting evidence on the role of GnRH in the intermediate postpartum period. Earlier work suggested that the administration of GnRH to cows 12-18 days post partum

may restore normal fertility to cows with an abnormal peripartum. More recent work demonstrated that cows with abnormal peripartum receiving GnRH 12-18 days post partum might have a significantly higher incidence of pyometra.

The late postpartum or postovulatory period is defined as the period after the first ovulation.

The primary uterine diseases of the postovulatory period are pyometra and metritis. Roberts defines pyometra as the retention of purulent to mucopurulent exudate in the uterus with retention of the corpus luteum (CL). The problem with this definition of pyometra is that the pyometra must persist for 21 days to demonstrate retention of the CL. Leaving a cow with a purulent endometritis associated with a CL untreated for three weeks to fulfill the requirements of diagnosis by this definition is impractical. Consequently, we define pyometra as a uterus filled with purulent exudate in association with a CL on one or both ovaries. The primary objective of therapy is to cause regression of the CL which stimulates uterine evacuation. Estrogens have been used in the past to cause luteal regression and uterine evacuation with a single treatment success rate of 55-65%. Prostaglandin F_2 alpha and its analogs have been used with a single treatment success rate of 80-90%. Fertility of cows following uterine evacuation appears to be related to the duration of the pyometra. Cows that conceive following uterine evacuation usually do so only after a lapse of about 60 days following treatment. This emphasizes the importance of early diagnosis and treatment through regular postpartum examination of all cows.

The role of local therapy in the treatment of pyometra has not been well defined. However, infusion of nitrofurazone into the uterus following evacuation of the exudate reduced subsequent fertility. It is important to appreciate that following evacuation of exudate, a minimum of 30 days is required for the endometrium to resolve the damage resulting from the infection. This increases the difficulty of evaluating the role of local uterine therapy.

Chronic metritis is also a common disease of the postovulatory period. The primary pathogen associated with chronic metritis is *C. pyogenes*. However, gram negative anaerobes may act synergistically with *C. pyogenes* in the postovulatory period to establish persistent infections because metritis of the late postpartum period is often associated infections of both *C. pyogenes* and gram negative anaerobes. These bacteria are commonly susceptible to penicillin, and few other bacteria are present to interfere with the bactericidal action of penicillin. Consequently, intrauterine infusion of penicillin is the treatment of choice. Single intra-uterine infusions have little effect on improving fertility. Treatments over time have not been evaluated but are more likely to be effective. As with pyometra, there is a period of reduced fertility between the time *C. pyogenes* is eliminated from the uterus and the time the uterus resolves its damage.

Selected Bibliography

1. Bostedt, V.H., Peche, E., Strobl, K.: Zur auswirkung fruhzeitig postpartum verabeichter GnRH-Gaben auf peurperalverlauf and knozeption-sergebnis bei kuhen nach retentio secundinarum. Berl Munch Tierarztl Wschr 93:184-188, 1980. 2. Bretzlaff, K.N., Ott, R.S., Koritz, G.D., et al: Distribution of oxytetracycline in the genital tract of cows. Am J Vet Res 43:12-16, 1982. 3. Bretzlaff, K.N., Ott, R.S., Koritz, G.D., et al: Distribution of oxytetracycline in the healthy and diseased postpartum genital tract of cows. Am J Vet Res 44:760-763, 1983a. 4. Bretzlaff, K.N., Ott, R.S., Koritz, G.D., et al: Distribution of oxytetracycline in genital tract tissues of postpartum cows given the drug by intravenous and intrauterine routes. Am J Vet Res 44:764-769, 1983b. 5. Davies, J.E., Yagisawa, M.: The aminocyclitol glycosides (aminoglycosides). In, Vining LC (ed): Biochemistry and Genetic Regulation of Commercially Important Antibiotics. Reading, Adison-Wesley Publishing Co., 1983, pp 329-354. 6. DeKruif, A., Van Der Wielen NJGJ, Brand, A., et al: Behandeling van runderen lijdende aan een pyometra met oestrogenen en prostaglanded. Tijdschr Diergeneesk 102:851-856. 7. Fazeli, M.H., Ball, L., Olson, J.D.: Comparison of treatment of pyometra with estradiol cypionate or cloprostenol following infusion or noninfusion with nitrofurazone. Theriogenology 14:339-347, 1980. 8. Fuquay, J.W., Harris, R.A., McGee, W.H., et al: Routine postpartum treatment of dairy cattle with intrauterine neomycin sulfate boluses. J Dairy Sci 48:1367-1369, 1974. 9. Ginther, O.J, Meckley, P.E.: Effect of intrauterine infusion on length of diestrus in cows and mares. Vet Med/Sm Animl Clin 67:751-754, 1972. 10. Griffin, J.F.T., Hartigan, P.J., Nunn, W.R.: Nonspecific uterine infection and bovine fertility. I. Infection patterns and endometritis during the first seven weeks post-partum. Theriogenology 1:91-106, 1974a. 11. Hartigan, P.J., Griffin, J.F.T., Nunn, W.R.: Some observations on Corynebacterium pyogenes infection of the bovine uterus. Theriogenology 1:153-165, 1974. 12. Huber, W.G.: Tetracyclines. In, Jones, L.M., Booth, N.H., McDonald, L.E. (ed): Veterinary Pharmacology and Therapeutics, 4th ed, The Iowa State Univ Press, 1977, pp 929-939. 13. Hjerpe, C.A., Routen, T.A.: Practical and theoretical considerations concerning treatment of bacterial pneumonia in feedlot cattle, with special reference to antimicrobic therapy. In, Proceedings 9th Annual Conference, Am Assoc Bovine Pract, 1976. 14. Ingham, H.R., Tharagonnet, D., Sisson, P.R., et al: Inhibition of phagocytosis in vitro by obligate anaerobes. The Lancet 2(8051):1252-1254, 1977. 15. Mandell, G.L., Sande, M.A.: Antimicrobial agents - penicillins and cephalosporins. In, Gilman, A.G., Goodman, L.S., Gilman, A. (ed): The Pharmacological Basis of Therapeutics, 6th ed, MacMillan Publ Co, Inc, 1980, pp 1126-1161. 16. Miller, H.V., Kimsey, P.B., Kendrick, J.W., et al: Endometritis of dairy cattle: diagnosis, treatment and fertility. Bovine Practitioner No. 15:13-23, 1980. 17. Roberts, D.S.: The pathogenic synergy of Fusiformis necrophorus and Corynebacterium pyogenes. I. Influence of the leucocidal exotoxin of F. necrophorus. Br J Exp Pathol 48:665-673, 1967a. 18. Roberts, D.S.: The pathogenic synergy of Fusiformis necrophorus and Corynebacterium pyogenes. II. The response of F. necrophorus to a filterable product of C. pyogenes. Br J Exp Pathol 48:674-679, 1967b. 19. Ruder, C.A., Sasser, R.G., Williams, R.J., et al: Uterine infections in the postpartum cow. II. Possible synergistic effect of Fusobacterium necrophorum and Corynebacterium pyogenes. Theriogenology 15:573-580, 1981b. 20. Sande, M.A., Mandell, G.L.: Antimicrobial agents - the aminoglycosides. In, Gilman, A.G., Goodman, L.S., Gilman, A. (ed): The Pharmacological Basis of Therapeutics, 6th ed, MacMillan Publ Co., Inc., 1980, pp1162-1180. 21. Sande, M.A., Mandell, G.L.: Antimicrobial agents - tetracyclines and chloramphenicol. In, Gilman, A.G., Goodman, L.S., Gilman, A. (ed): The Pharmacological Basis of Therapuetics, 6th ed, MacMillan Publ. Co., Inc., 1980, pp1181-1199. 22. Schallenberger, E. Schams, D., Zottmeire, K.: Response of lutropin (LH) and follitropin (FSH) to the administration of gonadoliberin (GnRH) in pregnant and postpartum cattle including experiments with prolactin suppression. Theriogenology 10:35-53, 1978.