Mastitis Therapy and Pharmacology of Drugs in the Bovine Mammary Gland

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Introduction

Mastitis remains a major concern of the dairy industry, despite frequent use of therapy and application of mastitis control programs. Prevention and control are the most productive approaches to mastitis. However, therapy is important for clinical mastitis and is a component of mastitis control. Approximately 20-80% of cows are affected by clinical mastitis annually (Dohoo, 1987, Wilesmith et al., 1986). The annual US market for intramammary infusion products is approximately $30 million (Gingerich, 1987). Mastitis therapy should be efficacious, cost-effective, and antibiotic residues in meat and milk should be avoided. The purpose of this paper is to discuss mastitis therapy and the pharmacology of drugs in the bovine mammary gland. Specific areas considered include:

1. Current status of mastitis.
2. The pharmacology of drugs in the mammary gland.
3. Therapeutic failures.
4. Current developments in mastitis therapy.

Current Status of Mastitis

Prior to the application of mastitis control programs, approximately 50% of cows were considered to be infected with mastitis pathogens (Dodd, 1981). Infection rates averaged one new infection per 500 milkings and once infected, the average cow remained infected for 75% of the year (Dodd, 1981). In studying the dynamics of udder infections, Dodd (1981) stated that the average level of infection in a herd was dependent upon the rate of new infections and the duration of infections. Mastitis was reduced by decreasing the new infection rate and/or the duration of existing infections. The impact of therapy includes reduction of new infections (dry cow therapy, DCT) and the duration of infections (lactational and DCT). The success of mastitis control is indicated by average decreases of infection levels of 50% or more (Dodd, 1981).

Therapy is a major method for reducing infection levels (Dodd, 1987). During a 3-year experiment in the U.S. (Natzke and Everett, 1975), 27% of infections were eliminated by lactational therapy and 34% were eliminated by dry-cow therapy (Table 1).

TABLE 1. Elimination of infections during mastitis control field experiments. (Natzke and Everett, 1975).

Infections eliminated via	%
Spontaneous recovery	18
Lactational therapy	27
Dry period therapy	34
Culling	14
Not eliminated	7
	100

The application of mastitis control has influenced mastitis prevalence and etiology. Mastitis due to *Str. agalactiae* has been markedly reduced, with less dramatic reductions for *St. aureus*. The most significant change has been the relative increase in the importance of the environmental mastitis pathogens (coliforms and streptococci) as causes of clinical mastitis. Smith (1987) reported a predominance of environmental pathogens as causes of clinical mastitis in well-managed herds (Table 2). Similar results have been obtained in North Carolina dairies known to be free of *Str. agalactiae* (Table 3).

TABLE 2. Clinical mastitis in well-managed dairy herds (Smith, 1987).

Etiology in 10 well-managed herds+
36% coliform
26% streptococcal
8% staphylococci
26% no isolations

+ = Rate of 45 intramammary infections/100 cow lactations; 53/100 cow years.

TABLE 3. Clinical mastitis in 5 North Carolina dairies free of Str. agalactiae (160 isolates).

33.8%	coliforms (89% E. coli)
33.8%	streptococci (72% Str. dysgalactiae
	24% str. uberis
	4% Str. spp.)
18.4%	staphylococci (53% St. aureus)
9.4%	Corynebacterium spp (73% C. pyogenes).

In a large study of clinical mastitis in British dairies, (45,000 cows in 378 herds) the following mean annual rates were reported (Wilesmith et al., 1986):

1. 48.5 cases/100 cows
2. 28.2% of cows affectd at least once
3. 9.7% of quarters affected at least once
4. 1.6 cases per affected cow.

These annual clinical mastitis incidence rates compare with an average of 66 cases/100 cows/year in reports from 7 European studies (cited by Wilesmith et al., 1986). Intramammary infusion tube usage in lactating cows averaged 2.7 tubes/cow/year and 6 tubes/clinical case. Annual mortality due to mastitis averaged 0.21%. Fatality rate for mastitis cases was 0.46%. Culling due to mastitis averaged 3% of cows per herd per year. A study of clinical mastitis in 3 herds over 3 years reported clinical mastitis by lactation (Table 4). Rates were lowest for first lactation, intermediate for lactations 2-4, and increased for lactations >4.

TABLE 4. Clinical mastitis by lactation (Pearson and Mackie, 1979).

Lactation Number	Clinical mastitis/100 cows/year
1	19
2	32
3	31
4	30
>4	51

Subclinical mastitis is generally considered to account for 70% of mastitis losses. Recently collected data from a Florida dairy (Donovan and Shearer, 1987) may challenge the assertion that subclinical mastitis is the most costly form of the disease. In this herd, losses from mastitis death and culling and the treatment of acute mastitis accounted for the majority of losses above goal. This herd was free of *Str. agalactiae*, *St. aureus* and *Mycoplasma* spp. and average linear SCC scores had been reduced to goal levels. In well mananged herd with effective mastitis control programs, losses from clinical mastitis, culling and death may account for a major portion of economic loss.

Target of Mastitis Therapy:

Mastitis therapy in the future is likely to be directed at:

Contagious Pathogens:

1. *Str. agalactiae* will remain a cause of mastitis, but its prevalence will quite likely continue to decline. Data from a California survey (Bennett, 1987) indicated that 28% of bulk tank milks contained *Str. agalactiae*. In an Ohio study (Hueston et al., 1987), *Str. agalactiae* was found in 13.8% of bulk tank milks. In a large British study, 7.2% of cows were positive for *Str. agalactiae* (Wilson, 1981). In a Virginia study, 0.6% of cows were infected with *Str. agalactiae* (Jones, 1986).

2. *St. aureus* remains the leading cause of subclinical and chronic mastitis. In a California survey (Bennett, 1987), 50% of bulk tank milks contained *St. aureus* and in Ohio (Hueston et al., 1987), 28.0% contained coagulase-positive staphylococci. In England, 20.7% of cows were infected with *St. aureus* (Wilson, 1981). In a Virginia study, 5.3% of cows were infected with *St. aureus* (Jones, 1986). The ability of *St. aureus* to invade udder tissues, cause intramammary abscesses, evade antimicrobial therapy and exist as an intracellular pathogen indicate that *St. aureus* will remain a common cause of mastitis.

Environmental Pathogens:

1. Coliform bacteria cause a major portion of clinical mastitis and in many surveys represent the most common cause of clinical mastitis.

2. The environmental streptococci (including *Str. uberis, Str. dysgalactiae, Str. faecalis* and others) are major causes of clinical mastitis.

Miscellaneous:

A variety of pathogens have been established as occasional but significant causes of mastitis. These include *Prototheca* spp., *Serratia* spp., yeasts, *Pseudomonas* spp. and others. *Mycoplasma* spp. are of major concern in some areas.

Therapy of Mastitis and Pharmacology of Drugs in the Mammary Gland

The goal of mastitis therapy is to maintain concentrations of antimicrobials at or above the Minimal Inhibitory Concentration (MIC) for the offending pathogen at the site of infection for sufficient time periods to eliminate the pathogen. The ultimate purpose is to allow rapid and complete return of the gland to normal function and milk production. The MIC is the concentration of antibiotic which prevents bacterial growth; actual elimination of the organisms may require the action of host defenses, especially when bacteriostatic drugs are used. The site of infection is a significant factor. *Str. agalactiae* results in minimal invasion of tissues, whereas *St. aureus* commonly invades tissues. The time requirement for clearance of infections is important, but not clearly defined.

Choice of Route and Considerations:

Routes for therapy of mastitis include the intramammary (IMM), systemic and intraparenchymal routes. The intraparenchymal route is not commonly used and is seldom rational.

Intramammary Therapy:

The IMM route provides the highest milk concentrations of antimicrobials. A major factor in the derived drug concentration is the volume of milk secreted and the time period since milking. The effect of these factors is obvious. The IMM route is particularly indicated for infections limited primarily to the ductular system, i.e., *Str. agalactiae* and other streptococci.

For more invasive infections (*St. aureus*) and in the presence of moderate to severe inflammation, limited distribution of antibiotics to infected tissues may limit the success

of therapy. For these reasons, many veterinarians prefer the systemic route as the sole route or in addition to IMM treatment.

The distribution of drugs in milk is related to milk composition. Milk is a suspension of fat particles in an aqueous phase containing proteins and minerals. Drugs may be distributed into the aqueous and/or the lipid fractions. Milk proteins may serve to bind drugs. The concentration of drugs in whole milk may not equal concentrations in the aqueous fraction (Rasmussen, 1971).

Experimental studies using autoradiographic methods have indicated that distribution of antibiotics to diseased udders may be limited following intramammary therapy. In normal udders, the distribution of penicillin following intramammary therapy was good (Ullberg et al., 1958). Distribution of penicillin to diseased udders showed considerable variation among cows. Distribution was primarily to the ducts and was limited to the parenchyma, with poor distribution to the interstitial tissues. Factors found to limit diffusion of antibiotics included edema, necrosis, desquamated epithelial cells, inflammatory debris, blood clots, proliferation of epithelial cells and connective tissue and abscesses. The authors concluded that systemic therapy may be preferred in such cases (Ullberg et al., 1958).

Systemic Therapy:

The milk concentration of antimicrobials following systemic therapy are explained by the property of passive diffusion of nonprotein bound, unionized molecules from blood to milk. In one experiment, a steady-state plasma concentration of a sulfonamide was established by continuous IV infusion in cows in which 3 quarters were milked out just prior to start of drug infusion and in which one quarter was unmilked (Rasmussen, 1971). Milk was collected and drug concentrations were determined at various times after treatment. Drug concentrations were approximately equal in all quarters at all times, indicating that passive diffusion was the means of transfer.

The extent of penetration of antimicrobials into milk from the systemic circulation is largely dependent upon three properties of the drug molecule (Ziv, 1980):

1. Lipid solubility
2. Degree of ionization.
3. Extent of protein binding in the serum and udder.

The transfer of drug from blood to milk is largely proportional to the concentration gradient of the lipid-soluble, nonionized, nonprotein bound moiety of the drug molecule.

Lipid Solubility: Lipid solubility influences the passage of drugs from blood to milk by affecting the capacity of the drug to pass biological membranes. In an example of drugs with similar pKa's (dissociation constants), compounds with a low lipid solubility were shown to achieve milk/serum concentration ratios below those experimentally predicted (Table 5).

TABLE 5. Influence of lipid solubility on mammary diffusion (from Boisseau and Moretain, 1983).

Drugs	pKa	Solubility	Milk/serum concentration ratio	
			Theoretical	Experimental
ACIDS:				
Sulfamethazine	7.4	moderate	0.51	0.59
Sulfadiazine	6.5	moderate	0.28	0.21
Penicillin G	2.8	moderate	0.16	0.20
Cloxacillin	2.8	high	0.16	0.22
Ampicillin	2.8-7.2	high	0.26	0.26
Rifampicin	7.9	high	0.85	1.10
Novobiocin	4.3	high	0.30	0.33
BASES:				
Neomycin	8.3	low	7.5	0.5
Erythromycin	8.8	high	6.2	8.5
Tylosin	7.1	high	6.0	4.5
AMPHOTERIC:				
Tetracycline	—	moderate	0.4-0.8	0.6-1.4

Degree of Ionization: The degree of ionization is dependent upon the pKa of the drug (the dissociation constant, i.e., the pH at which the drug exists as 50% ionized form and 50% unionized form) and the pH of the fluid(s) in which it is suspended. Most drugs are weak organic acids and bases with pKa's from 3-10 and exist in various proportions of ionized and unionized molecules (Ziv, 1980). In general, those antibiotics which are weak organic bases and lipophilic tend to accumulate in milk. Antibiotics which are weak organic acids tend to accumulate to limited degree in normal milk; however in mastitis, with its increase in milk pH, concentrations in milk may approach those in plasma.

Degree of Protein Binding: Antibiotics which are highly protein-bound in plasma are not expected to diffuse into milk as extensively as those which have lower binding. This factor appears to have limited influence upon the distribution of drugs into milk following systemic therapy. The ionization and lipid solubility characteristics appear more important.

Ziv (1980) has summarized these characteristics and has classified major antibiotics according to their potential to diffuse into the mammary gland (Table 6). Additional factors may also be important, including the ability of divalent cations (i.e., calcium) to bind and inactivate drugs such as the tetracyclines.

Cow Factors:

Response to mastitis therapy varies markedly among cows and among herds. Cow factors exert considerable influence on the response to therapy. In a large trial (636 treatments in 16 herds), response to lactational therapy for subclinical mastitis caused by *St. aureus* was highly variable among cows (Wilson et al., 1972). Response to therapy decreased with increasing age, increasing number of quarters infected, and with increases in WMT scores (Wilson et al., 1972)

Combined Intramammary and Systemic Therapy:

Many treatment protocols for mastitis include combined systemic and intramammary therapy. Ziz (1980) reported

greater effectiveness of combined therapy in treatment of chronic staphylococcal mastitis with spiramycin during lactation (Table 7).

TABLE 6. Expected distribution of antibiotics into the mammary gland following parenteral and intramammary therapy (modified from Ziv, 1980).

Parenteral	Intramammary
Good distribution:	Good distribution:
Sulfanilamide	Quinolones
Erythromycin	Sulfanilamide
Tylosin	Other sulfonamides?
Spiramycin	Nitrofurans
Lincomycin	Tylosin
Trimethoprim	Spiramycin
	Ampicillin
Limited distribution	Amoxicillin
Other sulfonamides	Trimethoprim?
Penicillin G	Novobiocin
Cloxacillin	Cephalexin
Ampicillin	Rifamycin SV
Amoxicillin	Erythromycin
Rifamycins	
Cephalosporins	Limited distribution
Tetracyclines	Penicillin G
Novobiocin	Cloxacillin
Rifamycins	Cephapirin
	Other cephalosporins
Poor distribution:	Tetracyclines
Dihydrostreptomycin	
Aminoglycosides	Poor distribution:
Spectinomycin	Dihydrostreptomycin
	Aminoglycosides
	Polymyxins

TABLE 7. Bacteriological cure rates for chronic St. aureus mastitis during lactation using spiramycin (modified from Ziv, 1980).

Treatment	Quarters treated	27-day cure rate
IM only	18	16%
Intramammary only	15	40%
Combined—IM plus intramammary	67	62%

Principles of Therapy:

The principles of clinical mastitis therapy can be summarized as follows (modified from Ziv, 1980):

1. Early detection/treatment critical.
2. Use of oxytocin/frequent milk-out to remove bacteria and toxins.
3. Appropriate use of antibiotic susceptibility data.
4. For intramammary therapy: Preference to drugs which are absorbed and well-distributed to the mammary tissues. Treat at least 2-4 times at 12-24 hour intervals.
5. For systemic therapy: Preference for drugs which are distributed to the mammary gland to a sufficient degree. Adequate dose and duration are important. Consider interaction with IMM drugs.

Response to Therapy:

Although there are considerable data on response to mastitis therapy, great differences in the criteria for successful response, drugs/dosages used and treatment protocols make it difficult to make meaningful comparisons (Plommet and LeLedouc, 1975). Therapeutic response summarized from many reports is given in Table 8. These data indicate the variable and poorer response for *St. aureus*, especially during lactation. *Str. agalactiae* responds well either during lactation or the dry period. Response for other streptococci may be slightly less than for *Str. agalactiae*.

TABLE 8. Therapeutic response for lactational and dry-cow therapy.

Organism	Lactational Therapy	Dry-cow therapy
St. aureus	20- 85%	58- 87%
Str. agalactiae	50-100%*	93- 99%
Other streptococci	50- 90%*	75-100%

*Most responses in the upper range.

The effect of quarter infection on quarter milk yield was measured in an experiment employing quarter milking (Morris, 1973). Milk yield in infected quarters decreased an average of 35%. Quarters in which infections were eliminated by lactational therapy did not show a recovery in milk yield during that lactation. Quarter milk yield recovered in the following lactation in quarters with infections successfully eliminated with lactational or dry cow therapy. This study indicated that the dry period is needed for repair and regeneration of the damaged tissue and recovery of milk production. These results have been substantiated by one study of lactational therapy based on high SCC, which indicated no increase in production from treatment and a net loss from treatment of $19.65 per treated cow (McDermott et al., 1983). In another study, the cost of treatment per cow was $38.19 and no benefit was reported in that lactation in response to treatment (Timms and Schultz, 1984).

In a report dealing with lactational therapy of *Str. agalactiae*, Goodger (1987) reported a return of $2.25/1.00 invested in a culture and treatment program. The most significant effect on economic return was the days in milk (DIM) of the treated cows. Cows from 0-60 and 60-120 DIM produced a net return from treatment. Beyond 120 DIM, treatment was not justified based upon the lack of expected economic benefit.

The effects of therapy on production responses and the economics of treatment are clear. Additional benefits of therapy include treatment of clinical infections, reduction of contagion, elimination of infection sources, prevention of infections (DCT) and avoidance of unsaleable milk. Production response is not the sole criterion for judging the response or success of therapy.

Treatment Failures

Failure of successful treatment in mastitis occurs all too

commonly for a variety of reasons (Table 9). A recent experiment has shown that clinical diagnosis is only reasonably accurate in predicting the microbiological cause of clinical mastitis (White et al., 1986). For this reason, the selection of broad-spectrum antibiotics appears indicated for treatment of clinical mastitis. The possibility of novel pathogens as a cause of mastitis suggests that laboratory assistance should be used in the diagnosis of unusual or unresponsive cases.

TABLE 9. Treatment failures in mastitis.

1. Incorrect diagnosis/novel pathogens
   - A. Clinical diagnosis only reasonably accurate (White et al., 1986)
   - B. Yeast, Prototheca spp., Nocardia spp., Mycoplasma spp., etc.
2. Therapy started too late
3. Inappropriate therapy
   - A. Agent, including resistance
   - B. Duration
   - C. Dose
   - D. Procedure
   - E. Distribution
4. Intracellular parasitism—S. aureus
5. Therapy simply does not work
   - A. C. pyogenes
   - B. Chronic
   - C. Cow factors
6. Therapy not performed

Successful mastitis therapy depends upon early and accurate detection of clinical cases. Experiments using a mouse model of mastitis has revealed some interesting results in this regard (Craven et al., 1984; Anderson, 1982). In a model of acute *St. aureus* mastitis in mice, 100-1,000,000 colony-forming units of *St. aureus* were introduced into the mammary glands. The staphylococci grew rapidly, producing toxins and tissue necrosis. Polymorphonuclear leukocytes (PMN's) were present within the glands by 6 hours after challenge. However, this response was inadequate to control the staphylococci and the mastitis was fatal within 24 hours. If cloxacillin was given at or shortly after challenge, the mice would survive. If cloxacillin was given later, it had no effect. Cloxacillin concentrations in mammary tissues were determined and were well above the MIC for staphylococci. Failure of antibiotic therapy was primarily due to the massive numbers of *St. aureus* and the fact that the bacteria were not multiplying. The authors stated that therapy for mastitis is only of value before microbiological/pathological stages of disease reach a refractory stage. In the cow, such acute reactions are often not recognized until too late.

In further studies, chronic *St. aureus* mastitis was produced in mice by first challenging glands with endotoxin to attract PMN's into the duct system and then challenging with *St. aureus* challenge. The PMN's failed to eliminate the *St. aureus* and an equilibrium was established, producing chronic mastitis and only rare instances of clinical mastitis. Intramammary administration of cloxacillin in these cases was not successful in eliminating the *St. aureus*. Reasons for failure of antibiotic therapy included impaired diffusion of antibiotics to infected sites as well as the itracellular existence of *St. aureus* within PMN's, macrophages and alveolar epithelial cells. Although inhibitory levels of antibiotic were attained, staphylococci survived within the PMN's in the presence of antibiotic. Intracellular *St. aureus* do not multiply and the low pH of the phagosomes appears to protect the organisms and may be detrimental to the activity of cloxacillin. The activity of various antimicrobials against intracellular *St. aureus* was studied. Cloxacillin, amoxicillin and cephadrine were unable to kill intracellular staphylococci, but were observed to cause increased lysis in response to lysostaphin. Clindamycin and neomycin had a slight killing effect, while rifampicin and rifamycin-SV exhibited good killing of intracellular *St. aureus*. These results correspond with the ability of the drugs to penetrate PMN's. Rifampicin was effective, but the rapid development of resistant staphylococci are observed. Additional studies are considering the effect of combinations of rifampicin and other antibiotics in treatment.

The method of treatment is critical. Aseptic preparation of teat ends of affected quarters prior to treatment must be assured. The importance of partial insertion of cannulae was shown in an experiment conducted by Boddie and Nickerson (Table 10).

TABLE 10. Full vs. partial (2-3 mm) insertion in DCT (Boddie and Nickerson, 1986).

	Full insertion	Partial insertion
New infection rate	9.9% (17/172)	4.1% (7/171)
DCT efficacy	57.9% (11/19)	85.7% (12/14)

Another common reason for failure of therapy is that therapy simply will not work for the given case. Mastitis caused by *C. pyogenes* is one notable example; chronic mastitis caused by *St. aureus* is another. Culling of chronic cases and those not responding to mastitis therapy is one of the 5 major points of mastitis control. An example of the benefit of culling a small percentage of cows with respect to eliminating a major portion of clinical mastitis is given in Table 11. Elimination of 10% of the cows would have reduced the incidence of clinical mastitis by 50%.

Therapy not performed properly can be a reason for therapeutic failure. This includes the tendency of producers to observe clinical mastitis and infuse the cow; frequently clinical response is rapid and dramatic and therapy is limited to a single infusion. In herds with hired labor, complete lack of treatment or failure to complete the full series of treatment may occur too commonly.

TABLE 11. Contribution of cows with repeated attacks of mastitis to the proportion of total clinical mastitis (720 cows in 14 herds; Dodd, 1981).

No. of clinical attacks	% cows	% all clinical mastitis
>8	3.5	24.2
>7	5.4	33.1
>6	7.1	40.1
>5	10.0	50.4
>4	13.1	59.0
>3	19.8	71.0
>2	30.9	88.2
>1	48.0	100.0

Susceptibility data is frequently used as a guide to selection of antimicrobials for mastitis therapy. Data on the percentage of isoates resistant to various antimicrobials collected by the New York State Mastitis Control Program for the years 1975-1985 are given in Table 12. Although results from the commonly performed disk susceptibility procedure correlate with MIC's for the pathogens tested, the current interpretation of such results is made based upon the blood levels of drugs obtained in humans following the use of common drug dosages (Woolcock, 1983; Prescott and Baggot, 1985; Roberts, 1985). Reasons for lack of correlation between such test results in mastitis include the fact that concentrations in the gland following systemic therapy may not reach therapeutic levels. For intramammary therapy, the concentrations in the gland may greatly exceed the tested concentrations. Another factor of importance is synergism, such as exhibited by penicillin-streptomycin (Rosselet et al., 1977; Schalm and Woods, 1952; Table 13). For these reasons and others, it is clear that the results of susceptibility testing in mastitis are not subject to strict interpretation.

A list of infusion products currently approved for use in the U.S. by the FDA is given in Table 14.

TABLE 12. Antibiogram data collected by the NYSMCP (1975-1985) (Sears, 1986).

Percent resistance of three organisms to various antimicrobials			
Antimicrobial	**St. aureus**	**E. coli**	**Klebsiella spp.**
Ampicillin	54	34	90
Amikacin	3	3	3
Cephalosporin	1	21	23
Cloxacillin	20	97	98
Erythromycin	6	91	97
Furadantin	1	4	23
Gentamycin	1	2	2
Lincomycin	9	99	99
Neomycin	2	20	12
Novobiocin	7	96	90
Penicillin	57	98	99
Polymyxin B	56	5	8
Streptomycin	36	46	52
Sulfathiazone	30	36	49
Tetracycline	8	33	35

TABLE 13. Synergism in lactational therapy of St. aureus (Schalm and Woods, 1952).

Drug—Intramammary	% Success
Procaine penicillin G (PPG)	30
Dihydrostreptomycin (DHS)	20
PPG/DHS	73

TABLE 14. Approved mastitis infusion products (U.S. F.D.A.).

Active Ingredient(s)	Milk discard Milkings	Hours	Withdrawal Days	Brand Name Examples
Amoxicillin	5	60	12	Amoxi-Mast
Cephapirin, benzathine	Not to be used 72 hours after calving		42	Cefa-Dry* Tommorrow*
Cephapirin, sodium	8	96	4	Cefa-Lak Today
Cloxacillin, benzathine	Not to be used 30 days prior to calving		30	Dry-Clox* Bovi-Clox*
	Not to be used 28 days prior to calving		28	Orbenin-DC*
Cloxacillin, sodium	4	48	10	Dari-Clox
Erythromycin	3	36	—	Gallimycin 36 Erythromast 36 Gallimycin 36*
Hetacilin, potassium	6	72	10	Hetacin-K
Novobiocin	6	72	15	Albamast
Oxytetracycline	8	96	4	Liquimast
Penicillin G, procaine	7	84	4	Formula A-34
	5	60	3	Hanford Aqua Pen True Antibiotic Formula 10 Go Dri Hanfords*
Penicillin G, procaine, novobiocin	6	72	15	Special Formula Albacillin Albadry Plus*
Penicillin G, procaine, dihydrostreptomycin	8 Not to be used within 6 weeks of freshening	96	60	Quartermaster* Dry Mast*

*Dry cows only. Source: Dr. Gerald B. Guest, US FDA, October, 1987.

Future Developments

In spite of the high cost of developing new products for treatment of mastitis, there is considerable on-going development in this area. New antibiotics in developmental stages include a quinolone, a 3rd generation cephalosporin and florfenicol. Novel drug delivery systems to the gland and to intracellular sites are being considered. An immunological apprach to mastitis therapy includes utilization of a macrophage stimulatory factor. Another novel approach is the use of lysostaphin, an enzyme lytic for *St. aureus* (Sears, 1987).

Public Health and Residue Avoidance

Protection of public health and prevention of residues should be of paramount importance in mastitis therapy.

Several recent articles have been devoted to these matters (McQueen, 1987; Kirk and Kaneene, 1984).

Conclusions

Therapy is only one part of the overall approach to reducing mastitis. In a Minnesota survey of 130 DHIA dairymen, Williamson (1983) reported that 63% of dairymen used veterinarians in a reproductive herd health program while only 5.4% used a veterinarian in a formal mastitis control program. Only 25% of dairymen surveyed used complete combined program of teat dipping and dry cow therapy. Producer application of existing knowledge in mastitis control with veterinary involvement and reinforcement would appear the most productive approach to reducing the incidence of mastitis.

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