Clinical Evidence for Individual Animal Therapy for Papillomatous Digital Dermatitis (Hairy Heel Wart) and Infectious Bovine Pododermatitis (Foot Rot)

Michael D. Apley, DVM, PhD

KEYWORDS
- Papillomatous digital dermatitis • Hairy heel wart • Infectious bovine pododermatitis
- Foot rot • Interdigital necrobacillosis • Therapy • Clinical trials
- Susceptibility testing

KEY POINTS
- Clinical evidence presented here was limited to randomized, prospective clinical trials conducted in naturally occurring disease with negative controls and masked subjective evaluators.
- In the case of papillomatous digital dermatitis (PDD), these trials support the use of topical tetracycline and oxytetracycline, lincomycin, a copper-containing preparation, and a non-antimicrobial cream; there is a significant effect of stage of disease on treatment success as measured by disease recurrence.
- Susceptibility testing of Treponema spp isolates and parallels with Treponema-associated disease in humans supports the potential for systemic use of macrolides and some β-lactams, but clinical trial confirmation is needed.
- In the case of individual therapy for infectious pododermatitis (IP), trial evidence is available to support systemic treatment with ceftiofur, florfenicol, tulathromycin, and oxytetracycline; clinical trial evidence was not readily available for common IP therapies such as penicillin G, sulfadimethoxine, and tylosin.

Author Disclosures: Author has accepted research funding and consulting fees from Zoetis (maker of cefitofur, a penicillin G, tulathromycin, lincomycin, and an oxytetracycline), Elanco (maker of tylosin), and Merial (maker of gamithromycin) for.

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http://dx.doi.org/10.1016/j.cvfa.2014.11.009
vetfood.theclinics.com

0749-0720/15/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
INTRODUCTION

The use of drugs to treat infectious disease, especially antimicrobials, is based on the clinician’s judgment that the drug will make a difference in clinical outcome in a population over time. Clinical trial reports are the pinnacle of evidence to support this judgment, followed by physiologic reasoning such as antimicrobial susceptibility testing combined with antimicrobial pharmacokinetic and pharmacodynamic characteristics. This article evaluates clinical trial and supportive data to inform clinician decisions on individual animal treatment of 2 common infectious diseases of the bovine foot.

To be included in the evidence tables of this article, clinical trials must have met the following criteria:

- Prospective
- Randomized
- Naturally occurring disease
- Negative controls
- Masking of subjective evaluators

Strict adherence to these requirements may have eliminated some studies that met these criteria, but for which reporting was incomplete. These situations underscore the importance of adhering to reporting guidelines such as the reporting guidelines for randomized controlled trials in livestock and food safety (REFLECT) statement, which are also helpful in study design in anticipation of successful publication. In particular, the requirement for masking of subjective evaluators eliminated several publications. Another observation is that investigators are well advised to consult statisticians during study design and to clarify the appropriate analysis and reporting of categorical data such as clinical scores.

The outcomes of the clinical trials were summarized and then characterized in the form of the number needed to treat (NNT) statistic. The NNT is calculated by first determining the absolute risk reduction (ARR), which is the actual difference in percentage clinical success between the treated and negative control groups. The ARR is then divided into 100%, with the resulting value representing the NNT; this is the number of animals that must be treated to make a difference in 1 animal. Because the NNT is based on the difference between treated and untreated animals in the same diseased population, it represents the effect of the drug in consideration of the spontaneous cure rate of the population, which in turn gives some insight into the severity of the disease challenge. Comparison of NNT values is only valid within the same study; comparing NNT values between studies to determine the most effective drug is inappropriate because of the potential differences in the disease challenge.

The external relevance of these trials is affected by the case definitions and the time of detection of disease in relation to field applications. An attempt has been made to describe case definitions, but the reader is directed to the original articles for more detail so that external relevance of the data may be further evaluated.

PAPILLOMATOUS DIGITAL DERMATITIS (HAIRY HEEL WART, STRAWBERRY FOOT ROT)

The therapy of PDD still lacks clarity as to the breadth of etiologic agents and pathogenesis. The multifactorial cause has been documented in the literature, with a consistent finding of spirochete organisms of the genus Treponema as well as multiple genera and species of bacteria.

Available clinical trials for individual animal therapy that met inclusion criteria for evidence tables were limited to topical therapy. No reports of systemic therapy for
PDD met inclusion criteria. There is substantial literature on the use of foot baths for control of PDD, which is not addressed here.9–17

**Randomized, Masked, Prospective Trials with Negative Controls for Topical Therapy for Papillomatous Digital Dermatitis**

Four studies involving PDD were identified and are summarized in Table 1. Study entry case definitions and success/failure definitions applied at the end of the study period are presented in the table. As with all clinical trials, these definitions have an effect on the external validity of the studies in relation to applicability in a practice setting.

Cutler and colleagues18 conducted a study in an Ontario dairy wherein 214 hooves were treated with tetracycline HCl powder (2–5 g) under a bandage for 2 days or a prepared tetracycline HCl paste (2–5 g) with no bandage, or were not treated. Cows that were severely lame were only assigned to one of the positive treatment groups because of welfare concerns. As part of the preventive program on the farm, all cattle walked through a foot bath 3 times a week regardless of the study status; the foot bath treatments were copper sulfate (58 g/L) twice weekly and tetracycline (1.16 g/L) once weekly. At 8 to 12 days posttreatment, healing rates were 57.1% in the tetracycline

<table>
<thead>
<tr>
<th>Case Definition</th>
<th>Success Definition</th>
<th>N</th>
<th>Treatments</th>
<th>% with Positive Case Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw, moist lesions with tufted or granular surfaces as scored by investigator</td>
<td>Lesion healing at 8–12 d posttreatment (no sign of moist surface or scab)</td>
<td>65</td>
<td>Untreated control</td>
<td>0.0%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>Tetracycline HCl powder with bandage for 2 d</td>
<td>57.1%</td>
<td>1.75 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79</td>
<td>Tetracycline HCl paste once</td>
<td>47.4%</td>
<td>2.11 (2)</td>
</tr>
<tr>
<td>Active, red digital dermatitis lesion</td>
<td>Decision not to retreat at 29 d—based on signs of pain, lesion activity, or both</td>
<td>33</td>
<td>Untreated control</td>
<td>3.1%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33</td>
<td>Lincomycin paste</td>
<td>93.7%</td>
<td>1.10 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>Nonantimicrobial cream</td>
<td>69.7%</td>
<td>1.50 (2)</td>
</tr>
<tr>
<td>Lesion with signs of severe pain</td>
<td>The reference reports pain and lesion scores at days 14 and 30. For this table, presence of pain at day 30 is reported</td>
<td>10</td>
<td>Control: tap water</td>
<td>20.0%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>Oxytetracycline solution</td>
<td>80.0%</td>
<td>1.67 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>Copper, peroxide, cationic agent</td>
<td>78.6%</td>
<td>1.71 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>5% copper sulfate</td>
<td>20.0%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>Acidified ionized copper solution</td>
<td>0.0%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>Hydrogen peroxide-peroxyacetic acid</td>
<td>0.0%</td>
<td>___</td>
</tr>
<tr>
<td>Pain with visually active lesion, also confirmed histologically</td>
<td>Healed based on assignment of a visual lesion score at 30 d</td>
<td>3</td>
<td>Control, bandage only</td>
<td>0.0%</td>
<td>___</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>Lincomycin paste (10 g)</td>
<td>72.7%</td>
<td>1.38 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>Oxytetracycline paste (10 g)</td>
<td>63.6%</td>
<td>1.57 (2)</td>
</tr>
</tbody>
</table>

Data from Refs.18–21
powder hooves, 57.4% in the tetracycline paste hooves, and zero in the negative controls.

Moore and colleagues\textsuperscript{19} evaluated the efficacy of lincomycin paste (10 g lincomycin and 3 mL deionized water as a paste) or a nonantimicrobial cream (soluble copper with peroxide and a cationic agent [Victory foot cream]), against negative controls in 98 dairy cows. The products were placed on a 4×4-in gauze sponge (similar volumes) and held in place on the lesion with an elastic bandage for 5 days, after which they were removed by farm personnel. A success or failure definition based on the signs of pain, lesion activity, or both was applied at 29 days, after which the failures would receive re-treatment with the same compound and negative controls would be allocated to one of the treatment compounds. Success rates for the lincomycin, nonantimicrobial cream, and controls were 93.7%, 69.7%, and 3.1%, respectively. All treatments were statistically significant in their differences from the control group with regard to lack of re-treatment. When compared with negative controls, the investigators calculated that cattle treated with lincomycin paste were 31 times more likely to not be re-treated and that the cattle treated with the nonantimicrobial cream were 22.3 times more likely to be not re-treated.

Hernandez and colleagues evaluated 5 topical treatments against a negative control.\textsuperscript{20} The treatments were (1) oxytetracycline soluble powder mixed at 25 mg/ml (Terramycin soluble powder, Pfizer Animal Health, Exton, PA); (2) a commercial formulation of soluble copper, peroxide compound, and a cationic agent (Victory, Babson Bros Co., Romeoville, IL); (3) 5% copper sulfate solution, (4) acidified ionized copper solution, (5) hydrogen peroxide-peroxyacetic acid (HPPA) solution (Hoof Pro Plus, SSI Corporation, Julesburg, CO), and (6) tap water negative control. Cows were enrolled with lesions involving a single hind foot which displayed pain categorized as severe. Treatments were applied daily by spray bottle for 5 days, no treatment was applied for 2 days, then treatments were applied every other day for three additional applications. Treatments 1 and 2 were significantly different from the other 4 based on pain at days 14 and 30, and based on visible lesions at day 30. On day 14, treatments 1 and 2 were not significantly different from each other based on visible lesions, but treatment 2 was also not significantly different from treatments 3 and 4. The results of this study summarized by treatment are presented in Table 1.

Berry and colleagues\textsuperscript{21} treated affected cattle with either lincomycin powder, 10 g, or oxytetracycline powder, 10 g, both mixed with sufficient water to create a paste. Bandages were left on for 4 days. On initial examination, both lesion identification and demonstration of pain were required to be enrolled in the study. The low number of controls\textsuperscript{3} was justified by minimizing untreated cattle in a commercial dairy, and response rates of both treated and untreated cattle are similar to those in other studies reported here. The response rates were not significantly different between the positive treatments, 72.7% and 63.6% in the lincomycin and oxytetracycline groups, respectively. This response rate was determined from visual evaluation of lesion healing. Unique to this study, the investigators also evaluated histologic samples from the lesions. Of the 15 lesions classified as healed on study day 30, 7 were still classified as active histologically and 5 were classified as in early stages of development. Histology could not determine if these lesions represented incomplete healing or the initial stages of reinfection. This fact speaks to the concerns about the common recurrence of disease in cattle initially classified as healed. This study also evaluated the microbiology of the lesions, confirming the presence of spirochetes and multiple bacterial species, most of which were not present in control skin cultures from nondiseased cattle. In another study, Berry and colleagues\textsuperscript{22} documented that variation in the type of lesion at treatment correlated
with the odds of being a healed lesion at the end of the 341-day study. These results emphasize the impact of lesion type on treatment success and disease recurrence and that prognosis and treatment strategies should be affected by lesion characterization.

**In vitro Susceptibility Testing of Papillomatous Digital Dermatitis Treponema Isolates**

Two publications have evaluated in vitro susceptibility of treponemes isolated from bovine PDD.\(^23,24\) These results are presented in Table 2, with comparison to approved

<table>
<thead>
<tr>
<th>DA2:D20</th>
<th>MIC(_{90}) (µg/mL)</th>
<th>MBC(_{90}) (µg/mL)</th>
<th>CLSI Veterinary Breakpoints for Other Diseases (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans, 2009 (16 isolates from UK cattle, 3 from an ovine outbreak)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.38</td>
<td>1.5</td>
<td>0.25(^a)</td>
</tr>
<tr>
<td>Enrofloxacin(^b)</td>
<td>96</td>
<td>192</td>
<td>0.25(^c)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.05</td>
<td>0.19</td>
<td>0.5(^d)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>24</td>
<td>96</td>
<td>2(^e)</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>24</td>
<td>48</td>
<td>0.5(^f)</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>0.75</td>
<td>6</td>
<td>2(^c)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.05</td>
<td>0.19</td>
<td>0.25(^c)</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>12</td>
<td>48</td>
<td>32(^c)</td>
</tr>
<tr>
<td>Evans, 2012 (12 isolates from the United Kingdom)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.38</td>
<td>1.5</td>
<td>0.25(^a)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.05</td>
<td>0.09</td>
<td>___</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>48</td>
<td>192</td>
<td>2(^g)</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>6</td>
<td>24</td>
<td>2(^c)</td>
</tr>
<tr>
<td>Gamithromycin</td>
<td>0.02</td>
<td>0.09</td>
<td>4(^h)</td>
</tr>
<tr>
<td>Ciprofloxacin(^b, i)</td>
<td>48</td>
<td>96</td>
<td>0.25(^c)</td>
</tr>
<tr>
<td>Colistin(^i)</td>
<td>&gt;384</td>
<td>&gt;384</td>
<td>___</td>
</tr>
<tr>
<td>Trimethoprim(^i)</td>
<td>192</td>
<td>384</td>
<td>___</td>
</tr>
</tbody>
</table>

**Abbreviation:** CLSI, Clinical and Laboratory Standards Institute.

\(^a\) CLSI susceptible breakpoint for canine skin and soft tissue and equine respiratory disease. The swine respiratory breakpoint is 0.5.

\(^b\) Both of these fluoroquinolones would be illegal for this extralabel use in the United States and some other countries.

\(^c\) CLSI susceptible breakpoint for bovine respiratory disease for ceftiofur, enrofloxacin, gamithromycin, oxytetracycline, penicillin, and spectinomycin.

\(^d\) CLSI susceptible breakpoint for *Enterococcus* spp and *Streptococcus* spp. adapted from human medicine.

\(^e\) CLSI susceptible breakpoints for specific organisms in canine and equine systemic disease.

\(^f\) CLSI susceptible breakpoint for clindamycin in canine skin and soft tissue disease.

\(^g\) CLSI susceptible breakpoint for cephalothin in canine diseases and cefazolin in canine and equine diseases.

\(^h\) CLSI susceptible breakpoint for bovine respiratory disease, approved to come out in next CLSI table edition.

\(^i\) Evaluated for use in *Treponema* isolation media.

*Data from* CLSI. VET01-S2 performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals: second informational supplement. Wayne (PA): Clinical and Laboratory Standards Institute; 2013. p. 16–30. Tables 2A and 2B.
susceptible breakpoints for other diseases from the Clinical and Laboratory Standards Institute (CLSI) VET01-A4 document. While none of these antimicrobials have an approved CLSI breakpoint for treatment of any disease due to treponemtes, it is at least possible to compare the minimal inhibitory concentration (MIC) values for 90% of the tested organisms (MIC$_{90}$) to established susceptible breakpoints for other veterinary diseases to rule out potential antimicrobials for which the MIC values are well out of the range of potential therapeutic effect. However, caution is appropriate because the disease is different, the pathogen is different (and therefore the drug pharmacodynamics may be substantially different), the site-specific pharmacokinetics may be different (both because of site and regimen), and there is a lack of correlation of MICs with the therapeutic regimen and clinical results. Also, in lacking CLSI-approved standards for this organism, the testing methods may give different results compared with those of other methods based on multiple criteria. Even between the 2 referenced papers, there are slight differences in the inocula and media. It cannot be overemphasized that although the investigators made significant efforts to provide appropriate susceptibility testing methods, these have not undergone the CLSI approval process.

Therefore, in evaluating Table 2, an MIC$_{90}$ well above the range of the ones established for systemic therapy for other diseases would likely require the potential for significantly higher drug concentrations at the site of infection to suggest consideration of use (eg, topical application at high concentrations), and therefore suggest significantly lower optimism for potential efficacy after systemic administration. For a discussion on the application of susceptibility testing in bovine therapeutics, see the article by Lubbers elsewhere in this issue.

The MIC$_{90}$ values for erythromycin, oxytetracycline, penicillin, spectinomycin, and gamithromycin (Zactran) are below the CLSI-susceptible breakpoints approved for these drugs in other diseases, in some cases in other animal species. Of these, oxytetracycline, penicillin, spectinomycin, and gamithromycin have breakpoints established for a specific regimen against bovine respiratory disease (BRD) based on systemic administration. Oxytetracycline and penicillin are CLSI generic BRD breakpoints based on pathogen MIC distributions along with pharmacokinetic and pharmacodynamic properties of the antimicrobials against bacterial pathogens, but without clinical trial correlation to clinical outcome. For all drugs with MIC$_{90}$ values that suggest potential systemic efficacy, all but oxytetracycline have MIC$_{90}$ values very close to the MBC$_{90}$ values, suggesting bactericidal activity against the pathogen. Confirmation of bactericidal activity through kill curve assays would be helpful in this interpretation. For these drugs, the close proximity of the MIC$_{90}$ values to the susceptible breakpoints for other bovine diseases suggests that evaluating systemic efficacy would be worthwhile; however, systemic efficacy is not assured.

Another issue in considering application of nonapproved breakpoints is topical versus systemic therapy; there are no CLSI veterinary breakpoints that are approved for topical therapy. For example, the comparison of lincomycin MIC values to the available veterinary clindamycin-susceptible breakpoint (clindamycin for canine skin and soft tissue disease) in Table 2 would suggest a poor prognosis for efficacy after systemic therapy, yet there are 2 clinical trials reported in Table 1 that show significant topical efficacy for lincomycin in PDD.

**Recurrence of Papillomatous Digital Dermatitis**

The treatment successes reported in the literature may not result in continued absence of disease. In a long-term monitoring study of 39 cases of PDD initially treated with topical lincomycin, Berry and colleagues observed that 54% required
re-treatment on at least 1 occasion during the 341-day monitoring period. An early report of the spread of PDD through California dairy herds reported a 48% recurrence and new lesion rate in cows initially responding to injectable penicillin G or ceftiofur, topical formaldehyde or hydrochloric acid, or surgical excision. These treatments are not included in the evidence table because of lack of information about the studies. One other reference to systemic ceftiofur efficacy for PDD was found in the lay literature, but communication with the investigator confirmed that although randomized with negative controls, the subjective evaluators were not masked.

**Potential for Milk Residues from Topical Papillomatous Digital Dermatitis Therapy**

As PDD occurs in both lactating and dry dairy cows, the potential for milk residues resulting from topical treatment is a concern. This potential was investigated by Britt and colleagues related to oxytetracycline in milk after 2 topical treatments for PDD. Analysis was by high-performance liquid chromatography (HPLC) (limit of detection of 3.3 ppb) and a tetracycline screening test (90% sensitivity at ≥19 ppb), both performed at the US Food and Drug Administration’ (FDA’s) Center for Veterinary Medicine. The tolerance for residues consisting of the sum of residues of the tetracyclines in milk is 300 ppb.

Treatment 1 (N = 16) consisted of approximately 15 mL of an oxytetracycline solution, 100 mg/mL, applied topically with a garden sprayer twice daily for 7 days. Samples were obtained 24, 48, 72, 96, and 120 hours after the first spray application. Of the 80 samples collected for this treatment, 72 had no oxytetracycline detected and 8 had residues detectable by HPLC at concentrations from less than 1 to 6.7 ppb. The screening test gave negative results for all 80 samples.

Treatment 2 (N = 12) consisted of 20 mL of an oxytetracycline solution, 100 mg/mL, soaked in cotton, applied to the lesion and held on by tape until the tape deteriorated and fell off. The PDD lesions were sprayed immediately after milking. Samples were obtained 17, 48, 72, and 120 hours after bandage application. Of the 48 samples for treatment 2, no oxytetracycline was detected in 39 samples by HPLC, and concentrations ranging from 3.5 to 12 ppb were detected in the other 9 samples. All 48 samples gave negative result by the screening test.

These results suggest that the chance for a violative residue in the bulk tank is minimal with the stated uses of oxytetracycline for the treatment of PDD. However, the use will result in oxytetracycline being used in the parlor, so contamination of milking equipment, and therefore potentially the milk, must be avoided. Also, the variation encountered in the trial does not preclude that a small proportion of the population may display residues in milk that would exceed the acceptable tolerance. This study related to oxytetracycline should not be extrapolated to indicate that other topical treatments would have similar residue characteristics. This is especially true for treatments such as lincomycin, where the lack of a lactating dairy cattle label for any purpose results in an effective tolerance of zero (any detected). With today’s testing technology, such as mass spectrometry, the potential for residue detection cannot be dismissed.

**Effect of Site of Infection**

Hernandez and Shearer evaluated the effect of topical treatment of PDD with topical application of an oxytetracycline solution, 25 mg/mL, based on the location of the lesion. Cows with PDD lesions on one hindfoot, characterized as early or mature according to study criteria and with lesion size determined, were classified as the lesion being located on the interdigital cleft (n = 14), heels, or dewclaw. Treatment of all lesions consisted of daily topical application of the oxytetracycline solution by sprayer,
after cleaning with water, for 5 days. Treatment was stopped for 2 days, then resumed for an additional 3 days. The proportion of cows with mature lesions or with large lesion sizes were not different between groups at the time of treatment initiation. Lesions were examined at 14 and 30 days after initiation of treatment. Evaluation of both pain scores and lesion size indicated that cows with lesions on the interdigital cleft were less likely to respond to treatment when compared with cows with lesions on the heels or dewclaw. On days 14 and 30, the proportion of cows with pain scores greater than 0 for lesions located in the interdigital cleft (85% and 91%, respectively) were greater than for cows with lesions located on the dewclaw (18% and 24%, respectively), at \( P < .05 \).

**Consideration of Human Treponema Infections**

Parallels in the treatment of treponeme-associated diseases in humans may be of interest in evaluating potential systemic therapies for PDD. *Treponema pallidum* is the causative agent of syphilis, for which penicillin G has long been the mainstay of treatment. With issues of treatment due to penicillin G allergies, the antimicrobials tetracycline, doxycycline, erythromycin, azithromycin, and ceftriaxone have been evaluated and used for therapy. However, macrolide resistance was reported in Irish and US isolates of *T pallidum* in 2004 and linked to a mutation in the 23S ribosomal RNA genes. This resistance is now appearing in multiple locations around the world. Yaws, bejel (endemic syphilis), and pinta are the other three classic human treponematoses. All human treponematoses share the characteristic of manifestation of multiple stages involving the skin. Single-dose azithromycin is being considered a pivotal tool to achieve worldwide eradication of yaws by 2020.

The parallels between PDD and human treponematoses are striking, as are the antimicrobials considered vital in treating the primary pathogen. The development of widespread resistance to macrolides in human therapy for *T pallidum* perhaps underscores a warning to wisely approach control measures. The single-injection macrolides currently available for respiratory disease therapy in cattle present challenges in both slaughter and milk withdrawal times in lactating dairy cattle, but may hold promise for limited individual animal therapy in beef cattle outbreaks, such as in feedlots.

**INFECTIOUS PODODERMATITIS (FOOT ROT, ACUTE INTERDIGITAL NECROBACILLOSIS)**

IP, when compared with PDD, has the advantage of multiple labels approved for therapy for this disease in cattle. For some of these drugs, there is the ready availability of freedom of information (FOI) summaries detailing pivotal studies demonstrating substantial evidence of efficacy.

**Randomized, Masked, Prospective Trials with Negative Controls for Systemic Therapy for Infectious Pododermatitis**

In 1995, ceftiofur sodium (Naxcel) was granted a supplemental approval for the treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. An induced model dose-finding study initially confirmed that both 1.1 and 2.2 mg/kg administered intramuscularly (IM) at 24-hour intervals for 3 days were equally effective in the treatment of IP. A multilocation dose confirmation study using the 1.1 mg/kg regimen was then conducted in 88 beef feedlot cattle and lactating dairy cows at 16 sites. As shown in Table 3, treatment with ceftiofur sodium was statistically significant in superiority to the negative control. Treatment success was based on a combination of a reduction in lameness score by 2 points with nil to moderate swelling and healed or healing lesions.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Case Definition</th>
<th>Success Definition</th>
<th>N</th>
<th>Treatments</th>
<th>% with Positive Case Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftiofur sodium FOI (1995) Study 2</td>
<td>Lesions and lameness</td>
<td>Lesion, lameness, and swelling scores on day 7</td>
<td>45</td>
<td>Control: sterile water every 24 h for 3 d; 1.1 mg/kg IM every 24 h</td>
<td>14.0%</td>
<td></td>
</tr>
</tbody>
</table>
| CCFA FOI (2008) | Lameness, lesion, and swelling score of 2 or 3 in 1 foot only for 2 consecutive days | Reduction of 2 or more score for lameness; and swelling and lesion score 0 or 1 on day 7 in qualifying foot | 89      | Vehicle-treated control; CCFA-SS 6.6 mg CE/kg BW SC (base of ear) single injection day 0 | 13.2%                          | 58.4% | 2.21 (2)
| Florfenicol FOI (1999) | 2 consecutive days of nonresolving lesions and lameness scores of 2 or greater | Day 0 lesion score ≥2 decreasing to 0 or 1; with reduction in lameness score of 2 points or returning to 0 | 90      | Control: same volume and timing as for the florfenicol IM regimen; Florfenicol 20 mg/kg IM dosed twice in a 48-h interval; Florfenicol 40 mg/kg SC single dose | 0.0%                          |     |
| Tulathromycin FOI (2008) Study 1 | Lameness, lesion, and swelling score of 2 or 3 in 1 foot only for 2 consecutive days | Reduction from day 0–7 of 2 or more scores in lameness, and swelling & lesion scores of 0 or 1 on day 7 in the qualifying foot | 50      | Control: saline SC single injection on day 0; Tulathromycin (2.5 mg/kg) SC single injection on day 0 | 8.0%                          | 60.0% | 1.93 (2)
| Tulathromycin FOI (2008) Study 2 | Lameness, lesion, and swelling score of 2 or 3 in 1 foot only for 2 consecutive days | Reduction from day 0–7 of 2 or more scores in lameness, and swelling & lesion scores of 0 or 1 on day 7 in the qualifying foot | 34      | Control: saline SC single injection on day 0; Tulathromycin (2.5 mg/kg) SC single injection on day 0 | 50.0%                         | 83.3% | 3.00 (3)
| Morck and colleagues, 1998 | Acute necrosis of skin causing swelling and lameness for a duration of 3 or more days | Lameness score 0 on day 4 and not re-treated for interdigital phlegmon within 10 d of initial treatment | 50      | Ceftiofur (1.0 mg/kg of BW IM every 24 h for 3 d; Oxytetracycline (6.6 mg/kg) IM every 24 h for 3 d | 73.0%                         |     |

Abbreviations: BW, body weight; CCFA, ceftiofur crystalline free acid; SC, subcutaneous.

Data from Refs. 33,35,37,38
Ceftiofur hydrochloride (Excenel sterile suspension) received supplemental approval for cattle in 1998. It carries the same label indication for IP as does ceftiofur sodium based on therapeutic equivalence through pharmacokinetic studies. A new formulation of ceftiofur hydrochloride was approved in 2008 (Excenel RTU EZ), which was confirmed as effective for all label indications for the previous formulation through a plasma bioequivalence approach.

In 2008, another formulation of ceftiofur, ceftiofur crystalline free acid (CCFA, Excede), received supplemental approval for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *F necrophorum* and *Porphyromonas levi* in beef, nonlactating dairy, and lactating dairy cattle. The dose confirmation study involved 177 cattle, which included 70 beef steers and heifers and 107 lactating dairy cattle. Study entry was based on the requirement for an elevated lameness score, swelling score, and lesion score for 2 consecutive days. Success on day 7 of the study required a greater than or equal to 2 score reduction in lameness (0 to 3 scale with 0 being normal), plus swelling and lesion scores of 0 or 1, on 0 to 3 and 0 to 4 scales, respectively. The treated animals had statistically significant improvements in clinical success rates, as reported in Table 3.

Florfenicol (Nuflor) is labeled for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, IP) associated with *F necrophorum* and *B melaninogenicus*. The clinical study contained in the 1999 supplemental approval FOI summary involved 90 crossbred beef steers with a mean weight of 436 kg. As reported in Table 3, the study involved a saline control group and a group for each of the two florfenicol label regimens. To be enrolled, the cattle had to display 2 days of nonresolving lesions and lameness based on the study scoring criteria of 0–4 for lesions and 0 to 3 for lameness, with 0 being normal for both scales. To be classified as a success on day 7, the lesion score must have decreased from $\geq 2$ on day zero to a score of 0 or 1, and the lameness scores must have decreased by at least 2 points. On day 7, 77% of the study animals in both florfenicol treatment groups met success criteria, while none of the negative controls were successes. There was no statistical difference between florfenicol treatment groups, but both were statistically significantly different from the control group.

The 2008 supplemental approval of tulathromycin (Draxxin) for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *F necrophorum* and *P levi* in beef and nonlactating dairy cattle reports the results of 2 studies. Each study is identically structured, with cattle entering the study based on lameness, swelling, and lesion scores for 1 foot. Once entered into the study on study day 0, the criteria for treatment success were applied on day 7. A treatment success required at least a 2 score reduction on a 0 to 3 lameness score scale where 0 indicated no lameness noted and 3 meant holding up the foot with reluctance to put weight on the foot or move. A success was also required to have a swelling score of 0, indicating no swelling, and a lesion score of 0, indicating no lesion. The differences between saline control cattle and cattle treated with tulathromycin, as reported in Table 3, were statistically significant in both studies.

Other antimicrobials also have labels for the treatment of IP as found on the “Animal Drugs @ FDA” site, which is an online searchable version of the FDA “Green Book” containing veterinary labels. These labels include oxytetracycline, tylosin, sulfadimethoxine, sulfabromomethazine, sulfathoxypyridazine, and sulfamethazine. The best search term for this site is “foot rot,” although results are also delivered for “foot-rot” and “pododermatitis.” The presence of a label in this database does not indicate that the label is currently marketed, only that it is approved and has not been withdrawn by the company; some labels are present on the site with an indication that the label has
been withdrawn by the company. Most of these labels are of a sufficient age such that the original freedom of information (FOI) summary is not available electronically on the FDA FOI site. In addition, other antimicrobials without approved labels specifically for IP have been used for therapy, including formulations of penicillin G. According to the Animal Medicinal Drug Use Clarification Act regulations, the veterinarian must first consider if labeled products are effective when used according to label.

In contrast to the pivotal clinical trials available for ceftiofur, florfenicol, and tulathromycin, clinical data to support the common use of other labeled antimicrobials for the treatment of IP are much less robust. At present, there are 50, 100, 200, and 300 mg/mL oxytetracycline products that are labeled for “treatment of … foot-rot and diphtheria caused by *Fusobacterium necrophorum*…” There is a published comparative trial of oxytetracycline and ceftiofur sodium that meets the reporting criteria for this review, although without a negative control. Morck and colleagues compared ceftiofur sodium, 1.0 mg/kg IM every 24 hours for 3 days, to oxytetracycline, 6.6 mg/kg IM every 24 hours for 3 days. This oxytetracycline regimen does not meet the current recommended uses of oxytetracycline as defined by route or dose. However, based on lameness scores and lack of re-treatment within 10 days of initial treatment, these ceftiofur sodium and oxytetracycline regimens were not statistically different in feedlot cattle, at 73.0% and 68% success, respectively. While not a clinical trial powered as to assure demonstration of non-inferiority of either product, these results do suggest that oxytetracycline is effective in the treatment of IP based on very similar results to ceftiofur, which has demonstrated efficacy in multiple trials utilizing different formulations.

**In vitro Susceptibility Testing of *F* Necrophorum**

While susceptibility testing data for bovine IP isolates of *F* necrophorum are lacking, there are data related to other bovine isolates of this pathogen. Mateos and colleagues tested multiple antimicrobial agents against *F* necrophorum isolates from liver abscesses in cattle. As summarized in Table 4, ampicillin, oxytetracycline,

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>CLSI Veterinary Breakpoints for Other Diseases (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>0.01</td>
<td>0.06</td>
<td>0.25&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>0.125</td>
<td>1</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16</td>
<td>64</td>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>0.5</td>
<td>2</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.01</td>
<td>0.01</td>
<td>0.25&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>16</td>
<td>32</td>
<td>256&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tylosin</td>
<td>0.5</td>
<td>1</td>
<td>___</td>
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</tbody>
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<sup>a</sup> CLSI susceptible breakpoint for canine skin and soft tissue and equine respiratory disease. The swine respiratory disease breakpoint is 0.5.

<sup>b</sup> CLSI breakpoint for chlortetracycline is adapted from the human tetracycline breakpoint and has not been assigned a veterinary generic breakpoint as has been done for oxytetracycline.

<sup>c</sup> CLSI susceptible breakpoint for specific organisms in canine and equine systemic disease.

<sup>d</sup> CLSI susceptible breakpoint for bovine respiratory disease.

<sup>e</sup> CLSI human derived breakpoint for sulfasoxizole as the representative for nonpotentiated sulfas. This breakpoint has not been correlated with any veterinary clinical outcomes.
penicillin G, and sulfadimethoxine seem to have MIC<sub>90</sub> values which appear favorable in relation to CLSI susceptibility breakpoints derived for other infections. Chlorotetracycline seems to be favorable in relation to the human-adapted CLSI breakpoint, but that breakpoint comes from systemic human therapy and chlorotetracycline is administered orally in cattle with poor bioavailability. In contrast, the oxytetracycline CLSI-approved breakpoint for BRD is based on bovine pharmacokinetics and the pharmacodynamics of oxytetracycline against bacterial pathogens. This origin of the oxytetracycline breakpoint gives more comfort to extrapolation of the BRD breakpoint to other diseases, such as IP. These susceptibility data support common approaches to treating IP with a sulfa formulation, oxytetracycline, or a formulation of penicillin G. However, readily available clinical confirmation of efficacy is only available for ceftiofur, tulathromycin, and florfenicol. Clinical trial confirmation for healing or prevention of IP cases while cattle are being administered oxytetracycline or chlortetracycline in the feed were not detected in the literature search for this article.

SUMMARY

Clinical evidence presented here was limited to randomized, prospective clinical trials conducted in naturally occurring disease with negative controls and masked subjective evaluators. In the case of PDD, these trials support the use of topical tetracycline and oxytetracycline, lincomycin, a copper-containing preparation, and a nonantimicrobial cream. Susceptibility testing of *Treponema* spp isolates and parallels with *Treponema*-associated disease in humans supports the potential for systemic use of macrolides and some β-lactams, but clinical trial confirmation would be appropriate. The therapy for PDD is complicated by a multipathogen cause, and recurrence of disease after an initial clinical resolution is a common problem. There were no clinical data found meeting criteria for inclusion in this article which support the systemic therapy of PDD. However, susceptibility testing and consideration of human treponematoses therapy suggest that clinical evaluation of drugs such as ceftiofur and macrolides should be furthered.

In the case of individual therapy for IP, trial evidence is available to support systemic treatment with ceftiofur, florfenicol, tulathromycin, and oxytetracycline. Clinical trial evidence was not readily available for IP standards such as penicillin G, sulfadimethoxine, and tylosin, although consideration of susceptibility testing, with the many appropriate caveats, seems to support the clinical impressions that lead to their common use for therapy for IP.

REFERENCES


