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Comparative effectiveness of interventions for treating interdigital necrobacillosis in cattle: A network meta-analysis

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Abstract: The aim of this study was to comparatively evaluate the efficacy of different antimicrobial agents against interdigital necrobacillosis (IN) in cattle to identify the treatment with the greatest benefit. A network meta-analysis was used to synthesise empirical results from randomised controlled trials. Four studies with five interventions for 565 animals were included. The meta-analysis found no significant differences between the risk ratios for the antimicrobials versus placebo. However, ceftiofur sodium administered intramuscularly at a dose of 1.0 μg/kg body weight every 24 h for 3 days showed a better clinical response than 6.6 μg of oxytetracycline, 2.5 μg of tulathromycin, the placebo and 0.1 μg of ceftiofur sodium. The results show the best efficacy for 6.6 μg of oxytetracycline and 1.0 μg of ceftiofur sodium. Nevertheless, the latter is likely to be superior to oxytetracycline in terms of its pharmacodynamic and pharmacokinetic properties. Thus, 1.0 μg of ceftiofur sodium appears to provide the best therapeutic activity against IN in cattle. Further well-designed studies are required.

Keywords: antibiotic; ceftiofur sodium; foot rot; oxytetracycline; tulathromycin

Concerning cattle, interdigital necrobacillosis (IN) is a disease of a polymicrobial nature with *Fusobacterium necrophorum* playing a crucial role in its inception and progression, besides *Dichelobacter nodosus* as a secondary aetiological agent (Bay et al. 2018; Kontturi et al. 2019). IN jeopardises the welfare of the affected animals, and it is associated with an increased risk of culling (Booth et al. 2004). The clinical presentation of IN includes lameness, which is associated with diminished animal fertility in the forms of delayed ovarian activity during the early postpartum period and an increment in the calving to first service interval (Kilic et al. 2007). The quantity and the quality of milk decline, owing to the stress caused by pain arising from lameness and to the reduced nutrient intake, since pasture grazing becomes difficult for lame dairy cattle (Ozsvari 2017). Recumbency related to lameness supposedly enhances the risk of mastitis (Afonso et al. 2020). Other clinical signs are necrotic, ulcerative, and foul-smelling lesions in the interdigital tissue, fever, body temperature elevation, appetite reduction, and swelling of the foot that may potentially turn into separation of the digits (Van Metre 2017; Scott

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2018). Secondary complications include septic arthritis of the distal interphalangeal joint, necrotic tendinitis, navicular bursitis, and abscessation of the retroarticular space (Desrochers 2008).

The prevalence of bovine IN on farms and clinical levels fluctuating from 2.2% to as high as 74.5% in a variety of countries has been recently documented (Oberbauer et al. 2013; Ramanoon et al. 2018; Davis-Unger et al. 2019; Dendani-Chadi et al. 2020; Islam et al. 2020; Mishra et al. 2020). Data on the approximate magnitude of cost per case for IN are contradictory. For instance, it was estimated to be 8 and 121 USD by Dolecheck et al. (2018) and Cha et al. (2010), respectively. Furthermore, the cost could reach 320 EUR, as transpires from the research carried out by Ozsvari (2017).

In the event of uncomplicated, early diagnosed IN, the disease management strategy may be limited to local treatment with diverse chemotherapeutic agents, such as *Lactobacillus acidophilus* (Tulemissova et al. 2020), salicylic acid powder (Persson et al. 2019) or leaves of *Helichrysum appendiculatum* and *Clausena anisata* (Masika and Afolayan 2003). Otherwise, the systemic administration of antimicrobial agents is required. Despite there being numerous approved drugs for the treatment of bovine foot rot, such as gamithromycin or enrofloxacin (Van Metre 2017; Strobel et al. 2018), the number of those presently used in cattle is very limited. For instance, sulfabromomethazine and sulfaethoxypyridazine are rarely applied nowadays (Papich 2018). The use of tilmicosin and florfenicol in adult dairy cattle is limited due to extremely long withdrawal times (Schrag et al. 2020). Beta-lactam antibiotics are known to inhibit the biosynthesis of peptidoglycans that are required for the formation of the bacterial cell wall. Although benzylpenicillin still being mentioned as an anti-foot rot remedy (Ibrahim et al. 2020), it has limited activity against gram-negative bacteria (among which is *F. necrophorum*) and is subject to hydrolysis by bacterial-produced hydrolysing enzymes, beta-lactamases (Soares et al. 2012). Ceftiofur, a broad-spectrum cephalosporin is now the drug of choice for treating foot rot, is active against gram-positive and gram-negative pathogens of veterinary importance, including β-lactamase-producing strains and it has no milk or meat withholding time. Oxytetracycline is also quite effective (Morck et al. 1998; Van Metre 2017).

A promising, but little-studied, approach to the disorder management is improving the clinical outcome through the regional intravenous perfusion of antibiotics, which is believed to augment the local drug concentrations markedly when compared to those achieved after systemic administration (Depenbrock et al. 2017).

Discussions are still ongoing about the costs related to the use of antibiotics in cattle, as well as the potential health and economic impacts of not using them (Lhermie et al. 2018; Sneeringer et al. 2020). Meanwhile, only a few well-planned trials assessing the curative efficacy of the drugs have been published. Due to the lack of investigations demonstrating the optimal therapy for cattle affected with IN, the current network meta-analysis was conducted in an attempt to overcome the problem of limited available comparisons and integrate robust evidence in this clinical area from randomised controlled trials (RCTs). A network meta-analysis is a statistical technique used to identify the best treatment for a condition by evaluating the comparative effectiveness and harm of three or more relevant medical interventions through indirect comparisons (Higgins et al. 2019).

MATERIAL AND METHODS

Search strategy and selection criteria

The inclusion criteria were that the publications must have been non-clustered randomised controlled trials comparing pharmacological interventions with a placebo or other active drugs as the treatment of naturally occurring interdigital necrobacillosis in cattle. The total number of animals allocated to each trial arm along with the cure rate percent must have been obviously indicated by the authors. Publications were identified from MEDLINE (through PubMed), the Cochrane Database of Systematic Reviews, the U. S. Food and Drug Administration database, and Embase from their inception to November 2020, with no language restrictions. The reference terms "interdigital necrobacillosis", "foot rot", "footrot", "panaritium", "infectious pododermatitis", "interdigital phlegmon", and "phlegmona interdigitalis" were utilised. The outcome of interest was the final cure rate of the treatment for the foot rot, as specified by the authors. The study selection and data extraction were carried out independently by the authors of this article (ERR and ASI). Following the extraction, the

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data were reviewed by another authors of this article (MAT and ZKT), with discrepancies resolved by a consensus-based discussion.

Data analysis

In order to the combine direct and indirect comparisons of the treatment's effectiveness for the different interventions, the data were synthesised using the Bayesian random-effects network meta-analysis model estimating the pooled risk ratios (RRs) along with their 95% credible intervals (95% CrIs). The ranking probabilities of the interventions were derived from the Bayesian mixed treatment comparison. The between-study standard deviation was observed as a measure of heterogeneity (variance in trial effects within a comparison). With the aim of assessing the between-trial variance in the underlying treatment effects between the comparisons, an evidence inconsistency evaluation was applied. All the computations were conducted by means of the online statistical tool developed by Owen et al. (2019). Details of the statistical analysis can be consulted in the same source. Since the set of studies included in our meta-analysis is small (n = 4), no subgroup analyses were performed.

Compliance with ethical guidelines

No ethics approval is required for this article, since there were no manipulations with human or animal subjects performed by any of the authors.

RESULTS

Overall, the analysis comprised four RCTs encompassing five interventions (active drugs or placebo) for 565 animals published between 1995 and 2008. More information on the included studies is provided in Table 1.

Figure 1 depicts the results of the evaluation of the inconsistencies among the included studies. Unfortunately, no P-values have been obtained from the analysis for some reason. Statistical experts emphasise that tests for inconsistency frequently fail to reveal the latter in view of their inherent underpower (Dias et al. 2014). Yet, these values for the differences between the direct and indirect evidence are comparable with those obtained by Owen et al. (2019) from their example dataset and for which no statistical significance was detected. Thus, a lack of between-study inconsistency may be assumed. The between-study standard deviation (Figure 3A – legend) reflecting the extent of heterogeneity was found to be smaller than most of the pooled effect sizes, therefore there is no reason to be uncertain about the validity of the findings.

It appears from the Bayesian multiple testing results (Figure 2) that the ceftiofur sodium injected i.m. (intramuscularly) at a dose of 1.0 µg/kg b.w. (body weight) every 24 h for 3 days was the best treatment option against IN in cattle. Meanwhile, although the RR for ceftiofur sodium (1.0 µg) was greater than the RR for oxytetracycline (Figure 3A), the upper limit of the 95% CrI of the RR for oxytetracycline was higher. That might lead to the primacy shared between these interventions within the effectiveness ranking (Figure 3B–C).

Table 1. Characteristics of the included randomised controlled trials comparing different intervention regimens for the treatment of interdigital necrobacillosis in cattle

Study	Intervention	Cured/treated
FDA (1995)	1.0 µg ceftiofur sodium per kg b.w. i.m. q24 h during 3 consecutive days	28/45 (62.2%)
	placebo: 5.0 µl sterile water i.m. q24 h during 3 consecutive days	6/43 (14.0%)
	0.1 µg ceftiofur sodium per kg b.w. i.m. q24 h during 3 consecutive days	5/50 (10%)
Morck et al. (1998)	1.0 µg ceftiofur sodium per kg b.w. i.m. q24 h during 3 consecutive days	94/129 (73%)
	6.6 µg oxytetracycline per kg b.w. i.m. q24 h during 3 consecutive days	87/128 (68%)
FDA (2008b) (study 1)	2.5 µg tulathromycin per kg b.w. s.c. as a single injection on Day 0	30/50 (60%)
	placebo: 0.025 µl saline per kg b.w. s.c. as a single injection on Day 0	4/50 (8%)
FDA (2008b) (study 2)	2.5 µg tulathromycin per kg b.w. s.c. as a single injection on Day 0	30/36 (83.3%)
	placebo: 0.025 µl saline per kg b.w. s.c. as a single injection on Day 0	17/34 (50%)

b.w. = body weight; h = hour; i.m. = intramuscularly; q = every; s.c. = subcutaneously

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Comparison	No.Studies	NMA	Direct	Indirect	Difference	Diff_95CI_lower	Diff_95CI_upper	pValue
Cef_01:Cef_10	1	-1.99	-1.99	NA	NA	NA	NA	NA
Cef_01:Oxy	1	-1.92	-1.92	NA	NA	NA	NA	NA
Cef_01:Placebo	0	-0.49	NA	-0.49	NA	NA	NA	NA
Cef_01:Tul	0	-1.68	NA	-1.68	NA	NA	NA	NA
Cef_10:Oxy	1	0.07	0.07	NA	NA	NA	NA	NA
Cef_10:Placebo	1	1.49	1.49	NA	NA	NA	NA	NA
Cef_10:Tul	0	0.30	NA	0.30	NA	NA	NA	NA
Oxy:Placebo	0	1.43	NA	1.43	NA	NA	NA	NA
Oxy:Tul	0	0.23	NA	0.23	NA	NA	NA	NA
Tul:Placebo	2	1.19	1.19	NA	NA	NA	NA	NA

Figure 1. Inconsistency between the direct, indirect and network effect estimates

Cef_01 = 0.1 μg ceftiofur sodium; Cef_10 = 1.0 μg ceftiofur sodium; CI = confidence interval; NMA = network meta-analysis; Oxy = oxytetracycline; Tul = tulathromycin

	Cef_01	Cef_10	Oxy	Placebo	Tul
Cef_01	Cef_01	6.6 (0.51, 94.99)	6.13 (0.45, 88.37)	1.38 (0.04, 56.55)	4.17 (0.07, 279.48)
Cef_10	0.15 (0.01, 1.95)	Cef_10	0.93 (0.07, 11.2)	0.21 (0.02, 2.8)	0.63 (0.03, 16.12)
Oxy	0.16 (0.01, 2.23)	1.07 (0.09, 13.46)	Oxy	0.22 (0.01, 8.63)	0.67 (0.01, 42.23)
Placebo	0.72 (0.02, 27.92)	4.81 (0.36, 65.8)	4.46 (0.12, 168.49)	Placebo	3.01 (0.52, 20.51)
Tul	0.24 (0, 13.59)	1.59 (0.06, 36.27)	1.49 (0.02, 81.9)	0.33 (0.05, 1.93)	Tul

Figure 2. Pairwise and network comparisons for all the treatment pairs from a random-effects frequentist network meta-analysis

Each cell contains the pooled effect size (risk ratio and its 95% credible interval) for each comparison estimated from the Bayesian random-effects network meta-analysis. The interventions are ranked alphabetically. The point estimate derived by comparing an intervention in a column heading with an intervention in a row heading refers to the first one

Cef_01 = 0.1 μg ceftiofur sodium; Cef_10 = 1.0 μg ceftiofur sodium; Oxy = oxytetracycline; Tul = tulathromycin

All the same, the Bayesian mixed treatment comparison method (Figure 3A) revealed no RRs significantly different (at the 5% level) from the null effect (1.0), since their credible intervals cross the no-effect vertical line, indicating that none of those active drugs can be observed as being significantly more effective against IN relative to a placebo.

Given that the Bayesian network is a probabilistic model (Mrad et al. 2015), the following interpretation may be employed: as the 95% CrIs contain the null hypothesised value, the population RR would lie within a value either lower or higher than 1.0 with a 95% probability. Thus, there is a 95% probability that the active drugs would present either a lower or higher risk of the cure rate for IN as opposed to a placebo (Hespanhol et al. 2019).

It can be argued, therefore, that all the formulations except 0.1 μg of ceftiofur sodium are likely to be more effective against IN in comparison with a placebo, albeit the network meta-analysis described herein yielded no statistical significance.

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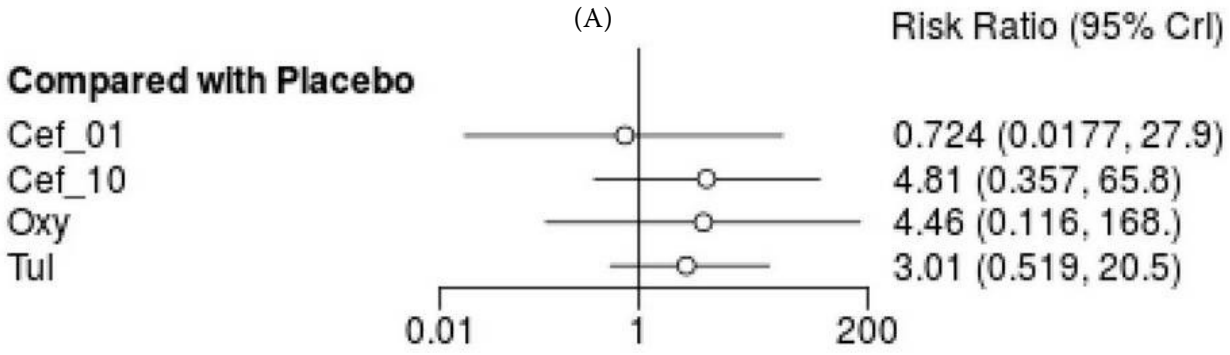
(A)



(B)

Ranking table for all studies - Probability for each treatment to be the best

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Cef_01	0.01619	0.04721	0.15677	0.22309	0.55674
Cef_10	0.33267	0.41636	0.19376	0.05044	0.00676
Oxy	0.36729	0.28828	0.18598	0.13035	0.02811
Placebo	0.00863	0.06835	0.13100	0.42683	0.36520
Tul	0.27522	0.17980	0.33249	0.16930	0.04319

Download

(C)

Ranking with all studies - network meta-analysis median rank chart

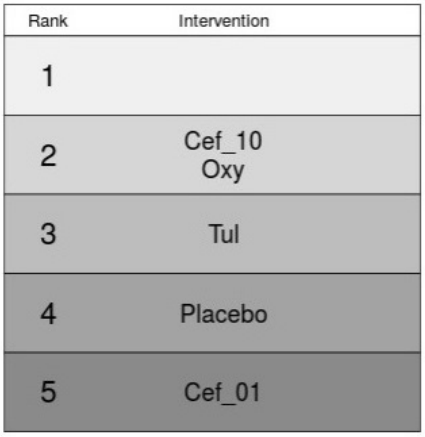


Figure 3. Bayesian network meta-analysis forest plot, ranking table and median rank chart for all the interventions
(A) Bayesian random-effects network meta-analysis forest plot of the active drugs versus placebo effect sizes. The horizontal line shows the 95% credible interval (95% CrI), and the circle in its middle corresponds to the estimate of the risk ratio. The between-study standard deviation: 1.11. 95% CrI: 0.29, 1.87. (B) Ranking table reflecting the median rank values for all the included interventions according to their effectiveness in treating bovine interdigital necrobacillosis. (C) Median rank chart displaying the treatments in order from the most to the least effective
Cef_01 = 0.1 µg ceftiofur sodium; Cef_10 = 1.0 µg ceftiofur sodium; Oxy = oxytetracycline; Tul = tulathromycin

DISCUSSION

A network meta-analysis is a matter of routine for human medicine and is becoming increasingly widespread in veterinary science.

In particular, mixed treatment comparisons have been utilised in reviews addressing mastitis (Winder et al. 2019) and bovine respiratory disease (O'Connor et al. 2019).

Conceivably, on account of the limited number of suitably designed studies available, no attempt had been undertaken earlier to carry out a meta-analysis addressing the subject matter. Apley (2015) calculated the number needed to treat (NNT) values for a few treatments used in five blinded RCTs, though it could not facilitate the ascertainment of a clinically superior intervention. As explained in the publication, florfenicol administered to cattle by two different regimens had the lowest NNT, suggesting the greatest effectiveness in the eradication of IN. However, the examination of the original text (FDA 1999) revealed there was no absolute clarity concerning how many calves were assigned to each trial arm. Withal, it was stated in the report that the investigators utilised an induced model of IN, which is in conflict with the data eligibility requirements. Moreover, in the same review, Apley (2015) described an experiment where ceftiofur crystalline free acid had been injected into 88 animals, resulting in a 58.4% positive outcome, but it has proven impossible to find an official record containing this evidence. Herewith, the results presented in the summary that referred to FDA (2008a) were inappropriate for our analysis. Curiously, there is a paucity of ongoing research activity with reference to IN eradication in cattle, and not a single proper

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RCT on cattle has been published over the past five years, unlike the field of ovine farming, where the anti-foot rot effectiveness of several footbath formulations (Allworth and Egerton 2018; Hidber et al. 2020), zinc supplementation (Bauer et al. 2018), and tilmicosin (Angell et al. 2016) have been evaluated, and even a five-point standard for the control of lameness in sheep has been elaborated upon and tested in recent years (Clements and Stoye 2014; Lovatt et al. 2019). The scope of our research, therefore, partially overlapped the work described above.

Oxytetracycline is a veterinary antibiotic of the tetracycline group commonly employed to prevent and treat some infectious diseases (Akyol et al. 2016). From the current mixed treatment comparison, there was approximately an equivalent effectiveness between 6.6 µg of oxytetracycline and 1.0 µg of ceftiofur sodium in terms of curing bovine IN. As summarised by Papich and Riviere (2018), the stipulated dosing for oxytetracycline injected i.m. to cattle is in the range of 6.6 µg/kg to 20.0 µg/kg b.w. every 24 hours. Hence, the lowest recommended dose applied might have been insufficient to obstruct the respective disease causative agents. The dose of ceftiofur was also at the minimum limit prescribed for cattle (Van Metre 2017). Nonetheless, taking that the efficaciousness of a medication correlates with the duration of its exposure at concentrations exceeding the minimum inhibitory concentration (MIC) for the susceptible microorganism into account (Levison and Levison 2009; Altan et al. 2017), ceftiofur sodium is supposed to possess an advantage over oxytetracycline. In the research by Samitz et al. (1996), antagonism of ceftiofur against *F. necrophorum* isolated from bovines was expressed as MIC90 of ≤ 0.062 5 µg/µl. *In vitro* tests conducted by Sheldon et al. (2004) identified the susceptibility of twenty-two cow-derived strains of *F. necrophorum* along with *Prevotella melaninogenica* to ceftiofur and oxytetracycline at MIC90 values of 0.125 µg/µl and 16.0 µg/µl, respectively, which allegedly indicates the therapeutical superiority of ceftiofur.

Discussing the results of their trial, Morck et al. (1998) speculated that although the efficacy of oxytetracycline and ceftiofur was found to be equivalent, ceftiofur has a shorter milk discard period in comparison with oxytetracycline, and is, consequently, preferable. It should nevertheless be noted that, as of November 2020, the withdrawal interval for ceftiofur is 72 h following the last dosing, whereas the interval is 96 h for oxytetracycline and the latter is prohibited for use in lactating dairy cattle altogether as specified by the United States Code of Federal Regulations (ecfr.gov). With regard to the American dairy cattle production sector, ceftiofur may be, therefore, considered a feasible treatment option.

Ceftiofur and oxytetracycline belong to the drugs with time-dependent kinetics (Nie et al. 2016; Poapolathep et al. 2020), whereas different killing patterns have been described for tulathromycin, depending on the target pathogen (Zhou et al. 2017a; Zhou et al. 2017b). On top of that, this semi-synthetic macrolide is not applicable to female dairy cattle 20 months of age and beyond (Van Metre 2017).

Turning to the question of safety, our searches have not retrieved any cases of adverse effects associated with the administration of ceftiofur sodium to animals, whilst oxytetracycline is mentioned among the preparations with nephrotoxic effects (Gesek et al. 2015). Some adverse events have been recorded in a number of tulathromycin-medicated species, such as injection-site reactions and cardiotoxicity (Rutenberg et al. 2017; Doster et al. 2018). In light of the fact that a large portion of tulathromycin is eliminated as non-biotransformed by biliary and renal excretion, the view was pointed out that this antibiotic can affect the microbiome of the lower gastrointestinal tract of cattle (Holman et al. 2019).

The network meta-analysis reported here is expected to inform clinical practice by comparing varied interventions for the treatment of IN-affected cattle.

The Bayesian network meta-analysis utilised herein has not revealed any significant differences between the antimicrobials and placebo in terms of the probability of a positive clinical response. However, almost all the formulations were more effective in relation to the control intervention. Concerning the effect size estimated as well as the pharmacodynamic and pharmacokinetic characteristics; ceftiofur sodium injected at the level of 1.0 µg can be considered superior to 6.6 µg oxytetracycline in the treatment of IN and is, thus, likely to provide the best therapeutic activity against the disease in cattle. Since the tests provided by the employed statistical application could not appropriately explore the extent of the inconsistency across the studies, the findings from the present meta-analysis

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should be interpreted with caution. Additional well-designed RCTs are necessary to make full-fledged statements upon formulation decisions.

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Conflict of interest

The authors declare no conflict of interest.

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