Combination therapy for mastitis in dairy herds: evidence and research

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James Breen, Chris hudson, Martin Green and Andrew Bradley discuss the merits of evidence-based medicine, considering study findings that look at the different antibiotic and NSAID options available

Summary

Evidence-based veterinary medicine can be described as a synthesis of research, experience and the requirements of the individual animal or group. As the research in an area strengthens, our reliance on experience should become less, although the treatment of clinical and subclinical mastitis in dairy cows is a good example of where personal opinion and experience predominate, as clinically relevant research is often lacking. Decisions regarding therapy are rarely based on an understanding of the current cure rate in the herd; monitoring of cure rates for clinical and subclinical mastitis represent an essential part of herd health. The fact that herds with excellent cure rates for the first clinical case in lactation are unlikely to have access to “better” drugs suggests that other factors are important. These are likely to include rapid identification and prompt treatment of clinical cases, administration of a full treatment course and pathogen patterns on that farm. Apparent cure rates are also affected by the rate of new infection and often the most cost effective (and most appropriate) way to enhance the apparent cure rate is to minimise the rate of new infection – this is particularly important across the dry period. This article discusses combination therapy in bovine mastitis treatment, including antibiotic dry cow therapy with an internal teat sealant, antibiotic dry cow therapy with systemic antibiotic, combination antibiotics to treat clinical and subclinical mastitis and the use of an antibiotic plus NSAIDs in clinical mastitis treatment.

Key words

dairy cows, mastitis, evidence-based medicine, combination treatment

EVIDENCE-based veterinary medicine (EBVM) can be defined as the integration of best research evidence with clinical expertise and patient values – in our case, the farmer and cow (Sackett et al, 2000).

EBVM should, therefore, be a synthesis of research, experience and the requirements of the situation, but as the research in an area strengthens, our reliance on experience should become less. However, this does require us to look at new evidence and evaluate it.

Treating clinical and subclinical mastitis in dairy cows is a good example of where personal opinion and experience predominate, as clinically relevant research is often lacking. Randomised clinical trials are few and far between, and we are forced to rely on anecdotes and opinion from areas of the profession. EBVM should help us make better clinical decisions, enhance mastitis control and help us direct future mastitis research. A strong trend exists for UK-based mastitis research to translate into changes on the ground. Examples include differential dry cow therapy (Bradley and Green, 2001), use of an internal teat sealant (Huxley et al, 2002), the national DairyCo mastitis control plan (Green et al, 2006) and dry period management strategies (Green et al, 2007).

Searching for research evidence for clinically relevant questions has now become much simpler with the development of the internet – as most publications and abstracts from all the references used in this article can be accessed using Pub-Med online (www.ncbi.nlm.nih.gov/pubmed).

This article attempts to summarise thinking surrounding a potentially difficult and often controversial topic for practitioners in dairy practice.

Expectations and implications

Effective intra-mammary infection (IMI) treatment remains a cornerstone of any mastitis plan to prevent the build up of infected cows within a herd. However, the interaction between bacteriological cure, resolution of clinical symptoms and a “true” failure to cure is complex.

Following infection of the gland and treatment, we could have persistence of the original IMI despite treatment, recurrence of clinical signs following a clinical (but not bacteriological) cure of the original IMI or a new IMI following bacteriological cure of the original IMI.

To make rational decisions regarding treatment for individual herds, it is important to assess treatment outcomes and measure cure rates.

Decisions regarding therapeutic strategies are rarely based on understanding the current clinical case cure rate in the herd, but this is an essential parameter to include in routine herd health monitoring.

In this context, it is worth considering how cure rates can be assessed. This clearly depends on an effective method of determining treatment outcomes in a clinical mastitis case. Routine bacteriology of cases pre and post-treatment would be extremely expensive, and has variable sensitivity for detecting different organisms.

Using individual cow somatic cell counts (SCC) is a much cheaper method, has been shown to be a good proxy for IMI and can be repeated to look for a reduction below a threshold over a certain period of time. In practice, a useful definition of a cure in lactation is a three-monthly cow SCC of less than 200,000 cells/ml or two-monthly cow SCC of less than 100,000 cells/ ml with no recurrence of clinical mastitis within that time.

The clinical mastitis cure rates from 413 herds monitored as part of the current DairyCo mastitis initiative during summer 2010 showed a mean figure of 41 per cent to the first case and 26 per cent for all cases, but the range was very large. In a 52-herd UK study, cure rates across the dry period averaged just more than 70 per cent, with no correlation between lactation and dry period cure rates for any herd – but large variations between herds (unpublished data). Examples of measuring cure rates are shown in Figure 1.

The fact that herds with excellent cure rates for the first clinical case in lactation are unlikely to have access to “better” drugs suggests other factors are important. These are likely to include rapid identification and prompt treatment of clinical cases, administration of a full treatment course and pathogen patterns on that farm.

Factors that affect clinical cure were investigated in a large European study and included pathogen (*Staphylococcus aureus*), rectal temperature, chronicity of infection, treatment (different cephalosporinbased intra-mammary preparations), country of origin and season (Bradley and Green, 2009).

Factors that affect the cure of subclinical IMI are well described and include parity, number of quarters infected, pathogen (species and strain), chronicity of infection, treatment duration, udder pathology and bulk milk SCC (Deluyker et al, 2005; Osteras et al, 1999; Sol et al, 2000; St Rose et al, 2003).

Antibiotic dry cow therapy (DCT) often represents the largest annual investment in dairy herd preventive therapy and may be supplemented with systemic antibiotics and internal teat sealants due to a belief that antibiotic DCT may not be as effective in certain herds. The role of antibiotic DCT is to cure existing IMIs (mainly gram-positive pathogens) and then prevent new IMIs (gram-positive and gramnegative pathogens), but not all products manage both – and antibiotic DCT can

never be a prop for poor management (Figure 2).

In the absence of antibiotic DCT, the prevalence of coagulasepositive *Staphylococci* is increased. However, for the majority of herds that use antibiotic DCT, the most prevalent pathogen in the udder at calving is *Escherichia coli*.

As in lactation, the relationship between cure and new IMIs across the dry period is a complex one (Figure 3) and the effect of “true” failure to cure is often over-played. For many dairy herds, the largest influence on apparent dry period cure rate is the rate at which new IMIs occur, with the dry period’s new infection rate responsible for 20 per cent of the variation seen in the dry period cure rate, according to one UK study (unpublished data).

This means that for many dairy herds, the most cost-effective (and the most appropriate) way to enhance the apparent cure rate across the dry period is to minimise the rate of dry period new infections, when the latter is poorly controlled and above target.

Examples of combination therapy used in practice

• Antibiotic DCT and internal teat sealant – to combine or not to combine?

The outcomes and consequences of antibiotic DCT will differ in different herds and in different cows within the same herd.

A consequence of increased antibiotic DCT use in herds is a potential shift toward more gram-negative mastitis, while a decreased use of antibiotic DCT is often associated with a shift toward more gram-positive mastitis.

A large, randomised control study in low-SCC UK herds compared the use of cephalonium and internal sealant alone and in combination in cows stratified by infection status at drying-off (both high and low SCC cows; Bradley et al, 2010). There were clear potential benefits from combination use, but this was most marked in infected cows at drying-off.

The effect of combination therapy in uninfected cows was more complex.

In uninfected cows at drying-off, combination treated quarters were:

• half as likely to be infected with *Staphylococcal* and *Streptococcal* species at calving (1.41 per cent versus 2.94 per cent);

• significantly more likely to have an SCC lower than 200,000 cells/ml post-calving; but

• twelve times more likely to develop clinical coliform mastitis when compared with low SCC

quarters that had just received internal teat sealant alone (1.47 per cent versus 0.12 per cent).

Practically speaking, cephalonium offers excellent grampositive major pathogen control, and supplementing cephalonium treatment with an internal teat sealant enhances the chances of a successful dry period outcome in cows infected at dry off.

However, supplementing an internal teat sealant with cephalonium in cows uninfected at dry-off, while enhancing grampositive mastitis control, came at the expense of gram-negative pathogen control in this study. This is a good example of where the breadth of antibiotic use needs to be tempered by the individual herd situation.

• **Antibiotic DCT and systemic antibiotic (such as macrolide)**

The use of a systemic antibiotic (usually administered at dryingoff) in combination with antibiotic DCT has been advocated by practitioners to increase the chance of curing an existing IMI.

True pathogen-specific cure rates (minimising and/or removing the effect of dry period new infections) in dairy herds using antibiotic DCT are usually very high to begin with – for example, one UK study reported apparent cure rates of existing IMI with major pathogens to be more than 90 per cent for quarters receiving cephalonium (Bradley et al, 2010).

This result suggests there is extremely limited scope to improve true cure rates across the dry period. Therefore, we must consider:

• Is a combination (intra-mammary plus systemic antibiotic) approach cost-effective?

• Is this prudent use of antimicrobials in production animals?

• Could it be justified for the “valuable cow”?

A search of the literature for peer-reviewed evidence in this area is unrewarding – for example, only one paper exists that compares the use of systemic tilmicosin with antibiotic DCT (Nickerson et al, 1999). The study used 44 cows split into three treatment groups, none of which included a group treated with antibiotic DCT and systemic tilmicosin. The group receiving systemic tilmicosin alone had a dry period cure rate of nine per cent, from which we could infer that this may be the maximum effect we might expect the apparent dry period cure rate to increase by if we advise a combination approach.

However, if true cure rates with antibiotic DCT are already more than 90 per cent, how many combination treatments would we need to perform to gain one or two “extra” cures above what we would already get?

• **Combination antibiotic to treat mastitis in lactation**

Field studies based in the UK, France and Germany compared the treatment of clinical mastitis using different cephalosporinbased intra-mammary tubes:

• a combination cephalexin and kanamycin; and

• cefquinome and cefoperazone (Bradley and Green, 2009).

Quarters in the combination cephalexin/kanamycin and cefquinome-treated groups were significantly more likely to be pathogen free post-treatment when compared to the cefoperazone-treated group.

However, in the study, actual cure rates in lactation probably exceeded the apparent cure rates, as new infection rates were high for some pathogens (secondary invasion with other pathogens is a likely sequela to treatment).

In reality, very few comparative studies look at the different antibiotics used to treat clinical mastitis in lactation, and attempting to answer questions relating to specific products on individual farms is almost impossible.

Very little published evidence exists to support the addition of systemic antibiotic to mastitis tubes. Studies that have been performed report no significant differences between treatment groups, although Schpigel et al (1997) reported the benefits of the combination use of cefquinome for treating clinical coliform mastitis.

• **Combination therapy in the treatment of subclinical mastitis in lactation**

Treatment of high-SCC cows with antibiotics during lactation is often performed (with or without segregation of infected cows), but cure rates for IMIs during the dry period will almost always be higher compared to cure rates in lactation.

Duration of intra-mammary antibiotic therapy is positively associated with rate of cure (Oliver et al, 2004; Deluyker et al, 2005) but no peer-reviewed evidence suggests that the addition of a systemic antibiotic results in a greater likelihood of cure, although in cows with multiple quarters infected, a systemic product would seem to be a logical choice.

• **Antibiotic and NSAID in the treatment of clinical mastitis**

A study concerning treating naturally occurring acute *E coli* mastitis compared supportive treatment with ketoprofen and fluid therapy with and without systemic enrofloxacin in 132 Finnish Ayrshire and Holstein Friesian cows (Suojala et al, 2010).

Overall, combination treatment with enrofloxacin and ketoprofen did not increase the bacteriological or clinical cure rate, cow survival or quarter milk production post-treatment. In addition, no reported difference between the treatment groups was evident when mam mary gland tissue damage was assessed using milk N-acetyl-?-d-glucosaminidase (NAGase) activity, providing evidence that antibiotic therapy may be of limited value compared to supportive treatments when treating *E coli* mastitis. However, the lack of a reported difference does not mean that a difference didn't exist – it may be that the difference was small and the study lacked sufficient power.

In another peer-reviewed publication, the effect of combination therapy using meloxicam and systemic penethamate in New Zealand was studied (McDougall et al, 2009). The authors hypothesised that treating clinical mastitis with a combination of meloxicam and parenteral penethamate hydriodide would result in lower SCC, reduced milk loss, an improved clinical outcome and reduced culling rate when compared to antibiotic alone. The welldesigned, double-blinded, randomised control study included 727 cows with clinical mastitis from 15 herds. There was no difference between the treatment groups in the number of cows that were defined as treatment failures or the milk yield over a period of 200 days post-treatment. However, the study did report a lower SCC and fewer cows culled in the combinationtreated cows.

While these are interesting findings, this paper is a good example of how we interpret research findings in the context of our decision making on farm. On the basis of this study, would we now advise blanket NSAID use for all mild and moderate cases of clinical mastitis? Farmers may interpret, for example, these findings as meaning that this combination approach will decrease their bulk milk SCC. However, although the geometric mean SCC was lower in the combination-treated group, there was no interaction between treatment group and days post-treatment (there was no significant difference between geometric SCC at day seven, 14 or 21 post-treatment).

The culling data also showed significantly fewer cows culled from the combination-treated group (39/237 versus 67/237, P