

# Peracute Toxic Coliform Mastitis

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## Introduction

The incidence of coliform mastitis has been on the increase since a serious effort has been made to eliminate *Streptococcus agalactia* and *Staphylococcus aureus* mammary infections in dairy herds throughout the U.S. As somatic cell counts decrease in dairy cows, they tend to be more susceptible to coliform mastitis. It is likely that this trend will continue as long as stringent controls are being placed on somatic cell levels and premiums are being offered for better quality milk.

"Coliform" is a general term for fermentative gram-negative bacilli that inhabit the intestinal tract of man and other animals normally without causing disease. These bacteria are classified within the family *Enterobacteriaceae*. Certain members of this group, *Escherichia coli*, *Enterobacter aerogenes* and *cloacae*, and *Klebsiella* have commonly been isolated from bovine mastitis.<sup>1</sup> Coliforms are ubiquitous in the cow's environment, but coliform mastitis is not highly contagious. It is usually described as an "environmental mastitis."

Cases of coliform mastitis are clinically described as being peracute, acute, subacute, or subclinical. Coliform organisms have been shown to be the principle cause of peracute toxic mastitis. Eberhart (1979) estimates that 10 to 15 percent of clinical coliform cases are peracute.<sup>1</sup> It is commonly the peracute case in which the cow is systemically affected by endotoxin release, and it is this aspect of the disease that will be discussed. Peracute cases may result in loss of function of the affected quarter, agalactia affecting all quarters and, occasionally, death of the cow.<sup>2</sup>

Most coliform mastitis is seen during the periparturient period or in early lactation. About two-thirds of coliform mastitis cases are seen in the first three

months of lactation.<sup>1</sup> Lactoferrin concentrations in the dry cow secretions strongly inhibit active infection of the dry cow.<sup>3,4</sup> It is only when these concentrations decrease near calving that susceptibility is greatly increased. The stress of calving also increases cortisol levels which may be immunosuppressive and lead to increased susceptibility.

Although there are exceptions, most cases of coliform mastitis are due to bacterial invasion of the mammary gland via the teat canal. Whether these infections are established at drying off and remain dormant, or whether infection occurs immediately prior to the clinical crisis, the clinical signs and prognosis are generally the same. This paper will review the current ideas on diagnosis, pathogenesis, and therapy of an animal experiencing endotoxic shock.

## Diagnosis and Clinical Signs

The diagnosis of an endotoxic crisis from coliform mastitis is not always clear-cut. In most instances, farmers are aware of the majority of the systemic signs and can associate them with acute mastitis. Dairymen are adept at noticing signs of udder inflammation and abnormal milk secretion. Difficulty may arise due to the sudden onset of some cases. A cow may be normal at one milking and severely ill before or at the next milking due to rapid multiplication of bacteria followed by release and dissemination of endotoxin.<sup>1</sup>

Another situation in which there may be difficulty in diagnosing a peracute case is when systemic signs of illness precede any detectable evidence of mastitis. In these instances, udder inflammatory changes may lag behind systemic effects by several hours.

The history often shows sudden onset of anorexia, fever, depression, shivering, and rumen stasis. Inflammatory signs in the udder may be minimal at this time and swelling may be detectable only after the quarter is milked out. Later, the quarter is swollen and hard. In some instances, the affect-

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ed quarter may be smaller than the others due to hypogalactia.<sup>1</sup>

Signs of endotoxic shock may appear within a few hours of onset. These include recumbency, marked depression, progressive dehydration, diarrhea, normal or subnormal temperatures, raised pulse and respiratory rates, diminished papillary response, dark toxic mucous membranes and cold extremities. At this time, the prognosis is guarded to poor.

The signs of intoxication due to peracute intramammary infection must be differentiated from signs of other severe systemic diseases such as parturient paresis, metritis, and ketosis. One must remember that the cow may be concurrently hypocalcemic because of the coliform infection.<sup>5,6</sup> Weakness and recumbency in recently calved cows resembles parturient paresis, but dehydration and diarrhea, if present, are not characteristic of parturient paresis and should prompt a further clinical examination, particularly of the udder.

The definitive diagnosis of the causative agent is not pertinent at this point beyond its susceptibility to certain antimicrobial agents. The severe systemic signs that are exhibited do not allow delaying therapy until positive culture results are available. One should apply systemic support while administering an antimicrobial agent that is either broad spectrum or has a history of clinical effectiveness in similar situations. Culture results can be a retrospective aid for treatment and prevention of future cases demonstrating similar clinical signs.

### Pathogenesis

The pathogenesis of endotoxic shock associated with coliform mastitis is complex and controversial. It is agreed that endotoxin is the mediator of the severe systemic signs. The effects of endotoxins are varied and often profound. The severity of these changes are dose and rate dependent. Surprisingly, endotoxins appear to have relatively little direct toxic effect; most of the severe changes are indirect, associated with cascades of biologic processes initiated by endotoxin.<sup>7</sup>

The term endotoxin refers to a part of the cell wall or envelope of gram-negative bacteria. It is synonymous with the O antigen, or somatic antigen, of these bacteria and is composed of polysaccharides, phospholipids, and small amounts of protein. These compounds are referred to as endotoxins, lipopolysaccharides, or endotoxic phospholiposaccharides.<sup>8</sup>

Endotoxin release from bacteria is commonly attributed to lysis of the organisms by phagocytes. However, it is important to note that endotoxin may be released from cells during active growth as

well as by cell lysis.<sup>1,9,10</sup> Schalm, et al,<sup>11</sup> postulated that destruction of the bacteria by these phagocytes causes release of the endotoxin which increases vascular permeability, and causes a subsequent influx of serum factors into the milk. Jain, et al,<sup>11</sup> concluded that one function of the neutrophil is to initiate the events leading to vascular permeability. The neutrophils and their lysosomes will then mediate the production of the cardinal signs of inflammation, pain, swelling and hyperthermia. A number of researchers have suggested that the accompanying severe systemic signs may be due to anaphylactic shock in response to the endotoxin.<sup>1,12</sup>

The existence of endotoxemia is the most controversial subject in the pathogenesis of endotoxic mastitis. Absorption of the endotoxin into the blood from the mammary gland has been demonstrated.<sup>13</sup> It appears that endotoxin is cleared more quickly from the blood than from the milk. This result suggests that endotoxin is detoxified rapidly after absorption into the circulation.<sup>1</sup>

Some investigators seriously doubt that the clinical signs of generalized disease in these animals may be caused by absorption of endotoxin by the udder.<sup>14,15</sup> They contend that systemic signs are predominantly due to the formation of endogenous mediators in the inflamed udder and their subsequent release into the circulation.<sup>14,15</sup>

It seems reasonable that endotoxin within the udder causes formation of endogenous mediators in the gland. These mediators cause increased vascular permeability which may allow for systemic distribution of endotoxin. It seems reasonable that most of the mediator production initiated by the endotoxin would take place in the udder where a high concentration of leukocytes and endotoxin are in contact. It is doubtful that endotoxin which gains access to the general circulation would be significant in comparison to the massive mediator production taking place within the mammary gland.

Increased vascular permeability is the initial event in the chain of reactions involved in endotoxin-induced peracute mastitis. The release of endogenous mediators such as histamine, serotonin, serum permeability factors, bradykinin, and kallikrein may be responsible for the increased vascular permeability in the early phase of mastitis.<sup>4,5</sup>

Bacteremia associated with coliform mastitis plays little role in the pathogenesis and, in fact, is uncommon. Powers, et al,<sup>17</sup> concluded that less than 15 percent of cows with pure or mixed toxic gram-negative mastitis had a gram-negative bacteremia.

Histamine is released from cells damaged directly by endotoxin and indirectly by the effects of inflam-

mation and ischemia associated with shock. Histamine appears to be the major factor responsible for early phases of circulatory shock.<sup>18</sup> It plays a very minor role in the pathogenesis of endotoxic cardiovascular shock relative to other factors after the first several hours.<sup>19</sup>

Arachidonic acid metabolites (AAM) are among the many biological compounds implicated in the mediation of acute inflammation.<sup>20,21</sup> The AAM, including stable prostaglandins, thromboxanes and prostacyclin, are produced when the multienzyme cyclooxygenase complex acts on arachidonic acid released from cell membranes during inflammation.<sup>20,21</sup> AAM appear to be involved in mediation of the local mammary inflammation and systemic signs observed in acute coliform mastitis. Nonsteroidal anti-inflammatory agents inhibit the multienzyme cyclooxygenase complex.<sup>20,21,22</sup>

The changes in glucose metabolism during an endotoxic crisis have been described by McClure (1976).<sup>19</sup> Early hyperglycemia is caused by endotoxin activation of hepatic membrane-bound enzymes that stimulate glycogenolysis and subsequent release of glucose to the blood stream. A secondary hypoglycemia rapidly develops. Liver glycogen is depleted as glycogenolysis continues and as endotoxin inhibits replenishment production of more hepatic glycogen. Hepatic gluconeogenesis is also depressed as endotoxin inhibits enzymes that catalyze glucocorticoid activation of the process and induces high levels of circulating insulin that directly antagonizes it. The characteristic cardiovascular insufficiency results in ischemic tissues that require increased amounts of glucose for metabolism. This increased need for glucose in the face of hypoglycemia results in cell dysfunction and death.

Only a few cases have been documented in regards to disseminated intravascular coagulation (DIC) in cows, although many deaths associated with endotoxic mastitis probably incorporate some degree of DIC. The inciting factors triggering the development of DIC are a response to an underlying illness, provoking a generalized activation of the hemostatic mechanisms. The usual hemostatic response is confined to an area of local vascular injury, but DIC is widespread, depleting fibrinogen and other clotting factors with activation of the fibrinolytic systems.<sup>23</sup>

Peracute coliform infections in cows may produce a hypocalcemic syndrome clinically resembling parturient paresis.<sup>1</sup> There is debate as to whether these are concurrent milk fever cases independent of the endotoxic mastitis or a direct result of endotoxin release. The pathogenesis of changes in serum calcium are not understood at this time, but are postu-

lated to be due to decreased intestinal absorption following endotoxin-induced alimentary stasis<sup>6</sup> and possible endotoxin-mediated humoral factors.<sup>5</sup>

### Prognosis

The prognosis for a peracute case of coliform mastitis is always guarded and often poor for recovery of both the cow and the mammary gland.

The animal with endotoxemia responds in at least two critical ways. The first way is to clear the organism, and the second is to clear the endotoxin without setting off an immunologic cascade of overreaction, which may itself destroy the animal. Contrary to the usual thoughts about response to infection, the response to endotoxin must be limited if the animal is to survive.<sup>8</sup> This type of overreaction is exemplified by those animals developing disseminated intravascular coagulation.<sup>23</sup>

If the cow does not die acutely, a protracted illness with poor appetite and progressive weight loss may ensue.<sup>24</sup> Bushnell estimated that 10 percent of cows with peracute coliform mastitis died, 70 percent became agalactic and 20 percent returned to milk. Cows that became agalactic often returned to normal production in subsequent lactations.<sup>25</sup>

The outcomes of severe coliform cases were recently studied.<sup>26</sup> Among 88 affected cows, all of which received appropriate therapy, 7 percent died as a result of the infection and an additional 17 percent were culled during the lactation. In 11 percent of the cases, the cow was retained in the herd but the affected quarter did not return to milk in that lactation. Half of these agalactic quarters secreted milk in the subsequent lactation, but the other half did not. In 59 percent of all cases, the quarter secreted normal-appearing milk during the lactation in which mastitis occurred. From these data, it appears that most cows with severe coliform infection do recover, but nearly 24 percent will either die or be culled as a direct result of the infection.<sup>2</sup> Fortunately, peracute cases comprise only a small proportion, perhaps 10 percent of all coliform infections.<sup>25</sup>

Successful therapy is dependent on a number of factors including the following: dose of endotoxin encountered, immune status of the animal, condition of the animal when therapy was initiated, intensity of therapeutic procedures, and proper selection of therapeutic agents. The economic value of the animal must be considered when determining the duration of costly therapy, especially in view of the guarded prognosis regardless of therapy.

## Therapy

All cases of peracute coliform mastitis should be treated promptly and aggressively. The sooner therapeutic measures are initiated, the better the prognosis will be. Dairywomen should not attempt to treat these cases alone, nor should they hesitate in calling a veterinarian.

By remembering the main therapeutic goals of removing bacteria and limiting the immune cascade set off by endotoxins, treatment can be approached rationally. Objectives for mastitis therapy are to preserve the life of the animal, restore function to the mammary gland, and improve the quality and efficiency of production. Specific therapeutic measures are directed at removal of causative agent, detoxification and support for systemically affected animals, reduction and elimination of toxic waste products, and promotion of healing of damaged tissue.

### A. Antimicrobial Therapy

Antimicrobial drugs are used to reduce the production of endotoxin. Selection of the proper drug can sometimes be very difficult. In toxic cases, one cannot wait for an etiological diagnosis. Immediate therapy with either a broad spectrum agent or one that has shown clinical effectiveness in the past is necessary. Commonly used agents are sulfonamides, gentamycin, oxytetracycline, and lincomycin/spectinomycin combinations. The choice of the appropriate antimicrobial agent is influenced by a number of considerations including the drug's spectrum of activity, toxicity, convenience of administration, withdrawal time, and cost.<sup>2</sup>

Systemic administration of appropriate drugs supplemented by intramammary infusion is usually recommended.<sup>1</sup> Polymyxins (polymyxin B and colistin) are narrow spectrum polypeptide antibiotics sometimes used for intramammary treatment. The unique property of these drugs is that they neutralize endotoxin *in vitro*<sup>27</sup> and *in vivo*.<sup>28</sup> Another study indicated that they inactivate toxins *in vitro* but that there was little clinical evidence to recommend use.<sup>9</sup>

### B. Removal of Bacteria and Toxins

The importance of frequent stripping of affected quarters to remove toxins cannot be overemphasized. This procedure may save the quarter and will reduce the amount of toxins in the system. Stripping the quarter at 1 to 2 hour intervals gives the best results. Simultaneous use of 10-30 units of oxytocin allows for better clearance of waste products. Antibiotics should be placed in the quarter after the last milkout at night.<sup>1</sup>

## C. Fluid Therapy

In peracute cases where systemic signs are exhibited, fluid therapy can be life-saving. Intravenous balanced electrolyte solutions reverse hypotension and increase cardiac output. They also help to maintain renal perfusion and allow diuresis of toxic metabolites. Up to 20 liters should be given in the first 1 to 2 hours. The remainder of the total dose (60 to 110 ml per kg BW) may be given over the next 10-12 hours.<sup>2</sup> Oral fluids may be beneficial in some cases and are commonly implemented in recovery stages.

### D. Corticosteroids

Corticosteroids tend to neutralize the effects of inflammation and endotoxic shock. Both a high dose of IV dexamethasone (40-80mg/100kg BW) administered only once and another treatment repeated after 8-12 hours have been shown to be beneficial.<sup>1</sup> The disadvantage of corticosteroids is that they tend to be immunosuppressive and inhibit bacterial clearance. Use of steroids has largely been replaced by nonsteroidal, anti-inflammatory drugs such as flunixin meglumine.<sup>3</sup>

### E. Nonsteroidal Anti-inflammatory Agents

Arachidonic acid metabolites are responsible for mediation of acute inflammation. They are produced through the multienzyme cyclooxygenase complex, and nonsteroidal anti-inflammatory agents inhibit the complex. These agents are therefore indicated for treatment of peracute toxic mastitis.

The most widely used agent is flunixin meglumine at 0.5 mg/lb IV.<sup>16</sup> Oral doses of aspirin may be effective at 100 mg/kg (0.67-1 gr/lb) BID,<sup>29</sup> and phenylbutazone may be given at 4-8 mg/kg orally or 2-5 mg/kg IV.<sup>30</sup>

### F. Glucose Therapy

Many of these animals are hypoglycemic due to effects of endotoxin. They may benefit from intravenous glucose administration. Usually, 250g of glucose is adequate. A 500 ml of 50% glucose solution can also be added the first 5-10 liters of fluid given IV.<sup>31</sup>

### G. Calcium Therapy

Intravenous calcium boro-gluconate has reversed the signs of hypocalcemia in both experimental cases of endotoxemia and clinical cases of peracute coliform mastitis.<sup>6</sup> Extreme care must be taken when administering calcium to a toxic cow. Endotoxin AAM and catecholamines all sensitize the myocardium.

<sup>3</sup>Banamine<sup>®</sup> (flunixin meglumine) Schering Corp., Kenilworth, NJ

um to calcium. Calcium therapy may be safer if delayed until after initial volume expansion with fluids or if administered subcutaneously.

#### H. Antihistamines

According to Allenstein (1977), antihistamines are of empirical value if administered repeatedly every 3 to 4 hours for at least 2 days.<sup>32</sup> Histamine appears to be the major factor responsible for the early phase of circulatory shock. It also plays a very minor role in the pathogenesis relative to other factors after the first several hours.<sup>19</sup>

#### I. Heparin

In cases where one suspects that DIC is a possibility, heparin may be given at 75 IU/kg BW (56,000 units)/day.<sup>23</sup>

#### Conclusion

Peracute toxic mastitis is a very frustrating disease to treat. Coliform organisms are ubiquitous in the cow's environment, and coliform mastitis does not respond to control measures as do gram positive infections. Therefore, it is likely the dairy industry will be living with this disease for some time to come. Clinically affected animals must be aggressively treated if endotoxic shock is to be reversed and the cow kept alive and economically functional.



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