



In Dairy Cows with Clinical Mastitis Do Systemic Antimicrobials in Addition to Intramammary Antimicrobials Improve Clinical Cure Rates Compared to Intramammary Antimicrobials Only?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

Clinical bottom line

In spite of limitations to the available studies, in cattle with clinical mastitis and an absence of systemic signs there is no evidence that combined systemic and intramammary antimicrobial therapy improves clinical cure rates compared to intramammary antimicrobial therapy only.

In two studies, cattle with severe coliform mastitis showed improved clinical parameters following combined systemic and intramammary antimicrobial therapy compared to intramammary antimicrobial therapy only.

Question

In dairy cattle with clinical mastitis do systemic antimicrobials AND intramammary antimicrobials versus intramammary antimicrobials only improve clinical cure rates?

The evidence

The PICO question in this case was not the focus of any of the studies, however the relevant comparisons were available within the results. With the exception of Swinkels et al. (2013), the studies generally included small numbers of cows.

Summary of the evidence

Erskine (2002)	
Population:	Dairy cows with severe clinical mastitis (mastitis and at least two indicators of systemic disease) across six herds.
Sample size:	n = 104
Intervention details:	<ol style="list-style-type: none">1. n = 51 treated with intramammary pirlimycin (50mg, every 24 hours, 3 day duration) and intramuscular ceftiofur (2.2mg/kg, every 24 hours, 5 day duration)2. n = 53 treated with intramammary pirlimycin (50mg, every 24 hours, max 3 day duration)
Study design:	Randomised positive controlled trial
Outcome studied:	Clinical cure rate, 30 day survival (culling or death)
Main findings: (relevant to PICO question):	<p>No significant difference between cure rates in either group.</p> <p>In cases of clinical mastitis caused by coliform organisms there was statistically higher survival in the group treated with combined treatment (intramammary pirlimycin and intramuscular ceftiofur) compared to the group treated with intramammary pirlimycin only.</p>
Limitations:	<ul style="list-style-type: none">• No blinding• Adjunctive therapy not standardised across sites, in some

	<p>situations adjunctive therapy included systemic corticosteroids which are controversial</p> <ul style="list-style-type: none"> • Duration of intramammary treatment varied between herds • Clinical cure assessed subjectively - no data regarding bacteriological cure or somatic cell count • Follow up limited to 30 days post-detection. Significant outcomes such as milk yield and long-term culling risk not included.
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Wenz (2005)	
Population:	Dairy cows on a single site with mild clinical mastitis in one quarter with a positive milk culture
Sample size:	n = 144
Intervention details:	<ol style="list-style-type: none"> 1. n = 35 treated with intramammary pirlimycin (50mg, every 24 hours, 2 day duration) 2. n = 36 treated with intramammary pirlimycin (50mg, every 24 hours, 2 day duration) and intramuscular ceftiofur (2.2mg/kg, every 24 hours, 3 day duration) 3. n = 40 treated with intramammary cephaparin (200mg, every 12 hours, 3 day duration) 4. n = 33 treated with intramammary cephaparin (200mg, every 12 hours, 3 days) and intramuscular ceftiofur (2.2mg/kg, every 24 hours, 3 day duration)
Study design:	Randomised positive controlled trial (Short communication)
Outcome studied:	Clinical cure rates, rate of recurrence 15 – 90 days post-detection, bacteriological cure at 7 days post-treatment, loss of quarter, culling and death.
Main findings: (relevant to PICO question):	<p>No significant difference in recurrence across groups</p> <p>No significant difference for any outcome across treatment groups. There was a numerical improvement in bacteriological cure at 7 days post-treatment for both groups treated with intramuscular ceftiofur in addition to the intramammary antimicrobial (27% vs 45% and 33% vs 52% for 1 and 2 and groups 3 and 4 respectively).</p>
Limitations:	<ul style="list-style-type: none"> • Small group sizes • Pre-intervention differences between treatment groups not discussed • Randomisation technique not stated • Culling decisions are usually multifactorial and although culling for mastitis is used as a negative outcome for this study, previous mastitis or cell count history and factors not related to udder health will influence the decision to cull • Only cases with a positive milk culture included which may reduce the applicability of the results to clinical practice (i.e. not applicable for empirical treatment) • Outcomes such as individual cow somatic cell count data

	<p>and milk yield not recorded</p> <ul style="list-style-type: none"> • Use of mastitis vaccine reduces clinical relevance of study to many herds in UK • Follow-up limited to 90 days post-detection
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Hillerton and Kliem (2002)	
Population:	Dairy cows on a single site, experimentally infected with <i>Streptococcus uberis</i> in two quarters
Sample size:	n = 54 (total of 81 quarters included in study). Of these, 39 quarters included that are relevant to PICO question.
Intervention details:	<p>(n refers to quarters not cows)</p> <ol style="list-style-type: none"> 1. n = 11 untreated 2. n = 10 treated with intramammary penthemate (150mg), dihydrostreptomycin (150mg), framycetin (50mg) and prednisolone (5mg); every 12 hours for a 3 day duration 3. n = 11 treated with intramuscular penicillin (8mg/kg) and dihydrostreptomycin (10mg/kg) every 24 hours for a 3 day duration 4. n = 18 treated with intramammary penthemate (150mg), dihydrostreptomycin (150mg), framycetin (50mg) and prednisolone (5mg); every 12 hours for a 3 day duration and intramuscular penicillin (8mg/kg) and dihydrostreptomycin (10mg/kg) every 24 hours for a 3 day duration 5. n = 11 treated with intramammary penthemate (150mg), dihydrostreptomycin (150mg), framycetin (50mg) and prednisolone (5mg); every 24 hours for a 3 day duration 6. n = 10 treated with intramuscular oxytocin (80IU at first milking then 20IU at the subsequent 5 milkings) 7. n = 10 treated with 11 treated with intramammary penthemate (150mg), dihydrostreptomycin (150mg), framycetin (50mg) and prednisolone (5mg); every 24 hours for a 3 day duration and intramuscular oxytocin (80IU at first milking then 20IU at the subsequent 5 milkings)
Study design:	Prospective cohort study (randomisation abandoned half-way through study)
Outcome studied:	<ul style="list-style-type: none"> • Clinical cure • Bacteriological cure • Somatic cell count recovery
Main findings: (relevant to PICO question):	No statistical difference in cure rate or bacteriological cure between groups receiving intramammary antimicrobials compared to group receiving intramammary and intramuscular antimicrobials.
Limitations:	<ul style="list-style-type: none"> • Randomisation replaced with allocation during the trial • One group (combined intramammary and intramuscular antimicrobials) expanded after initial results

	<ul style="list-style-type: none"> • Different quarters on the same cow included in different treatment groups – systemic treatments avoided but crossover of intramammary treatments between adjacent quarters may affect results. • Not all cows/quarters accounted for in results – missing data briefly mentioned but no detail relating which treatment groups. • No blinding • Trial over three phases so potential for environmental factors to change between treatment groups • Group comparisons at start of study not discussed • Strain of <i>Streptococcus uberis</i> used with known antimicrobial sensitivity which limits clinical relevance • Follow-up limited to 21 days post-infection
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Shipgel (1997)	
Population:	Dairy cows on a single site, experimentally infected with Escherichia coli in two quarters
Sample size:	n = 47
Intervention details:	<ol style="list-style-type: none"> 1. n = 12 treated with intramammary cefquinome (75mg, every 12 hours, 3 treatments) 2. n = 12 treated with intramammary cefquinome (75mg, every 12 hours, 3 treatments) and intramuscular cefquinome (1mg/kg, every 24 hours, 2 treatments) 3. n = 12 treated with intramuscular cefquinome (1mg/kg, every 24 hours, 2 treatments) 4. n = 11 treated with amoxicillin and cloxacillin (75mg and 200mg respectively, every 12 hours, 3 treatments)
Study design:	Randomised positive controlled trial
Outcome studied:	Clinical mastitis score (based on demeanour, milk appearance, quarter characteristics, rectal temperature, rumen contractions, heart and respiration rate) Milk cultures and California Mastitis Tests Haematology and biochemistry
Main findings: (relevant to PICO question):	<p>No significant difference in clinical cure (measured by clinical mastitis score) or bacteriological cure between groups receiving intramammary cefquinome compared to group receiving intramammary and intramuscular cefquinome.</p> <p>Bacterial cure rate numerically higher for intramammary and intramuscular cefquinome group than intramammary cefquinome group (95.2% vs 82.6%)</p> <p>Various clinical parameters indicated an improved clinical response in the group treated with intramammary and intramuscular cefquinome compared to cows treated with intramammary cefquinome only. The parameters where a statistical difference was noted were the decrease in rumen contractions, decrease in</p>

	<p>leukocytes, and peak in urea and creatinine.</p> <p>There was a statistically significant reduction in milk production post-infection in the group treated with intramammary cefquinome compared to the group treated intramammary and intramuscular cefquinome.</p>
Limitations:	<ul style="list-style-type: none"> • Trial designed to test different hypothesis to PICO question (cefquinome vs amoxicillin/cloxacillin) - therefore relevant results and statistical analysis not always easy to extract. • Clinical assessment with clinical mastitis score - individual parameters not given. • Randomisation technique not stated • California mastitis test used in place of quantified somatic cell count data. • Follow up limited to 14 days post-challenge • Strain of <i>Escherichia coli</i> used with known antimicrobial sensitivity which limits clinical relevance

Swinkels (2013)	
Population:	Dairy cows across three herds with high rates of recurrent, environmental clinical mastitis. Cows included with clinical mastitis of all grades (mild to severe).
Sample size:	n = 994 Of these, 689 treated in a way relevant to PICO question
Intervention details:	<ol style="list-style-type: none"> 1. n = 305 treated with intramammary cefquinome (75mg, two consecutive milkings on day one followed by the morning milking on day two) 2. n = 318 treated with intramammary cefquinome (75mg, two consecutive milkings on day one followed by the morning milking for four consecutive days) 3. n = 371 treated with intramammary cefquinome (75mg, two consecutive milkings on day one followed by the morning milking for four consecutive days) intramuscular cefquinome (1mg/kg, every 24 hours, five day duration)
Study design:	Randomised positive controlled trial
Outcome studied:	Cure rate assessed subjectively by trained personnel. Recurrence monitored until 105 days post-treatment. Cows followed for 105 days following initial treatment. Recurrence assessed at both cow and quarter level.
Main findings: (relevant to PICO question):	No statistical difference between cure rate or rate of recurrence between the group treated with intramammary cefquinome for 5 days and the group treated with intramammary cefquinome and intramuscular cefquinome for 5 days. No statistical difference at cow or quarter level.
Limitations:	<ul style="list-style-type: none"> • Trial not designed to compare outcomes between groups relevant to PICO question (groups 2 and 3) but lack of

	<p>difference in outcome apparent and discussed.</p> <ul style="list-style-type: none"> Missing data acknowledged but not clear from which treatment groups data are missing. 124 cows received NSAIDs in addition to antimicrobials; 106 cows received systemic antimicrobials off study protocol - these cows were not excluded from the trial and the group allocation is not stated. Although randomisation used, herd personnel had discretion to assign cows to treatment groups - number of 'non-randomised' cows not clear.
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Appraisal, application and reflection

The most pertinent question is whether in cases of clinical mastitis without systemic clinical signs there is a benefit to systemic antimicrobials in addition to intramammary antimicrobials. It may have been more helpful to look at treatment approaches for mild and moderate mastitis separately to severe mastitis, however, this approach would have resulted in the exclusion of at least one study (Swinkels et al 2013) where the study population included mixed severities of clinical mastitis.

The lack of demonstrable benefits of systemic antimicrobials in addition to intramammary antimicrobials for mild and moderate mastitis is relevant as this is relatively common practice; but the limitations of these studies should be considered. The benefits of combined systemic and intramammary antimicrobials for severe coliform mastitis are interesting although expected as the merits of systemic antimicrobials are more established in these cases.

The stated aims from these five studies were not directly focused on answering the PICO question, however, all provided the data for necessary comparisons to be made. The studies were of mixed but typically good quality and generally, with the exception of Swinkels et al (2013), included a small number of cows.

Clinical cure rate is a vague parameter with all studies using subjective assessment as the primary indicator of both clinical disease and cure. More objective and reliable outcomes such as bacteriological cure were used in some but not all studies.

Methodology Section

Search Strategy	
Databases searched and dates covered:	Pubmed and CAB Abstracts 1973 - Present
Search terms:	<p>cow OR cows OR cattle OR bovine OR bovines OR bos AND mastitis OR intramammary infection AND parenteral OR systemic OR inject* AND iotics OR antimicrobials</p>
Dates searches performed:	<p>Pubmed: 06/05/2016 CAB Abstracts: 01/09/2015</p>

Exclusion / Inclusion Criteria	
Exclusion:	Reviews, economic models, in-vivo studies, conference proceedings, book chapters, foreign language articles.
Inclusion:	Studies where comparison was possible between two groups treated with systemic antimicrobials in addition to the same intramammary antimicrobial. Mainly randomised control trials.

Search Outcome					
Database	Number of results	Excluded – not relevant to PICO question	Excluded – statistical model, review, book chapter etc.	Excluded – not available in the English language	Total relevant papers
NCBI PubMed	238	233	0	0	5
CAB Abstracts	849	838	6	2	3
Total relevant papers when duplicates removed					5

CONFLICT OF INTEREST

The author declares no conflict of interest.

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