Evaluation of 3-, 6- and 9-day post-treatment intervals following pradofloxacin for treatment of bovine respiratory disease in stocker cattle

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Abstract

Pradofloxacin is a fluroquinolone antimicrobial approved for treatment of bovine respiratory disease (BRD) in cattle in the United States. The primary objective of this study was to compare different post-treatment intervals (PTI) following therapy with pradofloxacin on first treatment success and case fatality in stocker cattle naturally affected with BRD. The days-to-death (DTD) following enrollment was evaluated as a secondary outcome. Cattle at 5 commercial stocker operations were identified with BRD by site personnel and were randomized in a 1:1:1 ratio to 3-, 6- or 9-day PTI within each cohort. Following treatment with pradofloxacin, cattle were followed for 45 days to monitor health outcomes. First treatment success was defined as no additional treatment for BRD and no mortality. Case fatality was defined as death due to any cause. Generalized linear mixed models were used for statistical analysis. Weight at treatment and rectal temperature were not different between PTI groups. First treatment success ($P = 0.51$) and case fatality ($P = 0.52$) were not different among PTI treatment groups. DTD was not different between PTI treatment groups ($P = 0.20$). These results will assist with determining optimal use of pradofloxacin in stocker cattle.

Key words: antimicrobial, BRD, health

Introduction

Pradofloxacin (Pradalex™ [a]) is a third-generation fluoroquinolone approved in the United States for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and dairy cattle between 2-12 months of age intended for slaughter or in breeding cattle less than 1 year of age. Pradofloxacin is a bactericidal antimicrobial agent with activity against Gram-positive and Gram-negative bacteria as well as *Chlamydia* and *Mycoplasma* species. Additionally, its spectrum also includes anaerobic bacterial species.[1] Establishment of pharmacokinetic and antimicrobial resistance performance is important for evaluation of an antimicrobial for treatment of disease.

Pharmacokinetic studies in cattle infected with experimentally induced BRD have demonstrated that therapeutic concentrations in the pulmonary epithelial lining fluid (PELF) are reached in 7 hours following a single injection of pradofloxacin at 10 mg/kg.[2] To date, no pharmacokinetic studies have been published in cattle treated with pradofloxacin for naturally occurring BRD. Pharmacokinetic data allows for understanding of therapeutic concentrations in the body and determination of appropriate dosage; however, determination of the optimal interval between treatment administration and evaluation of the treatment's success, called the post-treatment interval (PTI), should be based on clinical data.

In vitro analysis of bovine isolates of *M. haemolytica* and *P. multocida* reports mutant prevention concentrations (MPCs) of less than 0.063 microgram per milliliter. This is four-fold below the reported susceptibility breakpoint for pradofloxacin.[1] The same study reports that all 41 tested strains of *M. haemolytica* and *P. multocida* demonstrated minimum inhibitory concentration (MIC) values below the breakpoint for pradofloxacin.[1] These findings show that pradofloxacin has favorable in vitro activity against two main BRD pathogens and a low likelihood for antimicrobial resistance selection. As antimicrobial resistant isolates from BRD cases are reported more frequently, minimizing antimicrobial exposure may slow the progression of resistance.[2] Establishment of an optimal PTI for pradofloxacin in cattle treated for BRD would ensure adequate time for resolution of clinical signs and reduce unnecessary antimicrobial use.

While understanding pharmacological and antimicrobial resistance properties of an antimicrobial are important, clinical performance and determination of treatment success or failure is equally important. To date, a single study has compared the efficacy of pradofloxacin to tulathromycin and florfenicol in steers experimentally induced with BRD.[3] This study demonstrated no difference in time to resolution of clinical signs in the treatment groups. When evaluating clinical success or failure of a treatment, emphasis is placed on the PTI. Single injection antimicrobial therapy available for BRD treatment has placed even more importance on PTIs. Many studies have investigated the impact of different PTIs on the treatment outcome using other single injection antimicrobials in cattle diagnosed with BRD; however, no studies have been published investigating PTIs following pradofloxacin treatment for BRD in cattle.[4-8]

The primary study objective was to evaluate the effect of 3-, 6- and 9-day post-treatment intervals (PTI) on first treatment success and case fatality in naturally occurring bovine respiratory disease (BRD) in stocker calves. Secondary outcomes included days-to-death (DTD) in the same population. Our hypothesis was that the 6- and 9-day PTI treatment groups will demonstrate improved first treatment success rates and case fatality rates as compared to the 3-day group. Additionally, we hypothesized there would be no differences in DTD between PTI treatment group case fatalities.

Materials and Methods

This study was performed at 5 commercial stocker operations in Kansas and Indiana. The study began in October 2024 and concluded in February 2025. All procedures were approved by the Kansas State University Institutional Animal Care and Use Committee prior to initiation of the study (Protocol Number 5055).

Sample size calculation

First treatment success was used for sample size estimates. Sample size was calculated to detect a difference of 15% between the 3-day group (estimated 70% first treatment success) and the 9-day group (estimated 85% first treatment success). A 95% confidence interval (alpha set at 0.05) was selected with beta set to 0.80. Estimated sample size was calculated at 118 per treatment group. Study numbers were inflated by 5% and rounded up to account for missing data and loss to follow-up resulting in 125 animals per treatment group to achieve desired statistical power.

Study population

Cohorts of cattle arriving at each operation were required to meet certain criteria. The cohorts could only contain animals greater than 2 months of age and only native beef breeds. Dairy breeds and beef-on-dairy crossbred cattle were not eligible for enrollment. Mixed sex cohorts and those containing intact bulls were eligible for study inclusion. At cohort arrival, all operations were required to adhere to a standard processing protocol including metaphylaxis with tulathromycin (Increxxa™ [b]) at the label dose of 2.5 mg/kg, vaccination for respiratory pathogens (bovine viral diarrhea type 1 and 2, infectious bovine rhinotracheitis, bovine parainfluenza 3, bovine respiratory syncytial virus, and *M. haemolytica*) (Titanium® 5[c] and Nuplura®[d]) and parasite treatment with injectable moxidectin (Cydectin®[e]) at 0.2 mg/kg. Additional procedures (such as castration, dehorning, BVDV PI testing, and/or administration of growth implants) were allowable based on the determination of the veterinarian of record for each study site. A mandatory 5-day post-metaphylaxis interval (PMI) was required for all study animals; animals requiring antimicrobial therapy during this period were treated at the discretion of on-site personnel, but were not eligible for enrollment in the current study.

Inclusion criteria

Following the 5-day PMI, cattle were observed daily for clinical signs of BRD using a standardized BRD case definition for enrollment. An animal was considered a BRD case if it displayed at least two of the following clinical signs: anorexia, depression, increased respiratory rate or effort, nasal discharge, cough, or a rectal temperature greater or equal to 104 ˚F (40 ˚C). Individual cattle meeting the BRD case definition were administered a dose of pradofloxacin at 10 mg/kg and randomly assigned to a post-treatment interval (PTI).

Feed and housing

Site A is located in central Kansas and typically purchases high risk calves out of the southeast United States. Cattle for the trial were purchased from auction markets in Kentucky, Arkansas and Missouri. All enrolled cattle were steers, although some of the cohorts had 15-20% bulls at arrival. Average arrival weights ranged between 575 to 605 lbs (261 to 274 kgs). For the first 21 days on feed, cattle were fed a ration containing 14% ground hay, 14% corn, 35% wet distillers grains, 33.5% corn silage and 3.5% supplement mix. The ration changes after 21 days to incorporate 15% sorghum silage with a subsequent decrease in ground hay and corn silage.

Site B is located in central Kansas and is used primarily as a grow facility for a larger feedlot operation. Pens consist of traditional dirt floor pens and grass traps. Maximum capacity at the facility is approximately 11,000 head and cattle are kept on pasture from May to August. Cattle for the trial came from 2 cohorts of native breed heifers purchased from a sale barn in Oklahoma City at average weights of 450 lbs (204 kgs) and 550 lbs (249 kgs). At arrival, cattle started on a ration consisting of 22% rolled corn, 6.5% sorghum silage, 38% ground hay, 30% modified distillers grains, and 4% liquid protein. At this site, cattle remain on the starter ration for 3 weeks before beginning a step-up program to the final grow ration which contains a higher corn and modified distillers percentage. Cattle typically remain at this site for 90 days before moving to the finishing feedlot.

Site C starts 1,500 calves per year on grass in the Flint Hills region of Kansas. Calves receive brome and prairie hay ad libitum and the starter feed contains soybean hulls, dry distillers grains, oats and corn. Calves are fed until they are eating 2% of their body weight in hay and 1% of their body weight in starter feed. Typically, this operation feeds cattle from mid-October to mid-March. Trial calves at this site were all heifer calves sourced from a southwest Missouri auction market and shipped to central Kansas. Cattle weighed an average of 504 lbs (229 kgs) at arrival and all tested negative for persistent bovine viral diarrhea virus infection (BVDV PI) using an ear notch test.

Site D purchases cattle from livestock auction markets year-round to start on grass in central Kansas. Cattle had access to 30-acre pastures and were fed prairie hay ad libitum along with dry distillers grains and cracked corn in a 1:1 ratio. The cattle purchased for this study were purchased from northern Alabama and southern Tennessee auction markets over 3 days, most as singles or pairs, and transported for 12 hours. Approximately 80% of the cattle were bulls with the remaining 20% as steers. At arrival, cattle weighed 630 lbs (286 kgs) on average.

Site E is a row-crop and stocker operation in Kentucky. Cattle are purchased from several regional auction markets and transported to the facility in groups throughout the year. Cattle have access to grass pastures attached to dirt floor pens.

Site F feeds 6,000 calves per year, keeping about 1,200 head on site at one time, year-round. Pens are approximately 15 acres each and are a combination of dirt floor and pasture. Cattle are fed a ration consisting of hay, corn silage, wet distillers grain, hominy and mineral mix. Cattle for the study were sourced from multiple sale barns in Kentucky, Tennessee and Georgia in October. They were placed in groups of 70-80 head upon arrival to the operation in Indiana with an average arrival weight of 480 lbs (218 kgs). All cattle from this site were steers.

No feed-grade antimicrobials were administered in the rations at any sites. Other feed additives such as melengesterol acetate or amprolium were allowed, if necessary. Water access was provided ad libitum through automatic waterers at each operation. Enrollment was not restricted by site. Animals were enrolled on a rolling basis until a total of 400 animals was enrolled.

Enrollment

Animals were randomly assigned in a 1:1:1 ratio within each cohort to one of 3 PTI groups: 3-day, 6-day and 9-day. Study participants were given an enrollment form to use to assign animals to one PTI group in groups of 3. Complete blinding of study personnel to treatment group was not possible given that the same individuals were enrolling animals in the study and administering treatments.

A random number generator (Excel) was used to create a random number for each blank on the enrollment form. For each group of 3 rows on the enrollment form, the smallest number was assigned to the 3-day PTI, the largest number was assigned to the 9-day PTI, and the middle number was assigned to the 6-day PTI. The first calf meeting the BRD case definition was assigned to the first blank. The next calf from the same cohort was assigned to the second blank. This randomization strategy was performed in an effort to distribute PTI groups evenly between cohorts. Ear tags were used to denote the date the calf would be eligible for treatment. No information about the date the calf was originally pulled was included on the ear tag. Weight at the time of treatment and rectal temperature were recorded.

Observation period

Following drug administration and assignment to PTI group, cattle were returned to their home pen and followed for 45 days to monitor for subsequent health outcomes. Following the assigned PTI, cattle were eligible for retreatment if they met the initial case definition for BRD. Animals that required additional treatment(s) were treated according to individual operation protocol, but were not treated with pradofloxacin again. Health outcomes of interest were: first treatment success (FTS), case fatality (CF) and DTD. FTS and CF were determined at the individual animal level and converted to binary outcomes. Treatment success was defined as not requiring additional treatment for BRD and not experiencing mortality within 45 days of initial treatment. Case fatality was defined as mortality due to any cause within 45 days of initial treatment. The variable characterizing the number of days between initial treatment and death for those animals experiencing a case fatality was left as a continuous numerical variable and was calculated as DTD. Cattle for which 45-day observation data was unavailable and cattle which were treated before their assigned PTI was over were removed from final analysis. Post-mortem examinations were not performed consistently across sites to determine cause of death. As such, an animal was considered a case fatality if it died following enrollment without regard for true cause of death.

Statistical analysis

Data management steps and subsequent statistical analysis were carried out in R software.[9] Sex was not included in the models as it was confounded by site and cohort. Weight and rectal temperature were categorized for analysis. Weight was categorized into 4 groups: 450 lbs (204 kgs) or less, 451-550 lbs (205-249 kgs), 551-650 lbs (250-295 kgs), and greater than 650 lbs (295 kgs). Temperature was categorized: normal (below 104 ˚F, 40 ˚C) and febrile (greater than or equal to 104 ˚F, 40 ˚C) based on pre-established case definition.

Generalized linear mixed models were used for statistical analysis of FTS and CF with binomial distributions. To model DTD, a generalized linear mixed model with a Poisson distribution and log link function was utilized. In all models, a random effect of cohort nested within site was included to account for lack of independence. Fixed effects included rectal temperature category, weight at enrollment category, and PTI group. Rectal temperature and weight categories remained in the model as experimental design factors. Pairwise comparisons for PTI group were performed using Tukey's adjustment.

Results

A total of 446 animals were enrolled in the study. One animal was removed as it was enrolled twice, and 14 animals were removed due to re-treatment before their assigned PTI was completed. Site E was removed less than a week from the start of the study due to a higher-than-expected morbidity and labor constraints. All animals enrolled at Site E were removed from the study (n = 25). Table 1 displays the total number of animals enrolled at each site, excluding the 40 animals that were removed.

Descriptive characteristics for the 406 enrolled cattle are presented by treatment group in Table 2. A chi-square test of independence was applied to determine differences in sex between PTI treatments groups. There were no statistical differences between the counts of heifers, steers or bulls between the PTI treatment groups (*P*-value > 0.05). Site B experienced an outbreak of nervous coccidiosis approximately half way through the trial. The affected pens of cattle received a 5-day course of amprolium pellets at 454 mg per 100 lb of body weight. Three calves enrolled in the trial demonstrated neurologic signs and were independently treated with oral sulfa boluses and thiamine (vitamin B1) injection (n = 3). The treatment for nervous coccidiosis did not meet criteria for BRD re-treatment; however, 2 calves subsequently died following treatment, and these were included as treatment failures and case fatalities. The surviving calf was considered a treatment success as it did not require additional treatment for BRD and did not experience mortality.

First treatment success

First treatment success risk across all study sites was 61.8%. There were no statistically significant differences in first treatment success between PTI treatment groups ($P = 0.51$). Other fixed effects including rectal temperature category and weight at treatment category were not statistically associated with first treatment success. Numerically, the 9-day PTI group had the poorest treatment success risk and the 6-day group had the best risk.

Case fatality and days-to-death

There were also no significant differences in case fatality between PTI treatment groups ($P = 0.52$). Fixed effects including rectal temperature category and treatment weight category were not statistically associated with case fatality. DTD was not statistically different ($P = 0.20$) between the 3 treatment groups. Table 3 reports the model-estimated means and standard errors of the mean (SEM) by treatment groups for the 3 outcome measures (FTS, CF and DTD).

Table 1: Characteristics of cattle at study enrollment by study location.

Site	Total number enrolled	Average weight, lbs (kgs)	Sex
A	147	575 (261)-605 (274)	Steer
B	155	450 (204)-550 (249)	Heifer
C	29	504 (229)	Heifer
D	44	630 (286)	Bull, Steer
F	31	480 (218)	Steer

Table 2: Characteristics of cattle at study enrollment based on treatment group and across the study population.

	3-day PTI	6-day PTI	9-day PTI	Overall
% Bull*	7.4 (10/136)	8.3 (11/133)	9.5 (13/137)	8.4 (34/406)
% Steer*	39.7 (54/136)	39.8 (53/133)	35.0 (48/137)	38.2 (155/406)
% Heifer*	52.2 (71/136)	51.9 (69/133)	54.7 (75/137)	53.0 (215/406)
Weight at treatment, lbs (kgs)	547 (248)	548 (249)	546 (249)	547 (248)
Temperature at treatment, degrees Fahrenheit (degrees Celsius)	104.9 (40.5)	104.9 (40.5)	104.8 (40.4)	104.9 (40.5)

* Two animals in the study population were missing recorded sex information; denominator reflects the total sample size.

Table 3: Outcome means (± SEM) by treatment group from generalized linear mixed models with random intercept to account for lack of independence in cohorts within sites.

Outcome	3-day PTI	6-day PTI	9-day PTI	Overall *P*-value
First treatment success risk, %	71.24 ± 7.47	74.72 ± 6.74	68.82 ± 7.71	0.51
Case fatality risk, %	5.35 ± 2.59	6.84 ± 3.01	8.93 ± 3.80	0.52
Days-to-death	18.24 ± 2.47	16.28 ± 2.22	18.18 ± 2.15	0.20

Discussion

To the authors' knowledge, this is the first study to investigate PTIs for pradofloxacin in naturally occurring BRD. Furthermore, it is one of the first investigations evaluating PTIs in stocker calves for any antimicrobial. Results of this study indicate that there are no differences in FTS, CF and DTD between the investigated PTIs. These results help provide recommendations for antimicrobial use in stocker calves treated for naturally occurring BRD.

Previous studies in feedlot cattle with different antimicrobials have demonstrated the value of PTIs for improving treatment outcomes.[4-8] A multi-site investigation in feedlot cattle comparing 3-, 5- and 7-day PTIs following administration of ceftiofur crystalline free acid (CCFA) for BRD found statistically significant ($P < 0.05$) differences in 28-day treatment success rates between the 3- (65.6%) and 7-day (77.5%) groups. There were no differences in treatment success between other PTI groups and no differences in mortality rates between PTI groups.[5] Another study evaluating CCFA in feedlot cattle was repeated over a 56-day observation period.[6] This study found improved treatment success risk among the 7-day group as compared to the 3-day group. There were no other differences in treatment success and no differences in mortality between treatment groups.[6] The CCFA studies demonstrated similar findings despite evaluating treatment outcomes over different lengths of time (28 days vs. 56 days).

A study evaluating PTIs in feedlot cattle treated for BRD with tilmicosin found a significant ($P = 0.05$) difference in first treatment success rates between the 3- (67.9%) and the 9-day (86.9%) PTI groups. The study found no significant ($P = 0.39$) differences in case fatality between PTI groups.[7] These 3 studies demonstrate that first treatment success rates were improved by implementing PTIs greater than 3 days following initial treatment. Extension of the PTI to 7 or even 9 days in the aforementioned studies likely allowed the cattle in these studies to return back to a "healthy" appearance, resulting in fewer second or third treatments.

Post-treatment intervals of 7, 10 and 14 days were evaluated following treatment of BRD in feedlot cattle with tulathromycin.[4] Statistical analysis found no significant ($P > 0.05$) differences for first treatment success and case fatality rates between PTI treatment groups. This research demonstrated that longer PTIs (greater than 7 days) had no impact on treatment success or mortality rates. A study by Theurer et al. evaluated prolonged PTI intervals following therapy with gamithromycin.[8] The study compared 3-, 6-, 9- and 12-day PTIs in feedlot cattle. Differences in first treatment success ($P = 0.012$) and case fatality ($P = 0.032$) between the PTI treatment groups were notable. Specifically, differences in first treatment success were seen between the 3-day (56.8%) and 9-day (72.3%) groups. Differences in case fatality were observed between the 9-day (7.2%) and the 12-day (15.0%) groups. While previous BRD PTI studies demonstrated that longer PTIs improved clinical outcomes, the gamithromycin PTI study demonstrated that there is likely an upper limit to PTIs at which point clinical outcomes are negatively impacted.[8]

The current study found no statistically significant differences in case fatality rates between treatment groups. This finding is consistent with other reported PTI studies with the exception of the study by Theurer et al.[8] However, the longest PTI investigated in the current was 9 days whereas the Theurer et al. study found a significantly higher case fatality in their 12-day PTI group. The current study also found no significant differences in first treatment success, a finding that is at odds with other studies.[5-8] Original sample size calculations anticipated a greater difference in first treatment success risk between the 3- and 9-day group, so it is likely the current study is underpowered. Additionally, a permissive BRD case definition was used, meaning that the criteria for initial enrollment and retreatment were easily met. Doing so allowed for high external validity, as this is representative of current standard practice in the industry; however, it may have resulted in the treatment of animals that would have otherwise recovered without intervention. This could have led to higher treatment success rates and lower case fatality rates. Previous PTI studies utilized BRD case criteria for enrollment that differed from what was used in the current study which may have contributed to differences in study findings.[7,8]

At the time of this writing, only one study has been published evaluating the efficacy of pradofloxacin compared to other antimicrobials for the treatment of BRD. As a secondary outcome, Foster et al. evaluated clinical outcomes in dairy steers challenged with *M. haemolytica* and subsequently treated with pradofloxacin, tulathromycin or florfenicol.[3] All steers demonstrated rapid resolution of clinical signs following treatment administration and there were no statistically significant ($P > 0.05$) differences between groups with regard to depression score, respiratory score or rectal temperature from day of treatment to study endpoint (all steers were humanely euthanized on day 12 post-treatment).

DTD has not been evaluated in case fatalities in previous PTI studies. Motivation for investigation of DTD as an outcome was brought about by producer concerns that adhering to longer PTIs results in cattle dying later due to delayed retreatment. Median values for the current study's case fatality were all below 20 days with a maximum value of 43. Smith et al. reported on DTD following initial BRD treatment in feedlot cattle across several regions in the United States.[10] Their first and third quartile values are 4 and 43, closely matching our data. The current study demonstrated no significant differences in DTD between PTI treatment groups, indicating that the PTI investigated in this study do not impact timing of death. Furthermore, the distribution of DTD is similar to that reported in the literature for feedlot cattle.

Many meta-analyses have been published comparing efficacy of several antimicrobials for the treatment and control of BRD.[11-15] The meta-analyses were published before the approval for pradofloxacin for treatment of BRD but most report on the comparative efficacy of other fluoroquinolone antimicrobials. The meta-analyses summarize that both enrofloxacin and danofloxacin result in lower re-treatment risk compared to other antimicrobials except tulathromycin.[12-14] It is important to mention, however, that the meta-analyses reported here do not account for a PTI which is needed to direct comparisons between antimicrobials when evaluating efficacy.

One of the major strengths of this study is the external validity of the study population. This study was conducted in commercial operations with cattle procurement, feeding and management typical of current stocker cattle industry practices. Although processing and health evaluations were standardized by study protocol, they were also representative of stocker production practices. One of the limitations of this study is the incomplete blinding of cattle health evaluators to treatment groups. It was not possible to keep all individuals at these operations blinded to the treatment groups due to labor constraints; however, each site had multiple animals enrolling each day, making it more difficult to identify which animals belonged to each PTI treatment group due to the numerous eligible retreatment dates. Another limitation of this study is the permissive BRD case definition. This could have resulted in more spontaneous recoveries, leading to higher treatment success rates and fewer case fatalities. Additionally, permissive retreatment criteria could have led to a greater number of retreatments. Together with the spontaneous recoveries, the current BRD case definition could have led to few differences between PTI treatment groups. Despite this limitation, the enrollment criteria used in the current study was an accurate reflection of BRD case definitions on these operations, further contributing to external validity. As not all of the sites in this study typically use a rectal temperature cut-off for treatment, a rectal temperature cut point of 104 ˚F (40 ˚C) or greater was only included as one of the enrollment criteria.

Evaluation of clinical outcomes following treatment is important for determination of the optimal PTI. This trial found no significant differences in first treatment success and case fatality between PTI treatment groups. Other studies have concluded that longer PTIs demonstrate favorable FTS, although the findings are not consistent in PTIs 12 days or longer. Lack of statistical differences in case fatality between treatment groups is supported by the literature. Low statistical power and a permissive BRD case definition likely contributed to the findings in the current study. DTD was not statistically different by treatment group. Results of this study should not be extrapolated to other populations of cattle (such as those in the finishing phase of production) without confirmation of these findings in additional studies. The results of this study will help practitioners determine the optimal application of pradofloxacin related to health outcomes in beef stocker cattle.

End Notes

[a]Pradalex, Elanco Animal Health, Greenfield, IN

[b]Increxxa, Elanco Animal Health, Greenfield, IN

[c]Titanium 5, Elanco Animal Health, Greenfield, IN

[d]Nuplura, Elanco Animal Health, Greenfield, IN

[e]Cydectin, Elanco Animal Health, Greenfield, IN

Conflicts of interest
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Author Contributions
Lilli Heinen, writing original draft, review and editing, visualization, investigation, formal analysis, methodology; Brian V. Lubbers, writing, review and editing, conceptualization, investigation, supervision, funding acquisition, project administration; Ronald K. Tessman, writing, review and editing, conceptualization, methodology, supervision, project administration; Raghavendra G. Amachawadi, writing, review and editing, conceptualization, supervision, methodology; Brad J. White, writing, review and editing, supervision, project administration.

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