

BEYOND ANTIBIOTICS – WHAT ELSE CAN WE DO?

Dawn E. Morin
University of Illinois
Urbana, Illinois

A variety of non-antibiotic measures are frequently used in cows with clinical mastitis in conjunction with or in place of antibiotic therapy. Fluids and electrolytes are administered to combat circulatory changes and electrolyte disturbances. Steroidal and non-steroidal anti-inflammatory agents are used to reduce pain, inflammation, and fever. Oxytocin administration and frequent milk-out are used to promote milk ejection and removal of secretions. Concern about antibiotic residues in milk and frustration over poor cure rates associated with traditional mastitis treatments have prompted dairy producers and veterinarians to try many other systemic and local measures, most of which have not been scientifically evaluated. This paper will review published data for the best-documented non-antibiotic treatment practices and discuss potential uses and limitations.

Fluid and Electrolyte Therapy

Cows with clinical mastitis can develop fluid and electrolyte disturbances as a result of decreased feed and water intake, rumen stasis, ileus, or diarrhea. Severely affected cows, particularly those with coliform mastitis, may develop septic or endotoxic shock; in these cows death or organ damage can occur as a result of decreased effective circulating volume.

Hydration status has been associated with the outcome of clinical mastitis in several studies. In a field trial of 54 cows with clinical mastitis (Green et al, 1998), non-survivors (n=25) were compared with survivors (n=29). Non-surviving cows had a higher hematocrit (mean 46.4%) and eyelid skin tent duration (mean 6.7 seconds) than did surviving cows (39.5% and 3.6 seconds, respectively), indicating poorer hydration status. Similarly, in a study of 44 cows admitted to a teaching hospital with severe coliform mastitis (Cebra et al, 1996), non-surviving cows (n=12) had a higher serum creatinine concentration (median 2.5 mg/dl) than did surviving cows (n=32; 1.6 mg/dl). Hydration status appears to be important even in milder cases of mastitis. For example, in a field trial of 84 cows with mild to moderate clinical mastitis (Sischo et al, 1997), hematocrit on day 5 after mastitis onset was correlated with subsequent lactational milk yield; cows with a hematocrit > 32% had below median 305-day mature equivalent milk yield. Because of its perceived clinical importance, assessment of hydration status is often incorporated into mastitis severity scoring systems (Morin et al, 1998a; Wenz et al, 2001, Roberson, 2003).

Assessment of hydration status: The hydration status of an adult cow is usually assessed subjectively, by observing skin tent duration on the neck or eyelid and position of the globe in the orbit. Unfortunately, findings can be influenced by the body condition of the cow. Objective criteria for estimating the extent of dehydration have been reported for dairy calves (Constable et al, 1998a), but have not been established for adult cows. Extrapolating from calves, a healthy cow would be expected to have a cervical skin tent duration of ≤ 2 seconds and no recession of the eyeball. Skin tent durations of 4, 6, or 8 seconds, and eyeball recession of 2, 4, or 7 mm would correlate with 4, 8, and 12% dehydration, respectively. Other indicators of reduced

peripheral perfusion are cold extremities (ears, tail, fetlocks [only reliable at moderate ambient temperatures]) and a dry muzzle or mouth (Constable et al, 1998b). Hematocrit and serum or plasma protein concentration are not reliable indicators of hydration status in an individual cow due to the wide range of normal values and the effects of inflammation and stage of lactation on total protein concentration.

Acid-base balance: Most cows with clinical mastitis, even severe mastitis, have normal acid-base balance or metabolic alkalosis; metabolic acidosis is uncommon and is associated with a poor prognosis. For example, 18 of 37 cows admitted to a teaching hospital with severe coliform mastitis had a blood pH between 7.35 and 7.45 (Cebra et al, 1996). Fourteen of the 37 cows had a pH > 7.45 and only 5 had a pH < 7.35; non-surviving cows had a lower blood pH (median 7.35) than did surviving cows (median 7.45). In one field trial (Katholm and Andersen, 1992), blood pH values were similar for 12 cows with acute coliform mastitis and their control herd-mates. Such findings suggest that there is no need for routine IV administration of alkalizing agents, such as bicarbonate or lactate, to cows with clinical mastitis. Nor should oral products containing magnesium hydroxide be administered to mastitic cows, as these products can exacerbate metabolic alkalosis (Kasari et al, 1990).

Oral fluid therapy: Fluids can be administered by the oral (intraruminal) or IV route. The oral route is least expensive and is often adequate for cows with mild to moderate dehydration. Oral fluids should be hypotonic and contain sodium in order to create an osmotic gradient between ruminal fluid and blood and enable sustained absorption of fluid and electrolytes; hypertonic oral fluids must be avoided (Constable, 2003). A 600 kg (1,320 lb) cow that is 6% dehydrated needs to absorb 36 liters (approximately 9 gallons) of fluid to replace her deficit. This volume can be administered safely, but oral ingestion of larger volumes of hypotonic fluid might lead to hypothermia and intravascular hemolysis (Bianca, 1970). Oral fluids are not sufficient for cows with severe dehydration, as they do not allow rapid resuscitation.

Intravenous fluid therapy: Ringer's solution, which is iso-osmotic, mildly acidifying, and contains physiologic concentrations of sodium, chloride, potassium, and calcium is the fluid of choice for rapid IV resuscitation of adult ruminants (Constable, 2003). However, administration of Ringer's solution (or other iso-osmotic crystalloid solutions) can be difficult due to the large volume of fluid required and the need for IV catheterization. A 600 kg (1,320 lb) cow that is 8% dehydrated requires 48 L (approximately 12 gallons) of fluid just to replace her deficit. Ringer's solution can be made by mixing NaCl (8.6 g/L), KCl (0.3 g/L), and CaCl₂-dihydrate (0.3 g/L) with water. Although some practitioners mix the salts with tap water, this carries a risk of endotoxin administration; mixing with sterile distilled water is safer.

A practical (although inferior) alternative to iso-osmotic IV fluid therapy is IV administration of hypertonic (7.2%, 2,460 mosm/L) saline solution. This is administered through a large bore needle at a dose of 4-5 ml/kg body weight over 4-5 minutes and MUST be accompanied by oral administration of water (5 gallons). Rapid administration is required in order to rapidly increase blood osmolality and create an osmotic gradient to draw fluid from the intercellular spaces and gastrointestinal tract (mainly rumen) into the blood stream. Although hypertonic saline does not have a sustained effect and will not completely correct a large fluid deficit, it rapidly increases plasma volume and improves cardiac output and tissue perfusion. This may allow the cow to be

maintained by oral fluid therapy. Hypertonic saline administration was shown to be safe in cows with experimental endotoxic mastitis (Tyler et al, 1993a, Tyler et al, 1993b, Tyler et al, 1994).

Electrolyte disturbances: Clinical mastitis is often accompanied by mild to moderate hypocalcemia. Hypocalcemia has been documented for cows with coliform mastitis (Katholm and Andersen, 1992; Wenz et al, 2001) and the odds of hypocalcemia increase as the severity of clinical signs increases (Wenz et al, 2001). Less is known about the calcium status of cows with Gram-positive mastitis, but a retrospective study of cows admitted to a teaching hospital showed no difference in serum calcium concentration between cows with Gram-negative mastitis and those with Gram-positive mastitis (mean values below the reference range in both cases [Smith et al, 2001]). Therefore, calcium supplementation is logical. Supplementation can be by the oral, subcutaneous, or slow intravenous route depending on the severity of clinical signs, form of calcium used, and route of concurrent fluid administration. To my knowledge, no studies have scientifically evaluated the effects of calcium supplementation on the outcome of clinical mastitis.

Other serum electrolytes are variable in cows with clinical mastitis (Cebra et al, 1996; Katholm and Andersen, 1992; Smith et al, 2001). It is logical to assume that inappetent cows are hypokalemic. Hypertonic saline administration also causes a transient reduction in serum potassium concentration. Potassium chloride can be supplemented orally at a rate of up to 240 grams divided 2-3 times/day, with lesser amounts (30 to 120 grams) being satisfactory for mild to moderate hypokalemia (Sweeney, 1999). Sodium or chloride deficits are typically mild and can be addressed by balanced oral or IV fluids or hypertonic saline administration. Cows with clinical mastitis are not typically hypoglycemic and do not routinely require dextrose administration. However, IV dextrose may be warranted in cows with concurrent ketosis.

Anti-inflammatory Therapy

Anti-inflammatory agents are frequently used in cows with clinical mastitis. Anti-inflammatory therapy seems logical since many of the physiological and pathological changes associated with clinical mastitis are a result of the inflammatory response to infection. We must strive to control pain and suffering in mastitic cows, so anti-inflammatory agents (which also have analgesic effects) may be indicated for welfare reasons. However, the inflammatory response has beneficial as well as harmful consequences for the cow and anti-inflammatory agents can produce detrimental side-effects in some cases. The benefits and risks of anti-inflammatory therapy must be weighed. Some anti-inflammatory agents are quite expensive, making repeated doses potentially cost-prohibitive. Also, some of the anti-inflammatory agents used in the United States are not labeled for use in lactating dairy cows, which raises concern about extra-label drug use and milk and meat drug residues.

Pharmacokinetic parameters have been determined for many anti-inflammatory agents (eg, flunixin meglumine, phenylbutazone, ibuprofen, carprofen, ketoprofen, isoflupredone acetate) in cattle. Studies are often done in healthy cows and do not account for potential effects of clinical mastitis on drug distribution and clearance. Most efficacy trials have used cows with experimentally-induced coliform or endotoxic mastitis, with treatment administered before or soon after mastitis induction; results of these trials may or may not be applicable to cows with

naturally-occurring mastitis that are clinically ill at the time of first treatment. Only a small number of controlled field trials have investigated the efficacy of anti-inflammatory agents for naturally-occurring clinical mastitis, and the best drug and optimum duration of treatment have not been established. Cost-benefit analyses for different anti-inflammatory agents and dosing regimens have not been reported.

Anti-inflammatory agents used to treat bovine mastitis include glucocorticoids (GC) and non-steroidal anti-inflammatory drugs (NSAIDs). These agents reduce eicosanoid production by inhibiting arachidonic acid release (GC) or metabolism (NSAIDs), but a variety of other mechanisms contribute to their anti-inflammatory effects.

Glucocorticoids: Two GC used to treat clinical mastitis in the United States are dexamethasone and isoflupredone acetate (Predef[®]2X). Both are labeled for use in lactating dairy cows, are inexpensive (<<\$5/day), and have no milk-withholding requirement. Dexamethasone is labeled for IV or IM use for treatment of ketosis and a variety of inflammatory conditions, including mastitis. The labeled dose is 5-20 mg, repeated as needed, “provided infection is controlled by appropriate chemotherapeutic agents”. Isoflupredone acetate is labeled for IM use for treatment of ketosis or conditions requiring anti-inflammatory or supportive effect, including mastitis. The labeled dose is 10-20 mg, repeated in 12-24 hours if needed, and treated animals must be withheld from slaughter for 7 days. Each of these agents has potential adverse effects. Dexamethasone is immunosuppressive and can cause abortion in pregnant cows, especially after 5 months of gestation. Isoflupredone acetate is a less potent GC than dexamethasone, does not cause abortion, and presumably has less risk of immunosuppression. However, isoflupredone acetate has more mineralocorticoid activity, which can lead to hypokalemia and recumbency when repeated doses are used in sick cows (Sielman et al, 1997; Sattler et al, 1998).

Data on the efficacy of GC for treatment of clinical mastitis are limited. In one study, a single 30 mg IM dose of dexamethasone given at the time of *E. coli* inoculation in 3 cows reduced local signs of inflammation, rumen motility impairment, and 14-day milk production loss compared with untreated controls; however, dexamethasone-treated cows had higher rectal temperatures (Lohuis et al, 1988). In another study, a single IM dose of dexamethasone (30 mg) or flumethasone (5 mg) at the time of endotoxin infusion in 5 cows reduced glandular swelling, fever, and tachycardia compared with untreated controls (Lohuis et al, 1989a). The administration of dexamethasone before development of inflammation may have been responsible for the beneficial effects in these two studies. In a third study, a single IM dose of a product containing dexamethasone (0.025 mg/kg), colistin, and ampicillin reduced fever and hypocalcemia, improved rumen contraction rate, and shortened duration of high SCC when given 0 or 2 hours after endotoxin infusion, but not 4 hours, compared with untreated controls (Ziv et al, 1998). This implies that delaying treatment may reduce or prevent efficacy. A single large IV dose of dexamethasone (0.44 mg/kg) given to 6 goats 12 hours after *E. coli* infusion reduced fever and appetite suppression compared with untreated controls, but had no effect on attitude score, heart rate, rumen contractions, serum biochemical parameters, SCC, milk yield, or histopathologic changes (Anderson et al, 1991). Isoflupredone acetate (20 mg, IV) administered to 8 endotoxin-challenged cows after the onset of clinical mastitis had no beneficial effect on rectal temperature, heart rate, rumen contraction rate, mammary gland swelling, or milk production compared with untreated controls (Wagner and Apley, 2003). Because experimental

mastitis is transient and resolves rapidly without treatment, the relevance of any of these studies to cows with naturally-occurring clinical mastitis is questionable. A particular concern about dexamethasone is that repeated dosing (0.04-0.8 mg/kg IM for 3 days) of cows with subclinical intramammary infections resulted in increased bacterial shedding in milk and development of clinical mastitis (Spier et al, 1991; Burton and Kehrli, 1995). In summary, published studies do not provide compelling evidence to support the use of GC in cows with clinical mastitis.

Non-steroidal anti-inflammatory drugs: Non-steroidal anti-inflammatory agents used to treat clinical mastitis in the United States include flunixin meglumine, aspirin, and ketoprofen. Use of dipyrone is banned and use of phenylbutazone is strongly discouraged. The NSAIDs do not have immunosuppressive effects, but, like GCs, do carry a risk of abomasal ulceration and renal damage. These complications are not well documented in cattle and are probably of little concern if hydration is maintained and administration is not prolonged. Flunixin meglumine is labeled for IV or IM use in beef and non-lactating dairy cattle in the United States, but not in lactating dairy cows. It is labeled for control of fever or inflammation associated with respiratory disease or endotoxemia at 1.1-2.2 mg/kg once daily or divided twice daily for up to 3 days; treated animals must not be slaughtered for 4 days. Aspirin, although labeled for cattle, is not FDA-approved, and ketoprofen is not approved for use in cattle in the United States. Concern about residue risk is therefore higher with the NSAIDs than with the GCs, and both flunixin meglumine and ketoprofen are costly (may exceed \$15/day).

Most NSAID efficacy studies have been done using experimental mastitis and early treatment. For example, treatment of 3 cows with flunixin meglumine at 0 and 3-5 hours after *E. coli* inoculation abolished fever and improved rumen motility compared with untreated controls, but had no effect on gland or milk appearance, heart rate, or respiratory rate (Lohuis et al, 1989b). Similarly, treatment of 6 cows with flunixin meglumine every 8 hours beginning 2 hours after endotoxin infusion reduced fever and improved gland appearance and attitude score compared with untreated controls, but had no effect on milk appearance, heart rate, rumen motility, SCC, or milk production (Anderson et al, 1986). Treatment with ketoprofen (3 mg/kg IV) or flunixin meglumine (2.2 mg/kg IV) 2 and 8 hours after endotoxin infusion resulted in similar reductions in rectal temperature, heart rate, and gland inflammation, with no effect on SCC, 3-day milk production, or blood parameters; however, treated cows tended to return to milk production sooner (Ziv, 1991). I am not aware of studies on the efficacy of oral aspirin boluses for treating mastitis.

Field trials using cows with naturally occurring clinical mastitis are more likely to indicate the true efficacy of NSAIDs for mastitis treatment. In one 45-cow field trial, a single dose of flunixin meglumine (1 g IV) or phenylbutazone (4 g IV) given to cows treated with gentamicin did not alter rectal temperature at 24 hours or milk yield over 10 weeks compared with saline-treated controls (Dascanio et al, 1995). Similarly, administration of 1 g flunixin meglumine (2 doses 24 hours apart) with or without IV fluids did not improve the outcome (survival rate, return to milk production) of toxic mastitis in 54 cows treated with antibiotics, oxytocin, stripping, and calcium (Green et al, 1997). However, in a larger trial (Shpigel et al, 1998), 228 cows with coliform mastitis were treated with antibiotics (trimethoprim-sulfonamide) +/- NSAIDs. The NSAIDs were ketoprofen (2 g IM), dipyrone (20 g IM), or phenylbutazone (4 g IM). Cows treated with NSAIDs plus antibiotics (n=197) were 2.8 times more likely to recover than cows treated with

antibiotics alone. The most compelling evidence for use of NSAIDs comes from 2 trials using ketoprofen (Shpigel et al, 1994). Cows treated with antibiotics plus ketoprofen (2 g once daily) were 2.6 and 6.8 times more likely to recover (return to $\geq 75\%$ milk production) than were cows treated with antibiotics alone or antibiotics plus a placebo, respectively. Ketoprofen has a shorter half-life in cattle than does flunixin meglumine and shorter milk residue duration. Also, IM injection of ketoprofen is less irritating than IM injection of flunixin meglumine (Pyorala et al, 1999). The documented benefits of ketoprofen must be weighed against its extra-label status (in the United States) and cost. Meloxicam, although not available for use in cattle in the United States, is an NSAID that is receiving attention in Europe for use in severe clinical mastitis episodes (Banting et al, 2000).

In summary, there may be economic and welfare benefits to using NSAIDs in conjunction with antibiotics and fluid and electrolyte therapy in cows with severe clinical mastitis, but specific criteria for instituting NSAID therapy and the optimal duration of treatment remain to be determined.

Oxytocin Administration and Frequent Milk-out

Oxytocin is used to stimulate milk ejection and facilitate stripping of secretions from mastitic mammary glands. Frequent milk-out is performed to increase the frequency of removal of abnormal secretions and the pathogens, toxins, and inflammatory mediators they contain. Often these two practices are done concurrently. Although oxytocin administration and frequent milk-out seem logical, there is no solid evidence to support their routine use and some data to suggest that they can be detrimental. Oxytocin administration (20 iu, IM twice daily for 3 days) at milking time prevented development of clinical mastitis in only 2 of 8 cows experimentally inoculated with *Streptococcus uberis* and was ineffective at resolving the intramammary infections (Hillerton and Semmens, 1999). When initiated at the onset of clinical *S. uberis* mastitis, oxytocin administration (80 iu, IM initially followed by 20 iu, IM twice daily), accompanied by removal of strippings, resulted in no clinical or bacteriologic cures at 3 or 6 days (Hillerton and Kliem, 2002). In contrast, clinical and bacteriologic cure rates of 91 and 64%, respectively, were achieved by once daily intramammary antibiotic administration for 6 days. When oxytocin was used in conjunction with once daily intramammary antibiotic administration, clinical and bacteriologic cure rates at 6 days dropped to 10%, implying a significant adverse effect of oxytocin and stripping. Frequent milk-out (every 4-6 hours) in conjunction with oxytocin administration did not shorten the time to clinical or bacteriologic cure or resolution of systemic illness in cows with experimentally induced coliform mastitis, compared with no treatment (Leininger et al, 2003). When oxytocin administration (100 iu, IM, twice daily for 1 week) was compared with no treatment (udder massage only) in cows experimentally inoculated with *Staphylococcus aureus*, oxytocin administration reduced bacterial concentrations in the milk but did not improve the bacteriologic cure rate or reduce SCC (SCC tended to be higher in oxytocin treated cows; Knight et al, 2000). Oxytocin administration results in increased permeability of mammary epithelial tight cell junctions in a dose-dependent manner, so altered milk composition, increased SCC, or decreased milk production might occur even in non-mastitic mammary glands of oxytocin-treated cows, particularly if high doses (≥ 100 iu) are administered for prolonged periods of time (Allen, 1990; Prasad and Singh, 2001).

Oxytocin administration and frequent milk-out have not been evaluated extensively in the field. In a California study of cows with naturally-occurring mild clinical mastitis, oxytocin administration (100 IU, IM twice daily for 3 treatments) at milking time resulted in similar clinical and bacteriologic cure rates as did 2 or 3 treatments with intramammary antibiotics, but an untreated control group was not evaluated (Guterbock et al, 1993). There was no overall benefit of using oxytocin because recurrence rate of clinical mastitis was higher, particularly for environmental streptococcal mastitis (Van Eenennaam et al, 1995). In a Virginia study, frequent milk-out (6 times daily) in conjunction with oxytocin administration (20 iu) did not improve clinical or bacteriologic cure rates, time to cure, or return to milk production compared with no treatment (Roberson, 2003). In an Illinois herd, cows treated with supportive therapy alone (oxytocin administration [all cases], increased milking frequency [moderate and severe cases], anti-inflammatory therapy [severe cases], and fluid therapy [severe cases]) had a poorer outcome (lower clinical cure rate, lower bacteriologic cure rate [environmental streptococcal mastitis], higher recurrence rate, and worsening severity) than did cows given intramammary [all cases] or systemic [moderate and severe cases] antibiotics in addition to supportive therapy (Morin et al, 1998b). However, supportive therapy was not compared with no therapy.

In summary, oxytocin administration and frequent milk-out do not appear to be effective stand-alone treatments for clinical mastitis, particularly mastitis caused by streptococci, and may even be detrimental. In certain circumstances, when a cow clearly will not eject her milk or when garget in the milk prevents effective milk removal, these practices might be of some benefit. Otherwise, unnecessary administration of injections and frequent milking of painful teats should be avoided for welfare reasons.

Other Measures

A wide variety of other non-antibiotic measures are used to treat cows with clinical mastitis. These include massage, application of liniments, hydrotherapy, intramammary infusion of fluids, vitamin injections, and homeopathic treatments. In most cases, efficacy has not been scientifically evaluated or studies involve experimentally-induced mastitis. Massage and liniment application were of no benefit in resolution of experimental *Staphylococcus aureus* infection (Knight et al, 2000). Intramammary administration of hypertonic saline did not hasten recovery of cows with experimental coliform mastitis and the hypertonic saline was partially absorbed into the systemic circulation (Haddad et al, unpublished data). Ascorbic acid (25 mg/kg, SC, once daily for 5 days) in conjunction with intramammary antibiotic therapy appeared to shorten recovery time and reduce severity of illness in one small field study (18 cows), compared with intramammary antibiotics alone (Naresh et al, 2002). Twenty-five grams of ascorbic acid given IV 3 and 5 hours after intramammary endotoxin infusion did not reduce clinical illness but did increase milk production recovery (9% higher; Chaiyotwittayakun et al, 2002). Homeopathy is frequently practiced on organic dairy farms, but controlled clinical trials are difficult to perform due to the individual nature of the treatments; little efficacy data is currently available. Minimizing stress, feeding balanced diets with appropriate concentrations of vitamins and minerals, and maintaining cows in good nutritional condition are logical practices that should enable cows to respond effectively to clinical mastitis.

References

Anderson, K.L., A.R. Smith, R.D. Shanks, et al. 1986. Efficacy of flunixin meglumine for the treatment of endotoxin-induced bovine mastitis. *Am. J. Vet. Res.* 47:1366-1372.

Anderson, K.L., E. Hunt, and B.J. Davis. 1991. The influence of anti-inflammatory therapy on bacterial clearance following intramammary *Escherichia coli* challenge in goats. *Vet. Res. Commun.* 15:147-161.

Banting, A., H. Schmidt, and S. Banting. 2000. Efficacy of meloxicam in lactating cows with *E. coli* endotoxin-induced acute mastitis. *J. Vet. Pharmacol. Ther.* 23 (Suppl. 1):E4.

Bianca, W. 1970. Effects of dehydration, rehydration, and overhydration on the blood and urine of oxen. *Br. Vet. J.* 126:121-131.

Burton, J.L. and M.E. Kehrli, Jr. 1995. Regulation of neutrophil adhesion molecules and shedding of *Staphylococcus aureus* in milk of cortisol- and dexamethasone-treated cows. *Am. J. Vet. Res.* 56:997-1006.

Cebra, C.K., F.B. Garry, and R.P. Dinsmore. 1996. Naturally occurring acute coliform mastitis in Holstein cattle. *J. Vet. Intern. Med.* 10:252-257.

Chaiyotwittayakun, A., R.J. Erskine, P.C. Bartlett, et al. 2002. The effect of ascorbic acid and l-histidine therapy on acute mammary inflammation in dairy cattle. *J. Dairy Sci.* 85:60-67.

Constable, P.D., P.G. Walker, D.E. Morin, et al. 1998a. Clinical and laboratory assessment of hydration status of neonatal calves with diarrhea. *J. Am. Vet. Med. Assoc.* 212:991-996.

Constable, P.D., P.G. Walker, D.E. Morin, et al. 1998b. Use of peripheral temperature and core-peripheral temperature difference to predict cardiac output in dehydrated calves housed in a thermoneutral environment. *Am. J. Vet. Res.* 59:874-880.

Constable, P.D. 2003. Fluid and electrolyte therapy in ruminants. *Vet. Clin. N. Amer. Food Anim. Pract.* 19:557-597.

Dasciano, J.J., G.D. Mechor, Y.T. Grohn, et al. 1995. Effect of phenylbutazone and flunixin meglumine on acute toxic mastitis in dairy cows. *Am. J. Vet. Res.* 56:1213-1218.

Green, M.J., L.E. Green, and P.J. Cripps. 1997. Comparison of fluid and flunixin meglumine therapy in combination and individually in the treatment of toxic mastitis. *Vet. Record* 140:149-152.

Green, M.J., P.J. Phipps, and L.E. Green. 1998. Prognostic indicators for toxic mastitis in dairy cows. *Vet. Record* 143:127-130.

- Guterbock, W.M., A.L. Van Eenennaam, R.J. Anderson, et al. 1993. Efficacy of intramammary antibiotic therapy for the treatment of clinical mastitis caused by environmental pathogens. *J. Dairy Sci.* 76:3437-3444.
- Hillerton, J.E. and J. E. Semmens. 1999. Comparison of treatment of mastitis by oxytocin or antibiotics following detection according to changes in milk electrical conductivity prior to visible signs. *J. Dairy Sci.* 82:93-98.
- Hillerton, J.E. and K. E. Kliem. 2002. Effective treatment of *Streptococcus uberis* clinical mastitis to minimize the use of antibiotics. *J. Dairy Sci.* 85:1009-1014.
- Kasari, T.R., A.H. Woodbury, and E. Morcom-Kasari. 1990. Adverse effect of orally administered magnesium hydroxide on serum magnesium concentration and systemic acid-base balance in adult cattle. *J. Am. Vet. Med. Assoc.* 196:735-742.
- Katholm, J., and P.H. Andersen. 1992. Acute coliform mastitis in dairy cows: endotoxin and biochemical changes in plasma and colony-forming units in milk. *Vet. Record* 131:513-514.
- Knight, C.H., J.L. Fitzpatrick, D.N. Logue, et al. 2000. Efficacy of two non-antibiotic therapies, oxytocin and topical linament, against bovine staphylococcal mastitis. *Vet. Record* 146:311-316.
- Leininger, D.J., J. R. Roberson, F. Elvinger, et al. 2003. Evaluation of frequent milkout for treatment of cows with experimentally induced *Escherichia coli* mastitis. *J. Am. Vet. Med. Assoc.* 222:63-66.
- Lohuis, J.A.C.M., W. Van Leeuwen, J.H.M. Verheijden, et al. 1998. Effect of dexamethasone on experimental *Escherichia coli* mastitis in the cow. *J. Dairy Sci.* 71:2782-2789.
- Lohuis, J.A.C.M., W. Van Leeuwen, J.H.M. Verheijden, et al. 1989a. Effect of steroidal anti-inflammatory drugs on *Escherichia coli* endotoxin-induced mastitis in the cow. *J. Dairy Sci.* 72:241-249.
- Lohuis, J.A.C.M., W. Van Leeuwen, J.H.M. Verheijden, et al. 1989b. Flunixin meglumine and flurbiprofen in cows with experimental *Escherichia coli* mastitis. *Vet. Record* 124:305-308.
- Morin, D.E., P.D. Constable, and G.C. McCoy. 1998a. Use of clinical parameters for differentiation of gram-positive and gram-negative mastitis in dairy cows vaccinated against lipopolysaccharide core antigens. *J. Am. Vet. Med. Assoc.* 212:1423-1431.
- Morin, D.E., R.D. Shanks, and G.C. McCoy. 1998b. Comparison of antibiotic administration in conjunction with supportive measures versus supportive measures alone for treatment of dairy cows with clinical mastitis. *J. Am. Vet. Med. Assoc.* 213:676-684.
- Naresh, R., S.K. Dwivedi, D. Swarup, et al. 2002. Evaluation of ascorbic acid treatment in clinical and subclinical mastitis of Indian dairy cows. *Asian Austral. J. Anim. Sci.* 15:905-911.

- Prasad, J. and M. Singh. 2001. Somatic cell counts in milk of buffaloes administered oxytocin during early lactation. *Asian. Austral. J. Anim. Sci.* 14:684-692.
- Pyorala, S., T. Laurila, S. Lehtonen, et al. 1999. Local tissue damage in cows after intramuscular administration of preparations containing phenylbutazone, flunixin, ketoprofen, and metamizole. *Acta Vet. Scand.* 40:145-150.
- Roberson, J.R. 2003. Frequent milk-out and oxytocin use. *Proceedings of the 2003 North American Veterinary Conference, Orlando, Florida*, pp.105-109.
- Sattler, N., R.W. Sweeney, R.H. Whitlock, et al. 1997. Hypokalemia syndrome in dairy cows: 10 cases (1992-1996). *J. Am. Vet. Med. Assoc.* 210:240-243.
- Shpigel, N.Y., R. Chen, M. Winkler, et al. 1994. Anti-inflammatory ketoprofen in the treatment of field cases of bovine mastitis. *Res.Vet. Sci.* 56:62-68.
- Shpigel, N.Y., M. Winkler, G. Ziv, et al. 1998. Relationship between in vitro sensitivity of coliform pathogens in the udder and the outcome of treatment for clinical mastitis. *Vet. Record* 142:135-137.
- Sielman, E.S., G. Fecteau, C. Girard, et al. 1998. Description of 14 cases of bovine hypokalemia syndrome. *Vet. Record* 143:503-507.
- Sischo, W.M., D.A. Moore, and J.C. Fedon. 1997. Use of physiologic variables to predict milk yield after clinical mastitis in dairy cows. *J. Am. Vet. Med. Assoc.* 211:470-475.
- Smith, G.W., P.D. Constable, D.E. Morin. 2001. Ability of hematologic and serum biochemical parameters to differentiate gram-negative and gram-positive mastitis in dairy cows. *J. Vet. Intern. Med.* 15:394-400.
- Spier, S.J., B.P. Smith, J.S. Cullor, et al. 1991. Persistent experimental *Salmonella dublin* intramammary infection in dairy cows. *J. Vet. Intern. Med.* 5:341-350.
- Sweeney, R.W. 1999. Treatment of potassium balance disorders. *Vet. Clin. N. Amer. Food Anim. Pract.* 15:609-617.
- Tyler, J.W., F.J. DeGraves, R.J. Erskine, et al. 1994. Milk production in cows with endotoxin-induced mastitis treated with isotonic or hypertonic sodium chloride administered intravenously. *J. Am. Vet. Med. Assoc.* 204:1949-1952.
- Tyler, J.W., E.G. Welles, R.J. Erskine, et al. 1993a. Clinical and clinicopathologic changes in cows with endotoxin-induced mastitis treated with isotonic or hypertonic sodium chloride administered intravenously. *Am. J. Vet. Res.* 55:278-287.

Tyler, J.W., E.G. Welles, D.C. Sorjonen, et al. 1993b. Cerebrospinal fluid composition of cattle with endotoxin-induced mastitis treated with isotonic (0.9%) or hypertonic (7.5%) sodium chloride. *J. Vet. Intern. Med.* 7:91-94.

Van Eenennaam, A.L. I.A. Gardner, J Holmes et al. 1995. Financial analysis of alternative treatments for clinical mastitis associated with environmental pathogens. *J. Dairy Sci.* 78:2086-2095.

Wagner, S.A. and M.D. Apley. 2003. Pharmacodynamics of isoflupredone acetate in an endotoxin-induced mastitis model. *J. Dairy Sci.* 86:792-798.

Wenz, J.R., G.M. Barrington, F.B. Garry, et al. 2001. Use of systemic disease signs to assess disease severity in dairy cows with acute coliform mastitis. *J. Am. Vet. Med. Assoc.* 218:567-572.

Ziv, G. and F. Longo. 1991. Eficacia clinica comparada de ketoprofeno y flunixin en el tratamiento de mamitis causadas por endotoxina de *E. coli* en vacas lecheras en lactacion. In: *Proceedings of Congres Societe Francaise de Buiatrie*, pp.207-208.

Ziv, G., M. Shem-Tov, and F. Ascher. 1998. Combined effect of ampicillin, colistin and dexamethasone administered intramuscularly to dairy cows on the clinico-pathological course of *E. coli* endotoxin mastitis. *Vet. Res.* 29:89-98.