Abstract  Bovine mastitis is characterized by an inflammation of the mammary gland usually caused by an intramammary infection (IMI) of a wide variety of microorganisms. Pathogens including *Staphylococcus aureus*, *Streptococcus agalactiae*, coliform bacteria, coagulase-negative staphylococci and *Strep. uberis* are commonly isolated from mastitis cases and usually concerned for treatment. Various therapeutic strategies have been developed to control IMI and reduce losses due to clinical and subclinical mastitis. Antimicrobials have been one of the most common treatment plans for therapy of bovine mastitis. Because cure rates are highly depended on the pathogen, treatment of mastitis should be based on bacteriological diagnosis. If treatment decision has to be made without results of bacteriological diagnosis, such as in acute mastitis, the concept of evidence-based medicine should be applied and incorporated with herd data to initiate a proper treatment plan. Some common practices for treatment of clinical mastitis, such as frequent milk-out and oxytocin injection, have limited supporting evidences and should be recommended with caution. Treating subclinical mastitis is generally not economical during lactation because of high treatment costs and poor efficacy. Because bovine mastitis is the most common reason for the use of antimicrobials in dairy herds, treatment of bovine mastitis should be supervised by veterinarians. *Chaing Mai Veterinary Journal 2012; 10(2): 89-109*

**Keywords:** treatment, mastitis, lactating period, dairy cows
Introduction

Bovine mastitis is an important animal health disease leading to significant economic losses to the dairy industry throughout the world\(^\text{(1)}\). It is usually caused by IMIs of microorganisms which are commonly classified into contagious pathogens such as *Staphylococcus aureus* and *Streptococcus agalactiae*, opportunistic pathogens such as coagulase-negative staphylococci (CNS), and environmental pathogens such as coliform bacteria and environmental streptococci. Bovine mastitis can also be categorized as either clinical or subclinical mastitis. Cases of clinical mastitis are among the primary concerns for treatment due to the obvious losses from the disease. Treating subclinical mastitis is generally not economical during lactation because of high treatment costs and poor efficacy. However, treatment of subclinical mastitis may be considered to reduce the risk of becoming clinically infected and a long term detrimental effect on milk quality.

Antimicrobial treatment is one of the most common treatment plans for therapy of bovine mastitis\(^\text{(2)}\). A standard recommendation for most clinical mastitis is a 3-day intramammary treatment of an antimicrobial agent. However, several antimicrobial treatment regimens are also available, differing in antimicrobial compound, route of application, duration, probability of cure, and costs\(^\text{(3,4)}\). Other therapeutic approaches such as a symptomatic therapy using anti-inflammatory drugs\(^\text{(5-7)}\), immunotherapies using vaccines\(^\text{(8)}\) or cytokines\(^\text{(9-11)}\) and even homeopathy\(^\text{(12)}\) have also been described. Cure rates are highly depended on the causal pathogens\(^\text{(13,14)}\) and other cow factors\(^\text{(4,15)}\).

**Therapy of mastitis caused by *Staphylococcus aureus***

Treatment results of *Staph. aureus* IMI during lactating period are usually disappointing because this pathogen can apply some mechanisms facilitating resistant to host immune response such as micro-abscesses formation and invasion into host phagocytic cells\(^\text{(16-18)}\). As a result, most *Staph. aureus* IMIs are associated with chronic infection and low cure rates during lactation.

Variations in antimicrobial resistance of *Staph. aureus* isolates, particularly to penicillin, can affect treatment responses\(^\text{(19-21)}\). Cure rates for mastitis caused by penicillin-resistant strains of
Staph. aureus are lower than those for mastitis caused by penicillin-susceptible strains with the bacteriological cure rates of 29%-50% for mastitis caused by penicillin-resistant strains versus the bacteriological cure rates of 48%-75% for mastitis caused by penicillin-susceptible strains\(^{(15, 22-24)}\). The difference may be due to pharmacologic problems of the antimicrobials, or the association between virulence factors and β-lactamase gene of the resistant isolates\(^{(25)}\). Couple studies provided evidences supporting the relationship of β-lactamase gene and the virulence of Staph. aureus. In a study by Sol et al.\(^{(15)}\), clinical Staph. aureus mastitis caused by β-lactamase positive or negative isolates was treated with 5 different antimicrobial intramammary products. Even though the isolates included in their study were susceptible to the drug used for treatment, significant higher bacteriological cure rates of β-lactamase negative group (59%) compared to those of β-lactamase positive group were observed (41%)\(^{(15)}\). This phenomenon is also observed in another study by Taponen et al.\(^{(24)}\), where the efficacy of treatment of clinical mastitis caused by Staph. aureus using the combination of systemic and local antimicrobial therapy was compared to the efficacy of treatment when only systemic treatment was applied. They found that the bacteriological cure rate of the combination treatment for udders infected with β-lactamase negative Staph. aureus was higher than that for udders infected with β-lactamase positive Staph. aureus (75.6% versus 29.2%). Moreover, they further reported that combined treatment was superior over systemic treatment only when it was used to treat udders infected with β-lactamase negative Staph. aureus\(^{(24)}\). Based on these clinical evidences, determination of resistance to penicillin using β-lactamase test is recommended before treatment of IMI caused by Staph. aureus\(^{(20)}\).

**Therapy of mastitis caused by Streptococcus agalactiae**

Strep. agalactiae is a contagious mastitis pathogen causing subclinical and mild to moderate clinical mastitis in dairy cows. This microorganism can hardly survive in the environment, but it can persist indefinitely within the mammary gland. Therefore, the presence of Strep. agalactiae in bulk tank milk generally describes IMI of lactating cows in the herd. Herds with Strep. agalactiae mastitis usually have high somatic cell
counts (SCCs) together with increased total bacterial counts in bulk tank milk. Although low rates of clinical mastitis are generally observed in infected herds, subclinical mastitis due to *Strep. agalactiae* may cause a significantly economic loss from increased milk SCC and decreased milk quality\(^{(26)}\).

Treatment of *Strep. agalactiae* mastitis using intramammary infusion products usually results in high cure rates ranged from 85 to 100%\(^{(27-29)}\). A general recommendation is to use penicillin or its derivatives because *Strep. agalactiae* isolates are highly susceptible to penicillin as reported in many studies\(^{(30,31)}\). Because *Strep. agalactiae* generally resides in the mammary gland, eradication of *Strep. agalactiae* to be a *Strep. agalactiae*-free herd can possibly be achieved. Two treatment options are available to eliminate *Strep. agalactiae* from the herd. The first protocol is called "blitz therapy" which is a program of treating all quarters of all cows with a penicillin-based intramammary antimicrobial for 3 consecutive milkings. Another treatment scheme is a selective treatment based on culture results of all cows in a herd. The difference between the two programs is the cost of discarded milk versus the cost of additional bacteriological cultures. However, small-holder dairy farms may be more willing to apply the blitz therapy program than big commercial dairy farms do, due to an obvious large amount of discarded milk when antibiotics are used to treat all milk-producing cows in the farms. After treatment, a small percentage (5-15%) of treated animals may not be cured. Therefore, 3 weeks after treatment, cows that continue to have high SCC values should be cultured and retreated. Treatment of cows subclinically infected with *Strep. agalactiae* usually results in increased production and dramatic decreases in bulk tank SCC values. It is generally agreed that treating *Strep. agalactiae* infections are economically beneficial.

**Therapy of mastitis caused by coagulase-negative staphylococci**

Coagulase-negative staphylococci (CNS) have been classified as minor mastitis-causing pathogens with ability to opportunistically infect the mammary gland. CNS have become the predominant pathogens associated with subclinical mastitis in several countries\(^{(32-34)}\). Clinical mastitis cases caused by CNS do not frequently occur and the clinical
signs are usually mild. Due to the high prevalence, CNS have been increasingly important with a significant contribution in reduction of milk quality.

Treatment protocols for CNS mastitis are varied depending upon the specific characteristic of the causative species. Even though some studies reported cases of persistent IMI of CNS\textsuperscript{(35-38)}, it is generally assumed that the spontaneous cure rate of CNS mastitis is high as evident in several studies\textsuperscript{(39,40)}. As a consequence, treating subclinical and mild clinical mastitis due to CNS has been usually considered unnecessary. Moreover, several studies demonstrated a high level of susceptibility to antimicrobials commonly used to treat mastitis\textsuperscript{(19,41,42)} resulted in high bacteriological cure rates after antimicrobial treatment. The bacteriological cure rates of cows with CNS mastitis after treating with β-lactam antimicrobials have been reported as high as 70-90\%\textsuperscript{(13,23,35,39,43)}. However, Deluyker et al.\textsuperscript{(44)} reported lower cure rates, 53% and 73%, when pirlimycin was used for 2 and 8 days, respectively. Similar to what has shown with \textit{Staph. aureus} IMI, lower cure rates of cows infected with β-lactamase positive CNS could be observed compared to those of cows infected with β-lactamase negative strains\textsuperscript{(23)}.

Therapy of mastitis caused by coliform bacteria

\textbf{Coliform bacteria have been} accounted to be a major cause of acute and peracute bovine mastitis in many regions of the world\textsuperscript{(45)}. Mastitis caused by coliform bacteria, particularly \textit{Escherichia coli}, usually occurs in early lactation, and results in significant loss of milk production and severe tissue damage to the mammary gland\textsuperscript{(46,47)}. Coliform mastitis is generally considered self-limited with a short duration of severe clinical signs\textsuperscript{(48)}. Treatment of coliform mastitis has mainly focused on the symptomatic treatment using anti-inflammatory agents\textsuperscript{(5,49-51)}. Treatment of coliform mastitis using antimicrobials is still debating. Several studies have shown that using antimicrobials did not significantly reduce either the duration of infection or the severity of clinical signs\textsuperscript{(23,52,53)}. However, systemic administration of antimicrobials has been recommended to reduce the risk of bacteremia in severe cases which consequently improves the reduction of...
milk production and mortality rate of infected cows\textsuperscript{(54-56)}. Only a few antimicrobial substances were effective for Gram-negative organisms known to cause diseases in cattle\textsuperscript{(57)}. Drugs-of-choice against any Gram-negative bacterial infection such as trimethoprim-sulfonamide, gentamicin and colistin have been reported for a limited success when they were used for treatment of coliform mastitis\textsuperscript{(52,53)}. Fluoroquinolones have increasingly been used and recommended to treat cattle with coliform mastitis. Favorable results including a very good distribution in mammary gland with a high concentration of the drugs in milk and a significant decrease in milk loss, when fluoroquinolones; enrofloxacin, danofloxacin, and marbofloxacin, were applied systemically to treat experimentally induced \textit{E.coli} mastitis were observed\textsuperscript{(55,56,58-60)}. Additionally, cephalosporins have also been recommended to treat coliform mastitis. Systemic therapy of third and fourth generation of cephalosporins; ceftiofur and cefquinome, respectively, can also positively affect treatment response of severe cases of coliform mastitis\textsuperscript{(61,62)}. Based on these clinical evidences, systemic antimicrobial treatment, with or without symptomatic or supportive therapy, is more beneficial compared to local and non treatment of coliform mastitis.

\textbf{Therapy of mastitis caused by \textit{Streptococcus uberis}}

\textit{Strep. uberis} is a member of environmental streptococci and has been reported to be a major cause of bovine mastitis in many countries throughout the world\textsuperscript{(63-68)}. Approximately 45\% of \textit{Strep. uberis} IMI during lactating period are usually associated with clinical mastitis\textsuperscript{(69)}. Chronic infection of \textit{Strep. uberis} IMI can also occur and results in a prolonged elevation of SCC for several weeks\textsuperscript{(70)}. The significantly economical impact caused by \textit{Strep. uberis} IMI leads to a development of effective control and treatment strategies for this pathogen.

Different classes of antimicrobials have been tested for their efficacy against \textit{Strep. uberis} IMI during lactating period. High cure rates of \textit{Strep. uberis} IMI treated with a macrolide antimicrobial called tylosin\textsuperscript{(13)} and a lincosamide antimicrobial called pirlimycin have been reported\textsuperscript{(71,72)}. In addition, \textbf{β}-lactam antimicrobial is another drug group
suggested for treatment of *Strep. uberis* IMI. High cure rates of *Strep. uberis* IMIs when penicillin and its derivatives were used for treatment have been reported$^{[24,73]}$. Within this class, penethemate hydriodide, which is a diethylaminoethyl ester of benzylpenicillin, has also been used to treat clinical *Strep. uberis* mastitis and resulted in a high bacteriological cure rate$^{[13]}$. This compound has also been reported for its ability to kill bacteria even they are internalized into mammary epithelial cells$^{[74]}$. Furthermore, cephalosporins are another antimicrobials suggested to treat *Strep. uberis* IMI. First and second generations of cephalosporins including cephapirin sodium and cefuroxime, respectively, have been reported with high bacteriological cure rates when they were used to treat *Strep. uberis* mastitis$^{[73,75]}$. For third and fourth generations of cephalosporins, such as ceftiofur and cefquinome, respectively, high cure rates of clinical mastitis due to *Strep. uberis* could be observed only when they were used for an extended period of 5-8 days$^{[76,77]}$. These evidences suggest a cautious use of cephalosporin antimicrobials for therapy of *Strep. uberis* IMI according to variations in responses when they were used for different durations.

**Treatment of Subclinical Mastitis**

Treatment of subclinical mastitis during lactation is not commonly recommended due to an economical standpoint. However, dairy producers have been more encouraged to maintain a low level of bulk milk SCC to increase their profit. Effective therapy of subclinical IMI during lactation is therefore essential if it may increase the bacteriological cure, decrease SCC, and effectively complement preventive measures$^{[78-81]}$.

Treatment of subclinical mastitis has been focused on IMIs caused by Gram-positive bacteria because Gram-negative bacteria are generally associated with clinical, but not subclinical, mastitis. Economic justifications of treatment of subclinical mastitis caused by streptococci and *Staph. aureus* during lactation have been described$^{[80,81]}$. Treatment of subclinical mastitis can be performed using either intramammary treatment or systemic treatment. Many studies suggested the use of intramammary treatment$^{[44,71,82,83]}$ whereas some studies reported the use of systemic treatment of subclinical mastitis$^{[39,84,85]}$. Intramammary infusion of
antimicrobials (IMMA), such as amoxicillin\(^{40}\), pirlimycin hydrochloride\(^{71}\), ceftiofur\(^{76}\), cefquinome\(^{86}\), penethamate hydriodide\(^{85}\), have been shown to be able to successfully cure IMI and reduce SCC of subclinically infected cows. On the other hand, a number of antimicrobials including penethamate hydriodide\(^{87}\) and penicillin\(^{85,88}\) have been reported for systemic treatment to successfully treat subclinical mastitis.

When profitable effects of intramammary treatment were compared to systemic treatment, the later may be more preferable due to beneficial responses observed with uninfected quarters. Based on the fact that subclinical mastitis usually occurs with more than one quarter per cow\(^{89}\), treatment effects on both targeted and nontargeted quarters, as observed in the systemic treatment of clinical mastitis\(^{90}\) can be expected. This effect might be associated with benefits of antimicrobial treatment during lactating period, leading to the reduction of bulk tank milk SCC.

**Frequent milk-out and use of oxytocin**

Frequent milk-out (FMO) with and without oxytocin is a popular recommendation for the treatment of clinical mastitis\(^{91}\). The logical reason supporting this recommendation is that FMO can increase the removal of abnormal secretions, infectious agents, toxins and inflammatory mediators accumulated in milk of an infected quarter. However, evidences supporting this practice are very limited. The use of FMO with or without oxytocin injection does not give any benefit over the antimicrobial treatment as described in several studies\(^{92-94}\). Moreover, the use of FMO may be detrimental for some cases as reported by Roberson and co-workers\(^{92}\). This study showed lower clinical and bacteriological cure rates when either FMO or the combination of FMO and IMMA was used to treat cases of mastitis caused by environmental streptococci compared to those when only IMMA was applied (9% versus 40%)\(^{92}\). These findings indicate that the use of FMO alone should not be recommended for treatment of clinical mastitis and the effectiveness of using FMO together with IMMA can be varied depending on the causal pathogens.

In addition to FMO, the use of oxytocin to help emptying the mammary gland has also been recommended for treatment of clinical mastitis. However, the use of oxytocin alone has not shown to be
superior to the use of IMMA\(^{(95)}\). Therefore, oxytocin is also recommended to be used together with IMMA in order to achieve a high bacteriological cure rate\(^{(96)}\).

**Treatment with anti-inflammatory agents**

Treatment of clinical mastitis with a variety of anti-inflammatory agents is indicated especially for acute cases which are usually observed with coliform mastitis. Both glucocorticoids (GC) and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for treatment of bovine mastitis. Dexamethasone is one of the GCs used for treating acute mastitis. Parenteral treatment of dexamethasone helps reducing fever, surface temperature of infected mammary gland and rumen motility impairment\(^{(97)}\). However, some adverse effects including immunosuppression, abortion in pregnant cows and prolonged reduction of milk production are potentially observed when dexamethasone is used parenterally\(^{(98)}\). Isoflupredone acetate is another GC with lower potency compared to dexamethasone and has been used for treating acute bovine mastitis\(^{(99)}\). However, there are no data showing improvements of both local and systemic inflammatory signs of clinical mastitis when isoflupredone acetate was used\(^{(100,101)}\).

**Several NSAIDs**, such as phenylbutazone, flunixin meglumine, carprofen, ketoprofen and meloxicam, have been used for treatment of acute coliform mastitis\(^{(5,49-51,102-104)}\). Because of the prolonged half-life of phenylbutazone in cattle and a high-risk of hypersensitivity to this agent in human, phenylbutazone has been banned for treating adult cattle (>20 months old) as issued by Food and Drug Administration\(^{(105)}\). Effects of flunixin meglumine, carprofen, and ketoprofen in improving systemic signs of inflammation including reducing rectal temperature and increasing rumen motility have been described in many experimental studies\(^{(5,49,102,103)}\). However, only the use of ketoprofen has been shown to improve local inflammatory signs of the mammary glands including gland swelling and milk appearance\(^{(49,103)}\), and increase recovery rate when it was used with antibiotics as reported in couple field trials\(^{(50,104)}\). A field trial of applying meloxicam for treatment of mild clinical mastitis has been recently established\(^{(51)}\). The use of meloxicam together with antibiotics can lower quarter milk SCCs of affected cows and reduce the culling rates of treated herds\(^{(51)}\). In
Summary, combination of anti-inflammatory agents with antibiotics has been recommended for treatment of severe or acute clinical mastitis not only due to the concern of animal welfare but also because of the economical benefit to the farmers.

Conclusion

Treatment of bovine mastitis is the major use of antimicrobials in dairy cows\(^\text{(106)}\). Different groups of antimicrobials with different routes of administration have been used to treat mastitis. Clinical and bacteriological cure rates are varied and highly depending on the causative bacteria, cows’ factors and treatment duration. An appropriate treatment protocol should be selected based on the concept of evidence-based medicine\(^\text{(107)}\). Finally, it is very important that treatment decision should be planned and made together between the veterinarian and farm owner in order to achieve the goal of the farm.

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