

MASTITIS: PHARMACOLOGY



BASICS

OVERVIEW

- Mastitis is inflammation of the mammary gland that is produced by a pathogenic organism. In the United States, mastitis is caused mainly by environmental Gram-negative or Gram-positive bacteria.
- Clinical mastitis is characterized by abnormal milk composition, gland swelling, pain, and sometimes systemic illness in cows. Decreased milk production is observed, and bacteria are generally present in milk.
- Cows with subclinical mastitis may produce normal milk with an increased somatic cell count (SCC; mainly neutrophils), which is indicative of infection.
- Chronic mastitis is an infection that has a long duration (> 2 months) and which may show periodic clinical signs.
- Mastitis control programs that are effective and cost efficient rely heavily on prevention rather than treatment.
- Therapeutic intervention is an essential part of many control programs. This may include intramammary treatment with FDA-approved, intermediate spectrum antibacterial drugs in lactating or dry cows.

CLINICAL FINDINGS

- Subclinical mastitis is represented by an increased SCC (>200,000 cells/ml) in composite milk samples from all four quarters.
- Clinical mastitis varies in severity. Mild cases produce abnormal milk, moderate cases exhibit additional signs of udder inflammation, and severe cases manifest signs of systemic infection, such as weakness, inappetence, and fever.

CAUSES AND RISK FACTORS

- Bacteria causing subclinical or clinical mastitis are classified as either contagious or environmental.
- Contagious mastitis-associated bacteria are spread between cows in the course of milking. They include *Streptococcus agalactiae*, *Staphylococcus aureus* and *Mycoplasma* spp. Although *S. agalactiae* and *S. aureus* used to be major contagious pathogens in mastitis, effective control measures have reduced their prevalence. Antimicrobial drugs for mastitis are not effective against *Mycoplasma*, so infected cows are usually segregated or culled.
- Environmental bacteria are currently the main cause of mastitis in the United States. These bacteria, commonly found in the cows' habitat, include Gram-negative coliform bacteria (predominately *Escherichia coli*, *Klebsiella* or *Enterobacter*) and Gram-positive bacteria - *Streptococcus uberis* and *S. dysgalactiae* ("environmental streptococci"). *S. dysgalactiae* can also act as a contagious mastitis pathogen.
- A number of risk factors are associated with the incidence of mastitis and the success of mastitis treatment strategies. These include several patient- and pathogen-related variables.

PREVENTION

- Preventative measures for the control of mastitis are focused upon limiting the number of bacteria to which the teat is exposed. Udders are particularly susceptible to intramammary infections during the early dry period.
- Germicidal teat dip should be routinely applied before and after milking to reduce the incidence of contagious and environmental mastitis.
- Proper milking procedures should be followed and all equipment needs to be adequately cleaned and maintained.
- Segregation may be useful in herds that have a significant burden of *Mycoplasma* or other pathogens poorly responsive to antimicrobial drugs. Culturing milk samples for the presence of mastitis-associated bacteria will aid in identifying affected cows. Infected cows should be identified early and accurate management records must be kept.
- Culling will eliminate the source (i.e. the infected cow) of contagious bacteria, which is often *Mycoplasma* sp. Severe cases of mastitis that are associated with systemic illness should not be treated. Culling should also be considered for cases of chronic mastitis and mastitis caused by *Nocardia* sp., *Prototheca* sp., *Serratia* sp., *Pseudomonas* sp., *Actinomyces* sp., *Mycobacterium* sp., fungi and other unusual pathogens, which are usually not responsive to antimicrobial therapy.



TREATMENT

General Considerations

- Therapeutic management of clinical mastitis should take into account the efficacy of antimicrobial drugs and NSAIDs, the economics of the treatment approach and the possible drug residues remaining in milk after treatment. *Culture and sensitivity results should be evaluated for mastitic organisms prior to implementing a treatment program.*
- Treatment during lactation: mastitis control based solely on antimicrobial drug treatment is not recommended. Preventative measures are the most important part of a mastitis control program.
- Dry cow therapy: treatment is recommended after the last lactation with approved doses of antimicrobial drug(s) administered by the intramammary (IMM) route.
- Dietary vitamin E and selenium supplementation may help in reducing the incidence of environmental mastitis, especially in dry cows.
- Endotoxin-induced shock is a primary problem in severe cases of coliform mastitis and the infected cow may benefit more from fluid therapy rather than antimicrobial drug treatment.
- NSAIDs, which inhibit the formation of inflammatory prostanoids, may be helpful in treating acute environmental mastitis cases. They may relieve signs of endotoxic shock associated with coliform mastitis. Several different NSAIDs, including flunixin meglumine and phenylbutazone, have been tested in experimental coliform mastitis and in experimental endotoxin-induced mastitis. *However, treatment with anti-inflammatory drugs has not been clearly shown to positively affect the survival or production of cows.*
- Vaccines: J-5 (R mutant) *E. coli* antigen vaccines can be used to enhance resistance to intramammary coliform infections. Administration of the vaccine during the dry period reportedly reduces the severity of coliform infections in IMM challenge studies with *E.*

coli. Currently, there is no vaccine effective in controlling mastitis caused by environmental streptococci.

Antimicrobial Drugs

- There are several antimicrobial drug formulations on the U.S. market that have been approved for treatment of mastitis in lactating or dry cows. These products are FDA-approved for administration by the IMM route.
- IMM infections by Gram-positive bacteria, including environmental streptococci and contagious *S. aureus*, can be treated with FDA-approved *beta*-lactam antibiotics or the lincosamide antimicrobial drug, pirlimycin (Pirsue®). Because they are often broad-spectrum drugs, some *beta*-lactam antibiotics may be effective against Gram-negative coliform bacteria (from the family *Enterobacteriaceae*) as well.
- In lactating cows, the *beta*-lactam antimicrobial drugs indicated for mastitis include several penicillins and cephalosporins. The aminopenicillins **amoxicillin** and **hetacillin** (metabolically converted to ampicillin in cows) have activity against susceptible Gram-positive streptococci and staphylococci, as well as Gram-negative *E. coli*. The efficacy of a third penicillin, **cloxacillin**, against the current species of Gram-positive cocci responsible for mastitis in lactating cows is not well-defined. The first-generation cephalosporin **cephapirin** has broad spectrum activity against Gram-positive bacteria and Gram-negative members of the *Enterobacteriaceae* family. **Ceftiofur**, a third generation cephalosporin, has even greater activity than cephapirin against Gram-negative mastitis pathogens, but lesser activity against Gram-positive cocci.
- **Pirlimycin**, a lincosamide, can also be administered by the IMM route to lactating cows; it is active against Gram-positive mastitis cocci.
- Antimicrobial dry cow therapy (ADCT) is more effective than drug treatment of lactating cows because higher drug doses can administered by the IMM route, and high IMM drug concentrations can be maintained over a long time period because there is no diluting effect of milk and none of the periodic drug losses that occur with milking. Moreover, the potential for violative drug residues to appear in milk is greatly reduced. There are several FDA-approved, *beta*-lactam antimicrobial drug formulations for IMM administration at dry off. Some products combine one of these drugs with a bactericidal aminoglycoside or the bacteriostatic drug, novobiocin. These products are generally highly effective in reducing the incidence of udder infections by contagious mastitis bacteria. However, there are few studies of their effectiveness on the environmental bacteria that currently cause mastitis.
- Appropriate milk and meat withdrawal times must be followed for all FDA-approved compounds administered.

Other Considerations

- Untested combinations of products should not be used.
- Compounding of intramammary products is illegal and may result in violative antibiotic residues in both meat and milk.
- Multiple dose containers should never be used between udders due to the risk of contamination with organisms such as *Mycoplasma* sp. or drug-resistant *S. aureus* that can be spread to other quarters or other cows in the herd. These bacteria are not readily susceptible to antibiotic therapy.
- Care should be used when infusing dry cow products through the streak canal because environmental contaminants may be inadvertently forced through the canal and cause

additional infections. Environmental contaminants are generally not susceptible to dry cow treatment products.



MISCELLANEOUS

SEE ALSO

- Food Animal Residue Avoidance Databank (FARAD)
(www.fiveminutevet.com/ruminant)
- Mastitis: Coliform
- Mastitis: Fungal
- Mastitis: Minor Bacteria
- Mastitis: Mycoplasmal
- Mastitis: No Growth
- Mastitis: Staphylococcal
- Mastitis: Streptococcal

ABBREVIATIONS

- FDA = Food and Drug Administration
- IMM = intramammary
- NSAIDs = nonsteroidal anti-inflammatory drugs
- SCC = somatic cell count

Suggested Reading

Oliver, S.P., Murinda, S.E. Antimicrobial resistance of mastitis pathogens. Vet. Clin. North Am. Food Anim. Pract. 2012; 28: 165-185.

Royster, E., Wagner, S. Treatment of mastitis in cattle. Vet. Clin. North Am. Food Anim. Pract. 2015, 31: 17-46.

Suojala, L., Kaartinmen, D., Pyörälä, S. Treatment of bovine *Escherichia coli* mastitis – an evidence-based approach. J. Vet. Pharmacol. Therap. 2013; 36: 521-531.

Author David R. Brown

Consulting Editor Erica C. McKenzie