Treatment of mastitis during lactation

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ABSTRACT
Treatment of mastitis should be based on bacteriological diagnosis and take national and international guidelines on prudent use of antimicrobials into account. In acute mastitis, where bacteriological diagnosis is not available, treatment should be initiated based on herd data and personal experience. Rapid bacteriological diagnosis would facilitate the proper selection of the antimicrobial. Treating subclinical mastitis with antimicrobials during lactation is seldom economical, because of high treatment costs and generally poor efficacy. All mastitis treatment should be evidence-based, i.e., the efficacy of each product and treatment length should be demonstrated by scientific studies. Use of on-farm written protocols for mastitis treatment promotes a judicious use of antimicrobials and reduces the use of antimicrobials.

INTRODUCTION

Intramammary infection (mastitis) is the most common reason for the use of antimicrobials in dairy cows (Mitchell *et al.* 1998; Grave *et al.* 1999). Antimicrobials have been used to treat mastitis for more than fifty years, but consensus about the most efficient, safe, and economical treatment is still lacking. The concept of evidence-based medicine has been introduced to veterinary medicine (Cockcroft and Holmes 2003) and should apply also to treatment of mastitis. The impact on public health should be taken into account as dairy cows produce milk for consumption (OIE 2008). The aim of this article is to review current treatments of mastitis during lactation and seek for evidence-based, best practice treatment recommendations for bovine mastitis.

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

The bovine mammary gland is a difficult target for antimicrobial treatment. Penetration of substances into milk when administered parenterally or absorption and distribution throughout the udder when infused intramammarily (IMM) depends on their pharmacokinetic characteristics. These are lipid solubility, degree of ionization, extent of binding to serum and udder proteins, and the type of vehicle. Antimicrobial treatment of dairy cows creates residues into milk, and residue avoidance is an important aspect of mastitis treatment (Wagner and Erskine 2006).

Pharmacodynamics of the antimicrobial is another aspect which should be considered. Milk should not interfere with antimicrobial activity. The activity of macrolides, tetracyclines and trimethoprim-sulphonamides has been shown to be reduced in milk (Louhi *et al.* 1992; Fang and Pyörälä 1996). Selecting a substance with a low minimum inhibitory concentraton (MIC) value for the target pathogen is preferable, particularly when the antimicrobial is administered systemically. The antimicrobial should have bactericidal rather than bacteriostatic action, because phagocytosis is impaired in the mammary gland (Kehrli and Harp 2001).

Antimicrobial susceptibility determined in vitro has been considered as a prerequisite for treatment. However, activity in vitro does not guarantee efficacy in vivo when

treating bovine mastitis. Antimicrobial resistance amongst mastitis pathogens has not yet emerged as a clinically relevant issue, but geographical regions may differ in this respect. The biggest problem is the widespread resistance of staphylococci, particularly *Staphylococcus aureus*, to penicillin G (Pitkälä *et al.* 2004; Olsen *et al.* 2006; Hendriksen *et al.* 2008). Cure rates for mastitis caused by penicillin-resistant strains of *S. aureus* seem to be inferior to those of mastitis due to penicillin-susceptible strains (Ziv and Storper 1985; Pyörälä and Pyörälä 1998; Sol *et al.* 2000; Taponen *et al.* 2003). It is not known if this is due to pharmacologic problems of the drugs used, or virulence factors possibly linked to β-lactamase gene of the resistant isolates (Haveri *et al.* 2005). Using an in vitro β-lactamase test for determining resistance to penicillin G of staphylococci before treatment is recommended (Olsen *et al.* 2006).

Coagulase-negative staphylococci tend to be more resistant than *S. aureus* and easily develop multiresistance (Pitkälä *et al.* 2004; Sawant *et al.* 2009). Mastitis causing streptococci have remained susceptible to penicillin G, but emerging resistance to macrolides and lincosamides has been detected (Pitkälä *et al.* 2004; Loch *et al.* 2005). Antimicrobial susceptibility of coliform bacteria varies but normally is not a limiting factor for therapy (Lehtolainen *et al.* 2003; FINRES-Vet 2007; Wagner and Erskine 2006).

INTRAMAMMARY OR SYSTEMIC ADMINISTRATION?

An important question regarding the treatment of mastitis is whether the antimicrobial should accumulate in the milk or in the udder tissue (Erskine 2003). The target site may depend on the causative agent: streptococci are known to remain in the milk compartment, but *S. aureus* penetrates udder tissue and causes deep infection (**Table 1**). The most common route of administration of antimicrobials in mastitis is the IMM route. The advantages of this route are high concentrations of the substance achieved in the milk and low consumption of the antimicrobial as the drug is directly infused into the diseased quarter. For example, concentration of penicillin G in milk after IMM administration is 100-1000 times as high as the concentration after systemic (parenteral) administration (Franklin *et al.* 1984, 1986; Ziv and Storper 1985; Moretain and Boisseau 1989). A disadvantage of the

IMM administration is uneven distribution throughout the udder (Ullberg *et al.* 1958; Ehinger and Kietzmann 2000a, 2000b) and the risk of infecting the quarter when infusing the product via the teat canal. Efficacy of IMM treatment varies according to the causative pathogen, with the best therapeutic response being shown for mastitis caused by streptococci, coagulase-negative staphylococci, and *Corynebacterium spp.*.

The systemic route of administration has been suggested to be more efficient than IMM for the treatment of clinical mastitis as antimicrobials theoretically have better penetration of the udder tissue by this route (Ziv 1980; Erskine 2003). However, it is difficult to attain and maintain therapeutic concentrations in milk or udder tissue following systemic administration. Very few substances have optimal pharmacokinetic and pharmacodynamic characteristics for systemic mastitis treatment. With many commonly used broad-spectrum antimicrobials such as oxytetracycline, trimethoprim-sulphonamide and ceftiofur, it is difficult to produce and maintain therapeutic concentrations in the milk (Erskine *et al.* 1995; Kaartinen *et al.* 1999). They have been tested for systemic treatment and prevention of mastitis with poor efficacy (Erskine and Barlett 1996; Kaartinen *et al.* 1999; Duenas *et al.* 2001; Lents *et al.* 2002). Macrolides would have ideal pharmacokinetics (Franklin *et al.* 1986; Sanders *et al.* 1992), but clinical studies have failed to demonstrate efficacy when used for the systemic treatment of clinical mastitis (Pyörälä and Pyörälä 1998; Owens *et al.* 1999). In streptococcal mastitis, spiramycin and tylosin have shown reasonable efficacy (Pyörälä and Pyörälä 1998; McDougall *et al.* 2007). One additional problem for the bovine practitioner is that the recommended dosage for many antibiotic preparations for adult cattle may be too low when pharmacological aspects are considered, but residue studies have been carried out using the approved dosages. Repeated intramuscular injections of large volumes of antibiotics can be irritating and cannot be recommended from the animal welfare point of view (Pyörälä *et al.* 1994b; Kaartinen *et al.* 1999).

One substance used for systemic treatment is penicillin G, which as a weak acid penetrates poorly into the mammary gland, however, due to the very low MIC values of susceptible organisms, therapeutic concentrations can be achieved in milk (Franklin *et al.* 1984, 1986; Ziv and Storper 1985). Penethamate is a more liphophilic penicillin G formulation and diffuses better than penicillin G procaine into milk (Ziv and Storper 1985). The efficacy of systemic treatment with penicillin G or penethamate has been shown in clinical trials (Jarp *et al.* 1989; Waage 1997; Pyörälä and Pyörälä 1998; McDougall *et al.* 2007). Combinations of penicillin and aminoglycosides should not be used, as there is no scientific evidence demonstrating a better efficacy for the combination (Taponen *et al.* 2002) and aminoglycosides are known to produce long-lasting residues (Jones and Ward 1990; Whittem and Hanlon 1997).

The only type of mastitis where systemic treatment would be clearly advantageous may be mastitis caused by *S.*

Table 1: Where to target antimicrobial therapy in clinical mastitis due to different pathogens (Erskine 2003)

	Milk/ducts	Udder tissue	Cow
Streptococcus agalactiae	+++	---	---
Other streptococci	+++	+	---
Staphylococcus aureus	+	+++	---
Coagulase-negative staphylococci	+++	---	---
Arcanobacterium pyogenes (summer mastitis)	---	++	+++
Coliforms	+	--	+++

aureus (Taponen et al. 2003; Barkema et al. 2006). In severe mastitis due to coliform bacteria, parenteral administration of antimicrobials has been suggested to combat bacteraemia (Wenz et al. 2001). The general benefit of antimicrobial treatment in coliform mastitis has been questioned (Jones et al. 1990; Pyörälä et al. 1994a), but systemic antimicrobial treatment is recommended in cases of severe Escherichia coli mastitis with heavy bacterial growth in the udder. Fluroquinolones and cefquinome have shown efficacy in experimental trials (Shpigel et al. 1997; Dosogne et al. 2002; Rantala et al. 2002; Poutrel et al. 2008) and ceftiofur in a clinical field trial (Erskine et al. 2002). There is no evidence that administering bactericidal antimicrobials to cows with severe coliform mastitis causes the release of massive amounts of endotoxin (Dosogne et al. 2002). Finally, the antimicrobial used for systemic treatment of mastitis must be approved for dairy cattle. The availability of substances on the market differs between countries. For example, penicillin G procaine or fluoroquinolones are not approved for dairy cattle in the United States.

TREATMENT OF CLINICAL MASTITIS IN PRACTICE

Treatment of mastitis should be targeted towards the causative bacteria whenever possible, but in acute situations, treatment is initiated based on herd data and personal experience. Rapid or on-farm bacteriological diagnosis would facilitate the selection of the most appropriate antimicrobial. Treatment protocols and drug selection for each farm should be made by veterinarians familiar with the farm (Sawant et al. 2005; Wagner and Erskine 2006). The use of on-farm written protocols for mastitis treatment can promote judicious use of antimicrobials (Raymond et al. 2006; Passantino 2007). Therapeutic response of the cows can be monitored using individual somatic cell count data if available, or using the California Mastitis Test, and with bacteriological samples in herds with contagious mastitis.

In general, the use of narrow-spectrum antimicrobials is preferable (Table 2). Prudent use guidelines have been developed which also include antimicrobial treatment

of mastitis (Anon 2003; Passantino 2007). First choice antimicrobials for treating mastitis caused by streptococci and penicillin-susceptible staphylococci are β-lactam antimicrobials, particularly penicillin G. Broad-spectrum antimicrobials such as third or fourth generation cephalosporins should not be used as first alternatives for mastitis, as they may increase emergence of broad-spectrum β-lactam resistance. Systemic treatment is recommended in clinical mastitis due to S. aureus and in severe cases of coliform mastitis, preferably in combination with IMM treatment (Barkema et al. 2006). Too short a duration of standard treatment is probably an important reason for poor cure rates in mastitis therapy. A longer treatment improves cure rates, and duration of treatment should generally be extended in mastitis caused by S. aureus and Streptococcus uberis (Pyörälä and Pyörälä 1998; Oliver et al. 2004; Deluyker et al. 2005). Clinical mastitis should be treated for at least three days; this recommended treatment duration is longer than label treatments in many countries. All mastitis treatment should be evidence based i.e., the efficacy of each product and treatment length should be demonstrated by scientific studies (Cockcroft and Holmes 2003).

SUBCLINICAL MASTITIS

Treating subclinical mastitis with antimicrobials is generally not economical during lactation because of high treatment costs and poor efficacy. In a study with a large number of subclinical mastitis cases (Wilson et al. 1999), the overall bacteriological cure rate for antimicrobial treatment was 75% and that for no treatment 68%. The marginal benefit applied for streptococcal mastitis only; in mastitis due to S. aureus, antimicrobials were equal to no treatment. Treatment of subclinical mastitis will not affect the incidence of mastitis in the herd unless other preventive measures are taken. Studies on treating cows based on high somatic cell counts have generally shown that no effect on milk production has been achieved (McDermott et al. 1983; Shephard et al. 2000, Hallén Sandgren et al. 2008) In herd problems caused by very contagious bacteria such as S. aureus or Streptococcus agalactiae treatment of subclinical mastitis is advised (Wagner and Erskine 2006).

Table 2: Suggestions for antimicrobial treatment of clinical mastitis due to different pathogens. The availability of substance on the market mentioned in the table may differ between countries

Micro-organism	Species	Drug of choice	Alternative	Comments
Streptococci	Streptococcus agalactiae Streptococcus dysgalactiae Streptococcus uberis Enterococci	Penicillin G According to susceptibility testing		IMM treatment preferable. Prognosis for bacteriological cure is poor
Staphylococci	Staphylococcus aureus Coagulase negative staphylococci ß-lactamase -ve Staphylococcus aureus Coagulase negative staphylococci ß-lactamase +ve	Penicillin G No antimicrobials	Cloxacillin Macrolides Lincosamides	Combination treatment in S. aureus mastitis IMM and/or systemic treatment depending on the drug used. Prognosis for S. aureus mastitis is poor. Cloxacillin may select for methicillin-resistant
Coliforms	Escherichia coli Klebsiella spp.	No antimicrobials	Fluoroquinolones Cephalosporins	Antimicrobials necessary in serious cases and during puerperal period

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