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ADVANCES IN THE THERAPY FOR MASTITIS

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Effective and economic mastitis control programs rely on prevention rather than treatment. Herds practicing mastitis prevention produce higher quality milk more cost effectively than herds that do not. Nonetheless, practitioners are requested by clients to manage therapy for mastitis cases. This article describes therapeutic alternatives for bovine mastitis.

Therapy of infectious disease should either assist host defenses in eliminating invading pathogens or reduce pathophysiologic consequences of infection without degrading host defenses. Logically, emphasis in mastitis therapeutics has focused on the elimination of infectious agents by use of antimicrobial agents. Therapeutic success for some infections may be better measured by evaluating reduction of clinical symptoms, however, rather than total elimination of the pathogen from the gland. Ultimately, the best endpoints of efficacy are milk production and long-term survival.

The greatest advance in antibiotic therapy of mastitis has been philosophic rather than scientific: The single most noteworthy development is the growing consensus among veterinarians and dairy managers as to the limited role antibiotics play in treatment and control programs. Factors that have fostered this altered mindset have included economic assessment of treatment programs, changes in the Pasteurized Milk Or-

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dinance, and critical evaluation of clinical efficacy of therapy. Antibiotic therapy for mastitis must be restricted to instances in which the practitioner is reasonably assured of (1) therapeutic efficacy, (2) economic benefit (either improved production or reductions in the reservoir of infectious bacteria that offset direct and indirect treatment costs), and (3) production and sale of residue-free milk and meat. Clear evidence that antimicrobial therapy for individual cows can improve health and productivity may be restricted to dry cow intramammary therapy and lactating cow therapy for *Streptococcus agalactiae* mastitis. Clinical trials and experimental studies have demonstrated no benefits to antibiotic therapy in cattle with either clinical or subclinical gram-negative mastitis.[28, 38, 44, 85] Treatment of lactating cows with *Staphylococcus aureus* mastitis often is unsuccessful.[79] The question asked by practitioners and mastitis researchers has shifted from "Which antibiotic should I use?" to "Are antibiotics indicated?"

PHARMACOLOGIC CONSIDERATIONS

The ideal antibiotic for systemic treatment of mastitis would be weakly basic, poorly bound to plasma proteins, and lipid soluble. It would retain activity in inflammatory secretions and have antimicrobial activity against mastitis pathogens. Systemically administered sulfonamides, penicillins, aminoglycosides, and cephalosporins do not readily penetrate the mammary gland. Macrolides (erythromycin, tilmicosin), trimethoprim, tetracyclines, and fluoroquinolones distribute well to the mammary gland, but none of these compounds is approved for systemic use in the lactating dairy cow. New antimicrobial drugs are released on the veterinary market continually; some of these compounds likely will prove valuable in the therapy for mastitis. Recent areas of active investigation include systemic therapy for subclinical mastitis, distribution patterns of various antimicrobial agents, development of resistant L-forms following antimicrobial therapy, and resistance patterns of common mastitis pathogens. The reader is referred to articles on these topics published in a recent issue of this publication.[79, 89]

SUBCLINICAL MASTITIS THERAPY

Subclinical mastitis does not present an urgent potential loss of gland function or loss of the cow's life. Therefore, treatment is provided on the premise that costs will be outweighed by compensatory production gains following elimination of infection. In the case of contagious pathogens, elimination of infection also may result in a decreased risk of new infections in previously noninfected cows. Although host immune defenses play a critical role, the degree of therapeutic success in treating subclinical mastitis relies predominantly on the type of causative pathogen, and often not on the drug regimen selected. The predominant

pathogens causing subclinical mastitis most often are streptococci and staphylococci. In particular, the contagious pathogens *Streptococcus agalactiae* and *Staphylococcus aureus* offer a study in opposites with respect to therapeutic success.

"Blitz" treatment is one method that rapidly reduces the herd prevalence of *Streptococcus agalactiae*. With this method, an entire herd or substantial part of it is treated with antimicrobial agents. It is efficacious, cost-effective, and, because it uses Food and Drug Administration (FDA) approved antimicrobial products, should not result in drug residue problems in milk.[25, 86] Much of this success relies on the high degree of antimicrobial susceptibility of *Streptococcus agalactiae*, as well as it being essentially an obligate udder pathogen.[25, 55, 83] Whole herd culture and treatment of infected cows, followed by repeat culture and treatment at routine intervals, is a frequently successful approach to blitz treatment. Alternatively, Dairy Herd Improvement somatic cell count (SCC) data from herds with a high prevalence of *Streptococcus agalactiae* (≥ 25% of the herd infected) can offer a cost- and labor-efficient means of identifying cows for treatment, provided that preliminary milk cultures of selected cows have identified *Streptococcus agalactiae* as a major herd problem.[25] Finally, failure to use post-milking teat dipping and total dry cow treatment to complement blitz treatment will ultimately result in considerable expense and frustration on the part of the producer, as well as possible reinfection of the herd.

Other streptococci causing intramammary infections (IMI) are *Streptococcus dysgalactiae, Streptococcus bovis, Streptococcus uberis,* and the enterococci.[55] As with *Streptococcus agalactiae,* most of these streptococci are very sensitive in vitro to antibiotic agents, especially penicillin. In one study, virtually 100% of *Streptococcus uberis, Streptococcus dysgalactiae, Streptococcus bovis,* and group G isolates were sensitive to penicillin.[56] Only 63% of the enterococci were sensitive to penicillin, however.[56] Despite this apparent sensitivity, some streptococcal infections remain refractory to therapy. Information on the therapy of streptococcal infections is not extensive. Wilson et al[84] reported 74% of clinical cases caused by *Streptococcus uberis* and 84% of cases caused by *Streptococcus dysgalactiae* resolved after a single intramammary infusion of cefoperazone.[84] Bacteriologic cure was achieved in only 60% to 65% of the cases.[84] A comparison of cure rate in treated versus untreated cows was not reported, however. Procaine penicillin G, administered at 22,000 IU per kilogram body weight twice a day would appear to be the drug regimen of choice. Efficacy and cost-effectiveness of this therapeutic regimen is difficult to assess, however, and withholding periods for milk and meat would be extended considerably compared with the use of labeled doses. Furthermore, penicillins are poorly distributed to the mammary gland following parenteral administration.

IMIs caused by *S. aureus* often result in deep-seated abscesses.[55] Treatment is difficult, especially because *Staphylococcus aureus* resistance to antimicrobial drugs (particularly β-lactams) is more common than among streptococci[55] and *S. aureus* may survive intracellularly following phagocytosis where antimicrobial concentrations are reduced. In addi-

tion, *S. aureus* has numerous extracellular substances that impart an ability to survive in the presence of a hostile host immune system.[37, 40] As a result, elimination of infections by antimicrobial treatment often is not successful.

Studies of efficacy of treatment of *Staphylococcus aureus* mastitis indicate cure rates of 25% to 55% of infected quarters in experimental infections that were evaluated for 21 to 60 days after infection.[60, 63] Natural infections are usually of longer duration, however, and therefore more refractile to therapy. Wilson et al[84] reported that intramammary cefaperazone for the treatment of clinical *Staphylococcus aureus* mastitis resulted in bacteriologic cures for only 39% of the cases, measured 14 days after treatment. These results may be optimistic given that assessment of bacteriologic cures may depend on the time period the infection is monitored after treatment; a greater number of infections relapse as time after treatment increases.[26, 60]

Alternatively, treatment of dry cows rather than lactating cows may be more effective in eliminating existing streptococcal and staphylococcal IMI.[22, 57, 65, 73] Dry cow treatment may decrease the incidence of new infections in quarters that are uninfected at the start of the dry period.[57] Efficacy of conventional dry cow treatments in eliminating and preventing new *Staphylococcus aureus* IMI may be low, however. In a retrospective study, Ziv et al[90] determined that new infection rates of *Staphylococcus aureus* in quarters were 11% when treated with one of three commercially available intramammary infusion products containing (1) cloxacillin, (2) neomycin and cloxacillin, or (3) a combination of nafcillin, procaine penicillin, and dihydrostreptomycin, versus 4.9% in nontreated control quarters. Soback et al[75] determined that dry cows administered intramammary cephapirin benzathine had a cure rate of 30.8% and a new IMI rate of 51.7%, versus 33.3% and 29.3% in untreated quarters.

Consequently, novel combinations of drugs—including treatment regimens not approved by the FDA for use in dairy cattle—may be needed to eliminate a higher proportion of infections. In experimental infections in lactating cows, Owens et al[63] reported the combined use of intramuscular procaine penicillin G and intramammary amoxicillin achieved a better cure rate (18 of 35 infected quarters) than intramammary amoxicillin did alone (10 of 40 infected quarters). Similarly, Soback et al[74] determined that subcutaneous norfloxacin nicotinate administered at the start of the dry period achieved a better cure rate (66.6%) and lower new infection rate over the dry period (17.1%) for *Staphylococcus aureus* infections than those of untreated cows (33.3% and 29.3%, respectively) or cows administered intramammary cephapirin benzathine preparations (30.8% and 29.3%, respectively).

These studies provide evidence for three important considerations in the treatment of *Staphylococcus aureus* mastitis: (1) FDA approved and labeled drug use is not likely to result in a high frequency of cures. (2) Because of increased discarded milk costs and risk of residues in milk following extra-label drug use, dry cows should be treated preferentially over lactating cows. And (3) treatment should include systemic drug regimens, preferably antimicrobial agents that distribute well in mammary tissue and abscesses—i.e., tetracyclines, macrolides, and fluoroquinolones. Alternatively, the most effective treatment of *Staphylococcus aureus* may be to cull the infected cow from the herd.

Numerous cytokines, which regulate cell function during immune and inflammatory processes, recently have been identified and purified from cattle. With subsequent identification of the genes responsible for cytokine synthesis, recombinant production has been made possible.[17] Cytokines that have demonstrated promise for use in the prevention or treatment of bovine mastitis are interleukin-1 (IL-1) and interleukin-2 (IL-2), interferons, and colony stimulating factor.[17, 61, 62, 76] Intramammary IL-1β and IL-2 increased mammary gland polymorphonuclear leukocyte diapedesis.[18] In addition, IL-2 activated inducible superoxide production and phagocytosis in neutrophils.[18] Preliminary trials with cows experimentally infected with *Staphylococcus aureus* determined that 38% of infected glands were cured when treated intracisternally with recombinant bovine IL-1β and 42% with IL-2.[17] This was similar to cure rates achieved with different intramammary formulations of sodium cephapirin. Thus, interleukins may modulate and even enhance nonspecific cellular defenses, although clinical availability is not yet a reality.

Novel uses of antimicrobials and other potential treatments such as cytokines have not been studied extensively under field conditions, and potential gains in efficacy derived from these treatments therefore are speculative at best. Whether or not an increased rate of therapeutic success would be justified by the increased costs in drugs and labor in treating dry cows also needs to be determined, but reduced potential for discarded milk compared with antimicrobials may make cytokine use attractive.

THERAPY OF CLINICAL MASTITIS

Although bacteriologic culture of milk is indicated to determine the most appropriate treatment, therapy usually is initiated before results can be obtained. Selecting an initial therapeutic regimen for clinical mastitis cases therefore usually is based on severity of infection, past bacterial culture history, and the experience of the practitioner. Mild cases that display little more than abnormal milk may respond well to "stripping out" the affected quarter regularly. Oxytocin may be administered to assist in milk letdown. Commercial intramammary antimicrobial preparations may be indicated to reduce clinical signs if abnormal signs persist for several days, or in moderate cases with marked swelling of the gland. It is questionable whether antimicrobial therapy has any benefit for recurring or persistent infections, and repeated attempts to treat these infections likely will result in no therapeutic benefit, with increased discarded milk costs. In a large Florida dairy in which streptococci were the predominant clinical mastitis pathogen, only 6.1% of lactations had more than 28 days of discarded milk, but these lactations were responsible for 52.7% of the milk discarded because of mastitis.[59] Bartlett et al[9] reported that 70% of lost marketable milk resulting from clinical mastitis was due to withholding, as opposed to 30% from decreased production.

Antibiotics may be indicated in more severe cases. Labeled products with known milk withdrawal periods are preferred for initial treatment, whereas "extra-label use" drugs must be used judiciously.

ANTIMICROBIAL THERAPY OF ACUTE CLINICAL MASTITIS

Veterinary and drug costs are higher for the treatment of severe (systemic involvement) clinical mastitis cases than for less severe cases.[34] In addition, veterinary practitioners probably intervene more frequently in therapeutic management of acute mastitis caused by coliform bacteria (lactose fermenting, gram-negative rods) than in infections caused by any other pathogen. This, in part, is because coliforms are the single most common causative agent isolated from clinically severe mastitis cases.[7, 35] In addition, most antimicrobial therapeutic regimens used as treatment of coliform mastitis in the United States are not labeled by the FDA for use in dairy cows. Cows managed with extra-label drugs are a potential residue liability for both dairy farmers and practitioners.

Experimental challenge models have clarified much of the pathophysiology of mastitis resulting from infection with gram-negative organisms.[13, 27, 30, 70] Following infection, bacterial numbers in milk increase rapidly. Depending on the size of the challenge, peak bacterial concentrations in milk often occur within a few hours.[27, 70] Typically, a rapid decline in bacterial concentration follows neutrophil migration into the gland. Although often severe, experimental coliform infections usually clear spontaneously and rarely last more than 4 to 9 days.[27, 70] The resulting inflammation and leukocytosis in the affected quarter may persist for several weeks, or the quarter may become agalactic, despite the inability to isolate bacteria on culture.[23, 27]

Many of the inflammatory and systemic changes observed during the course of acute coliform mastitis result from the release of lipopolysaccharide endotoxin (LPS) from the bacteria.[13, 23] Most LPS release occurs following bacterial phagocytosis and killing by neutrophils.[13, 23] This results in subsequent activation of the cyclooxygenase and lipoxygenase pathways, releasing prostaglandins, leukotrienes, and thromboxanes, compounds that are potent mediators of local inflammatory and systemic circulatory events.[6, 88] Also, endotoxin induces the release of macrophage-derived cytokines, initiating a wide range of systemic responses to inflammation, often termed *the acute phase response*. As a result, to reduce the severity of acute coliform mastitis, either bacterial growth must be inhibited to reduce exposure of the quarter and the cow to LPS, or the effects of the LPS release must be neutralized. From a practical standpoint, therapy of acute coliform infections cannot begin until clinical signs appear. Clinical recognition of coliform mastitis usually occurs after peak bacterial numbers have been attained.[13, 27, 30] Thus, by the time therapy is initiated, maximal release of LPS likely has occurred. This raises concerns regarding any advantage of antimicrobial therapy in alleviating the effects of acute coliform mastitis.

Selection of a potentially efficacious antimicrobial agent for the therapy of acute coliform mastitis primarily depends on in vitro culture and sensitivity.[4] Antimicrobials such as aminoglycosides and cephalosporins, therefore, often are selected for use, based on favorable in vitro antimicrobial susceptibility patterns.[4]

Jones and Ward determined that 2 g of intramuscular gentamicin every 12 hours were not more efficacious in preventing agalactia or death resulting from acute clinical mastitis than intramuscular erythromycin or no systemic antimicrobial agents.[38] Systemic gentamicin also was no more effective in restoring appetite in affected cows than seen in the other groups.[38] Cows experimentally challenged with *Escherichia coli* and dosed with 500 mg intramammary gentamicin every 12 hours did not have lower peak bacterial concentrations in milk, shorter duration of infection, lower convalescent somatic cell or serum albumin concentrations in milk, or lower rectal temperatures than untreated challenged cows.[29] Antimicrobial inhibition was detected in milk from infected quarters of two cows at least 7 days following the last infusion of gentamicin.[29] In addition, gentamicin readily diffused through the milk–blood barrier, as indicated by detectable concentrations in serum throughout the treatment period and the first 12 hours after the last dose. Urine gentamicin concentrations were detectable in two cows 14 days after the last infusion. Two gentamicin-treated cows that were culled 6 months after the trial were found with kidney tissue concentrations of 1 μg gentamicin/g.[29] With increased interest and sophistication in drug residue testing among regulatory agencies, practitioners should carefully consider the 30- to 45-day half-life of aminoglycosides in the bovine kidney.

Ceftiofur sodium, a third-generation cephalosporin, has been reported to have excellent activity against gram-negative pathogens,[75, 87] with a suggested MIC for *Escherichia coli* of 0.25 μg/mL. Although not approved as a treatment for mastitis, ceftiofur is approved for use in lactating dairy cattle, and if the labeled dose of 1 to 2.2 mg/kg every 24 hours is administered intramuscularly, no milk withholding time is required. The efficacy of ceftiofur as a treatment for clinical mastitis remains unproved, however. Owens et al[64] determined that systemic ceftiofur was not more efficacious in curing IMIs caused by *Staphylococcus aureus* than intramammary infusions of ceftiofur or cephapirin. Mammary tissue and milk concentrations of ceftiofur following systemic treatment remained less than 0.04 and 0.4 μg/g, respectively.[64] Similarly, experimentally *Escherichia coli*-challenged cows dosed intravenously with 3 mg of ceftiofur/kg every 12 hours had concentrations less than 0.2 μg/mL of milk throughout the trial (Erskine RJ, unpublished data). Thus, despite extra-label dosing and acute mammary inflammation, systemic ceftiofur is not likely to attain concentrations in milk that are effective in reducing bacterial numbers. If systemic ceftiofur has a benefit in the treatment of acute coliform mastitis, it likely would be for sepsis.

It may be time we shift the emphasis of our treatment strategy from "What antimicrobial will result in a cure?" to one of "What treatment alternatives exist?" Unlike most clinical mastitis episodes caused by

other pathogens, in which presence of the pathogen in the gland is the primary problem, the pathogenesis of acute coliform mastitis often confronts us with endotoxin-induced shock.

Although antimicrobial therapy may be of secondary importance relative to treatment of endotoxic shock, it may be indicated for acute mastitis. Coliform infections occasionally result in chronic mastitis. Septicemia may occur, although a Cornell University study suggested this is an infrequent result of infection.[69] In addition, although coliform organisms are the predominant clinical mastitis agent in many herds, numerous other pathogens cause clinical mastitis that is not distinguishable from that caused by coliforms. Consequently, until culture results can confirm the causative agent, antimicrobial agents may be indicated. Caution should be exercised in continuing therapy in cows that have already eliminated the infection, but continue to display clinical signs of mammary inflammation. Thus, antimicrobial therapy in cows with grossly abnormal milk, but with improved appetite, attitude, and milk production should be evaluated critically. Milk culture may assist in making the decision.

FLUID AND ELECTROLYTE THERAPY

Oral fluid therapy has documented efficacy in the treatment of hypovolemic shock syndromes (vibrio cholera in humans and diarrhea in calves). Recently completed studies, however, have observed static body weight and expanded plasma volume in cows with endotoxin-induced mastitis.[80, 81] These results directly question dehydration as a primary shock mechanism in cows with acute mastitis. The mechanisms involved in endotoxic shock and, hence, coliform mastitis are more complex than simple dehydration. Cardiogenic, peripheral vascular capacitance, neurogenic, and other mechanisms contribute directly to decreased tissue perfusion and indirectly to the clinical manifestations of shock. Furthermore, effective oral fluid therapy hinges on normal gastrointestinal absorption of administered fluid. At least gastrointestinal motility and probably other gut functions are impaired in the endotoxemic state.[51] A general rule of thumb is that oral fluid administration is most effective in subjects with a primary dehydration, normal gastrointestinal absorption, and less than 10% dehydration. Many cows with acute mastitis are effectively excluded using these criteria.

Although cumbersome, difficult, and potentially time consuming, intravenous fluid therapy deserves strong consideration. Effective fluid therapy is recognized as one of the most beneficial treatment options in cases of endotoxin-induced shock. Further, the absence of any potential for violative residues in milk or meat makes this method of treatment particularly attractive.[28] Intravenous fluids may be administered rapidly in the first hour of treatment (40 mL/kg or 20 L) and at a reduced rate (10–20 mL/kg) thereafter. More rapid fluid administration rates may increase central venous pressures and create risks for pulmonary edema.

Total doses will vary from 20 to 60 L depending on cow size, hydration status, and presence of ongoing fluid losses.[4, 16] Fluids generally are administered using a 12- to 14-gauge catheter, but 3- to 4-inch 12-gauge needles may be sufficient for short-term use in placid, well restrained cows.

Rational fluid therapy is logically premised on the correction of deficits and replacement of ongoing losses. Unfortunately, mastitis case summaries describing perturbations in serum chemistry are noticeably lacking in the veterinary literature. Textbook descriptions of serum chemistry results in cases of clinical coliform mastitis are cursory.[11, 16] Common abnormalities identified in these texts and anecdotal observations include hypocalcemia, hypoglycemia, acidosis, and hypovolemia. Serum chemistry data from eight cows treated at the Auburn University Large Animal Clinic for clinical coliform mastitis are presented in Table 1. These data are drawn from cows with clinical signs consistent with acute mastitis and a bacteriologically confirmed diagnosis of gram-negative mastitis. Given the varying stage of the disease process at the time of presentation and the referral nature of this practice, these data probably are not entirely representative of the clinicopathologic status of cattle treated in ambulatory practice. The data presented in Table 2 are drawn from four cows administered an intramammary infusion of 1 mg endotoxin. Each cow was treated with a small volume (approximately 3 L) of isotonic saline 4 hours after intramammary challenge.[82] We will use these tables and referenced material to illustrate anticipated serum chemistry changes in cattle with coliform mastitis. Hypoglycemia probably is a minor consideration in the development of fluid therapy protocols in cattle with acute mastitis. Although low serum glucose concentrations are commonly seen in the late phases of septic shock,[52] this observation is less consistent in ruminant models of gram-negative sepsis.[82] Data in

Table 1. SELECTED SERUM CHEMISTRY RESULTS IN EIGHT CATTLE WITH CLINICAL COLIFORM MASTITIS

	Reference Range	Case Range	Case Mean	Comments
Glucose (mg/dL)	48–70	55–92	70.5	4 of 8 cows > 70 mg/dL
Calcium (mg/dL)	8.2–10.0	6.3–10.5	7.88	6 of 8 cows < 8.2 mg/dL 1 of 8 cows > 10.0 mg/dL
Creatinine (mg/dL)	0.2–1.4	0.6–5.6	1.68	3 of 8 cows > 1.4 mg/dL
Urea nitrogen (mg/dL)	7–17	9–64	29.0	5 of 8 cows > 17 mg/dL
Total protein (g/dL)	5.8–8.5	6.3–8.0	7.05	All cows within reference range
Sodium (mmol/L)	134–144	136–144	140.9	All cows within reference range
Potassium (mmol/L)	3.77–4.89	2.0–4.9	3.58	2 of 8 cows < 3.77 mmol/L
Total CO_2	20.9–26.1	15–28	22.0	2 of 8 cows < 20.9 mmol/L 1 of 8 increased
Sorbitol dehydrogenase (IU/L)	13–18	5.0–27.3	12.4	5 of 8 cows < 13 IU/L 2 of 8 cows > 18 IU/L

Table 2. SELECTED SERUM CHEMISTRY RESULTS IN 4 COWS WITH ENDOTOXIN-INDUCED MASTITIS AT VARIOUS TIMES AFTER ENDOTOXIN INFUSION

	0 hrs	3 hrs	6 hrs	12 hrs	24 hrs	48 hrs
Glucose (mg/dL)	50.8	62.0	64.3	66.0	68.3	61.0
Calcium (mg/dL)	9.3	8.8	7.7	8.4	8.4	8.4
Creatinine (mg/dL)	0.78	0.80	0.88	0.75	0.63	0.85
Urea nitrogen (mg/dL)	23.5	23.8	23.8	24.8	24.0	19.3
Total protein (g/dL)	8.20	7.45	7.20	7.03	7.43	7.85
Sodium (mmol/L)	135.0	132.5	133.3	131.5	130.0	130.3
Potassium (mmol/L)	3.98	4.10	3.68	3.75	4.13	4.25
Total CO_2 (mmol/L)	25.0	25.5	23.0	22.0	24.3	24.5
Sorbitol dehydrogenase (IU/L)	22.1	18.7	18.5	17.6	17.0	13.9

the tables substantiate the relative rarity of true hypoglycemia in cases of coliform mastitis. The authors (Erskine, Tyler) have seen serum glucose concentrations greater than 200 mg/dL in a cow with peracute *Staphylococcus aureus* mastitis. Although recommended by some sources,[11] large volume replacement with isotonic (5%) dextrose or frequent administration of 50% dextrose in 500-mL increments probably is of minimal clinical benefit unless novel therapies that promote cellular uptake and utilization of glucose are employed. Excessive glucose supplementation will raise serum glucose concentrations in excess of the renal threshold and promote free water losses in animals with already suspect hydration status. Some cows likely will benefit from daily administration of 500 mL 50% dextrose, administered directly or added to large volumes of intravenous fluids, particularly in the later stages of acute coliform mastitis.

Hypocalcemia frequently has been documented in experimental gram-negative sepsis.[51, 52] Clinical observations in cows with gram-negative mastitis substantiate these results. Not all down cows are hypocalcemic, however. In the absence of serum chemistry results, physical examination findings should be used to support the diagnosis of hypocalcemia. These findings include ataxia, muscle fasciculation, delayed pupillary light responses, dilated abdominal viscera on auscultation and percussion, cool extremities, and bloat. Cows with these abnormalities may require calcium therapy. Cows with fulminant sepsis, recognized by marked scleral injection, fever, heart rates greater than 100 beats/minute, and diarrhea, are at greater risk for calcium-induced arrhythmias. The subcutaneous route of calcium administration has a wide margin of safety in cases of acute mastitis and, consequently, is favored by some practitioners, although it may not be adequate for advanced cases and may result in abscess formation. Ideally, 500 mL of a calcium borogluconate solution (10 g calcium), is administered in 10 to 20 L of an intravenous electrolyte solution. The carrier solution should not contain bicarbonate or bicarbonate equivalent salts because these alkalinizing agents complex with calcium and form precipitates. When economic or practical considerations preclude large-volume intravenous fluid therapy, calcium should be administered slowly, with concurrent cardiac auscultation.

Hypokalemia is expected in any disease condition causing prolonged anorexia. Balanced electrolyte solutions typically contain 5 to 7 mmol/L, but higher concentrations of potassium can be administered safely as long as the rate of administration remains below 0.5 mmol/kg/hour. No toxicity would be anticipated when administering solutions with a potassium concentration less than 12 mmol/L, as long as fluid administration is limited to 20 L/hour.

Although some cows with acute mastitis develop metabolic acidosis,[52] this is not a consistent finding (see Table 1). Consequently, bicarbonate administration should be limited to cows with documented, substantial decreases in serum bicarbonate or total carbon dioxide ($Co_2 < 18$ mmol/L). Total deficit may be calculated as 0.5 × body weight in kg × (25 − total serum Co_2). Many clinicians dilute the 5% solution 3 to 1 using distilled water, yielding a 1.3% (isotonic) solution. Serum acid–base status may be re-evaluated at 3- to 4-hour intervals, with incremental bicarbonate administration performed as dictated by test results. Total Co_2 measurement devices premised on liberation of serum Co_2 and bicarbonate are readily adapted to on-farm testing using heparinized whole blood (Ruffin DC, Tyler JW, Spano JS: Comparison of plasma and whole blood total Co_2 determinations with traditional acid–base determinations in cattle, J Am Vet Med Assoc, submitted).

Hypertonic fluids have been advocated for use in cattle with mastitis, dehydration, and neonatal diarrhea.[32] Few controlled studies examining this form of therapy have been performed. Although positive changes have been observed in hemodynamic parameters following rapid intravenous administration of 5 mL/kg 7.5% sodium chloride solution, no clear benefit has been established when this form of therapy has been compared with equimolar amounts of sodium salts administered as isotonic solutions.[10, 14, 15] Intravenous hypertonic fluid therapy was used in an endotoxin-induced mastitis model.[81] Therapy caused significant expansion of circulating plasma volume and modest decreases in the amount of lost milk production when compared with cows receiving equal volumes of isotonic sodium chloride.[80, 82] Neither clinical nor biochemical evidence of salt poisoning was observed in these studies.[82] Practitioners are cautioned that this form of therapy is experimental. Dehydrated cows with impaired renal function maintained at high ambient temperatures may be at an increased risk for sodium ion toxicosis. Interest in this mode of therapy has arisen because of economic rather than medical reasons. Practical considerations preclude large volume isotonic fluid therapy in many farm settings. Small volumes of hypertonic solutions may be administered rapidly and inexpensively during ambulatory visits.

When economically justifiable and feasible, intravenous fluid therapy is an important adjunct in the treatment of acute mastitis. In the absence of serum chemistry results, near-isotonic sodium chloride-based solutions supplemented judiciously with calcium, potassium, and glu-

cose likely are the most suitable choices for intravenous fluid in cattle with acute mastitis.

STEROIDAL ANTI-INFLAMMATORY THERAPY

There is experimental evidence that corticosteroids stimulate the production of lipocortin. This may prevent phospholipase A_2 from contacting its substrate and, as a result, prevent arachidonic acid release.[33] This corticosteroid mechanism would prevent the formation of arachidonic acid metabolites, which would disrupt the formation of cyclooxygenase and lipoxygenase products. The time lag for lipocortin production makes early administration of corticosteroids necessary for maximal effectiveness. Because corticosteroids affect the initial phase of arachidonic acid release, experimental models of endotoxemia often require pretreatment with corticosteroids to significantly reduce mortality rates. The efficacy of corticosteroids is greatly reduced when administered after signs of disease are present because large amounts of arachidonic acid metabolites have already been produced. Corticosteroid impairment of immune function also may play a role in clinical outcome of disease. However, bacterial clearance was not adversely influenced by dexamethasone administration in a coliform challenge model of mastitis in lactating doe goats.[5] This supports the observation of dairy practitioners that corticosteroids may be effective (or at least not detrimental) in the therapy of coliform mastitis.

The use of steroids in the treatment of acute coliform mastitis has been widely advocated. Dexamethasone, nine α-fluoroprednisolone, betamethasone, and flumethasone have been used in the treatment of experimental coliform mastitis.[48,49] Dexamethasone and isoflupredone have been approved for use in lactating dairy cows in the United States. Corticosteroids can be expected to reduce clinical signs of systemic disease, udder edema, and swelling. The influence of steroid therapy on survival and production has not been studied adequately.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins and thromboxanes by cyclooxygenase inhibition. All NSAIDs inhibit the formation of prostaglandin E_2 in the brain to reduce fever.[4] This response is not necessarily always beneficial because the inflammatory response may be an important host defense mechanism. All NSAIDs do not necessarily act in the same manner. This suggests that there may be other mechanisms of action, some of which may be of more therapeutic benefit than cyclooxygenase inhibition.[31] It has been demonstrated that several NSAIDs chelate iron, potentially making it unavailable to catalyze the production of extremely toxic hydroxyl radicals from less toxic superoxide anions and hydrogen peroxide.[8,31]

Other mechanisms, such as lipoxygenase inhibition and lysosomal membrane stabilization, also may be important.[19,58] Differences in efficacy and toxicity also may be explained by the physicochemical characteristics of NSAIDs.[12] Characteristics such as polarity, acidity, and lipophilicity cause different NSAIDs to achieve different concentrations in various tissues within species and in similar tissues across species.

NSAIDs have been used for symptomatic relief of the clinical signs of endotoxic shock in several species of domestic animals and are widely used by dairy practitioners.[39,47] NSAIDs that have been used in experimental coliform mastitis or in experimental endotoxin-induced mastitis include aspirin, flunixin meglumine, phenylbutazone, flurbiprofen, carprofen, and ibuprofen.[20,50,53] NSAIDs used to treat acute coliform mastitis can be expected to reduce the severity of systemic clinical signs—e.g., rectal temperature, heart rate, respiratory rate, and udder pain. The effect of NSAIDs on survival and milk production has not been studied adequately, and NSAIDs have not been approved for food animals in the United States.

THERAPY OF UNUSUAL PATHOGENS

With the exception of Mycoplasma, the pathogens discussed in this section are common inhabitants of the dairy cow's environment. Strict attention therefore is required in the collection of milk samples for microbiologic analysis to avoid contaminants and maintain the reliability of the diagnosis. Selective media and extended incubation periods often are necessary. Bacterial cures from treatments are not common and many animals eventually are culled with chronic, refractory mastitis. In many cases, the organisms are susceptible only to medications not approved by the FDA for treatment of lactating cows. Caution should be taken under these conditions to prevent antibiotic contamination of meat and milk going to market. Some therapeutic agents thought to be effective by mastitis researchers in other countries are banned in the United States.

Pseudomonas

Treatment of individual cows should be based on antimicrobial culture and susceptibility test results. Although some clinical improvement is possible, bacteriologic cures seldom are attained. Aminoglycoside susceptibility often is reported. Outside the United States, chloramphenicol, polymixin B or C, and furazolidin have been reported to have success.[21,43] β-lactams and tetracyclines are the least effective. Effective control, by reducing the exposure of udders to the reservoir of infection, is critical when approaching mastitis outbreaks caused by this organism. Water, especially that used to prepare udders for milking, often is the source of the organism and methods to eliminate this reservoir of infection have been described.[24,44]

Serratia

Serratia are not readily invasive, and for IMIs to occur, large numbers of bacteria must be placed on or near the gland.[43] About half the infections are reported to be clinical,[78] although subclinical herd outbreaks are possible.[69] The clinical nature of the organism may depend on the initial exposure, and chronic infections that last much longer than typical gram-negative infections may result.[69, 78, 85] Spontaneous recovery has been reported. Many infections occur during the first half of the dry period. Thus, as with *Pseudomonas*, treatment for the purpose of bacteriologic cure is not likely to be beneficial.

Actinomyces pyogenes

Actinomyces (Corynebacterium) pyogenes is one of several organisms involved in the etiology of European "summer mastitis." It frequently is associated with teat injury and clinical mastitis in dry cows.[72] Cases predominantly are malodorous and clinical. Because the clinical signs are not specific, diagnosis and therapy should be based on milk culture and antimicrobial susceptibility testing.[68] Long-acting antibiotic treatment has been reported to be successful at dry off,[2] and tylosin has been reported to be effective in Denmark.[41] Because of decreased production and low rate of cure, however, affected animals often are culled.

Yeasts/Fungi

Infection with Nocardia and Candida is characterized by sudden onset of udder swelling and lack of positive clinical response to conventional antimicrobial therapy.[1, 45, 46, 66, 71] Some cases, particularly those caused by *Candida*, are subclinical. Clinical cases often are associated with extended antimicrobial treatment and contaminated udder infusions or devices.[46, 54, 66, 77] Given that clinical signs are similar to those of bacterial infections, diagnosis should be based on milk culture. Treatment should include discontinuation of antimicrobial therapy and culling of chronically infected cows.[45] Clinically recovered cows may shed organisms for up to 8 months.[46] Clotrimazole, ketoconazole, miconazole, nystatin, and sulfamethoxypyridazine all have been used, with reported clinical success, in treating *Candida* infections.[43] These studies were based on clinical impressions, however, and none of the drugs just mentioned are approved for use in the United States.

Other Pathogens

Prototheca zopfii, a colorless algae, is a common inhabitant of the dairy environment associated with wet areas contaminated with manure. Chronic subclinical and clinical infections occur, and successful treatments have not been reported.[43] Infected cows should be isolated and removed from the herd. Mycoplasmal infections occur primarily during milking, and carrier cows are the major reservoir of infection.[36] Routine microbiologic identification procedures will not detect the presence of these organisms in milk; special media and growth conditions are required. Successful treatments have not been discovered for mycoplasmal mastitis and, because of the potentially contagious nature of the infection, affected cows should be segregated from non infected cows in the herd or culled.

Premature agalactia in chronically infected quarters, particularly quarters infected with pathogens refractile to therapy, occasionally is promoted as an alternative to culling the cow. This may have some benefit in genetically superior animals within a herd, or for cows to be maintained until calving. The goal is to eliminate the infection by fibrosing the affected quarter, thus reducing the risk of further pathogenic change or systemic effects on the cow, as well as reducing risk of infection for other cows. One method frequently used by practitioners is the infusion of 60 mL of 2% chlorhexidine-diacetate solution, into the affected quarter twice, 24 hours apart. The quarter should be stripped out before the second infusion. Care should be taken that milk from noninfected quarters is not sent to market before prior testing for inhibitors in milk. This regimen is not recommended for a majority of chronically infected animals, and should be used judiciously.

SUMMARY

Methods to enhance mammary resistance to bacterial infection and to reduce the effects of existing infections without the use of antimicrobial agents are becoming more attractive, primarily because of increasing pressure from consumers and regulatory agencies to decrease the risk of drug residues in milk. Because of the difficulty in obtaining satisfactory results with existing drug formulations, new approaches in the treatment of mastitis should emphasize better understanding of mammary gland pharmacokinetics, ameliorating the pathologic effects of infection, and enhancing natural defenses. Efficacy studies should emphasize milk production and long-term survival of cows to allow economic evaluations.

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