Original research

The effect of tilmicosin in minimizing atrophic rhinitis, pneumonia, and pleuritis in swine

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Summary

Objective: To determine whether nursery pigs fed tilmicosin for 3 weeks would be protected against progressive atrophic rhinitis (PAR) when housed with clinically diseased pigs.

Methods: Recipient pigs, exposed to donor pigs that demonstrated clinical signs of PAR, either did not (NME group) or did (ME group) receive tilmicosin in feed for 3 weeks; a third Control group was neither exposed nor medicated. Pig weights and nasal swabs for bacterial culture were collected on study days 0, 21, and 42. Feed intake was also monitored. On study day 21, all medication was removed from the ME feed and the donor animals were submitted for postmortem examination. On study day 42, NME, ME, and Control pigs were euthanized and submitted for postmortem examination. Snout scores, pneumonia, and pleuritis were assessed grossly and scored. Turbinate perimeter ratios were also scored using a digital image processing and analysis program.

Results: Overall, rate of gain was greater in the Control pigs than in either the ME or NME pigs. Average daily gain and feed intake were significantly greater ($P<.05$) in the ME pigs compared to the NME pigs throughout the study. Feed efficiency did not differ significantly among groups. All recipient pigs were culture negative for *Bordetella bronchiseptica* and *Pasteurella multocida* on day 0. The Control pigs remained negative for *P. multocida* types A and D throughout the study and only one pig was positive for *B. bronchiseptica* by culture at the end of the study. A higher percentage of NME pigs than ME pigs were culture positive for *P. multocida* on days 21 and 42. From study days 21–42,

there was a marked increase of positive *P. multocida* type A cultures in ME pigs. At slaughter, Control pigs showed no gross pneumonia lesions and had lower visual snout scores compared to both the ME and NME pigs. Visual atrophic rhinitis scores were significantly higher ($P<.05$) in the NME pigs compared to the ME pigs.

Implications: Treatment with tilmicosin resulted in lower snout scores and better growth in ME pigs than in NME pigs.

Keywords: swine, progressive atrophic rhinitis, *Pasteurella multocida*, tilmicosin

Progressive atrophic rhinitis (PAR) remains a significant global economic problem in the swine industry.[1] Typically more severe than nonprogressive atrophic rhinitis (NPAR), which is caused by toxigenic *Bordetella bronchiseptica*,[1,2] PAR is a multifactorial disease complex that is caused by coinfection with toxigenic *Pasteurella multocida* types A and D and *B. bronchiseptica*.[1–3] The etiology of PAR is attributed to concurrent infections with *B. bronchiseptica* and toxigenic *Pasteurella multocida* types A and D;[1–4] nontoxigenic strains of *P. multocida* types A and D have also been observed to contribute to the syndrome.[1,5] Although infectious organisms play an important role in the progression of the disease, the barn environment and management also contribute to its severity.[1]

Infection with *B. bronchiseptica* usually results in an inflammatory reaction in the mucosa and submucosa of the turbinates, causing a mild turbinate atrophy that allows toxigenic *P. multocida* to colonize

and damage osteoclasts and osteoblasts. Thus, concurrent infection with *B. bronchiseptica* and toxigenic *P. multocida* can result in a more severe and progressive atrophy and septum deviation than infection with *P. multocida* alone.[1,3,4] Overall, PAR has a detrimental impact on growth performance and also provides opportunities for more severe secondary pathogens to invade.[6]

Concurrent infections with *B. bronchiseptica* and *P. multocida* (toxigenic and nontoxigenic strains of both types A and D) remain a reality in modern United States production systems, whether they use a conventional one-site system[1] or wean prior to 21 days and move the nursery pigs to an off-site unit.[7]

Tilmicosin is a long-acting macrolide antibiotic, closely related to erythromycin and tylosin. It was approved under the Veterinary Feed Directive (VFD) 1996 for use in swine for treatment of pneumonia caused by *Actinobacillus pleuropneumoniae* and *P. multocida*.

In an earlier pilot study, tilmicosin fed at 200 g per ton for 6 weeks appeared to minimize AR in nursery pigs.[8] According to the current label instructions, the drug's use is limited to 183–363 g per ton for 3 weeks. The current experiment was designed as a controlled continuous disease transmission study to determine whether tilmicosin, fed at 363 g per ton for 3 weeks, would protect nursery pigs exposed to infected pigs from contracting atrophic rhinitis and prevent a decrease in growth rate. Previous investigators have reported the natural transmission of AR from positive donor pigs to negative recipient pigs.[9]

Materials and methods

Donor pigs
A 100-sow, farrow-to-finish herd with severe endemic PAR served as the "donor" farm for this study.

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One month before the initiation of the trial, a slaughter check of 27 market hogs from this farm revealed gross AR lesions in 91% of the hogs (36% had mild lesions and 55% had moderate to severe lesions). Pneumonia lesions were observed in 14 of these market hogs. Seven of the 27 market hogs were bled and serological analysis was performed (Bayer Veterinary Diagnostic Center, Worthington, Minnesota) using an indirect ELISA to measure antibody titers to *A. pleuropneumoniae, Haemophilus parasuis, Mycoplasma hyopneumoniae,* and swine influenza virus (SIV). A microagglutination test was used to test for *Streptococcus suis.* All seven of the bled hogs were positive for *H. parasuis* and *M. hyopneumoniae.* Six of these seven were positive for *S. suis* and one was positive for SIV. Ten of the 27 market hogs were nasal swabbed; all were positive for nontoxigenic *P. multocida* type A and one was positive for toxigenic *P. multocida* type D.

After the initial screening of the donor herd, 24 pigs with clinical signs of atrophic rhinitis were selected to serve as the donor pigs in this study. Nasal swab cultures were performed on eight of the 24 pigs on day 0 and all 24 donor pigs on day 21. Blood samples were also collected from the 24 donor pigs on day 21 to test for the same respiratory pathogens analyzed in prescreening of the donor herd. The donor pigs received no medication during the trial.

Recipient pigs

Seventy-two crossbred barrows, free of AR on the basis of herd history, nasal cultures, and slaughter checks, were purchased from a high-health facility at weaning (12–14 days of age) and designated as "recipient" pigs. Neither the recipient pigs nor their dams had been vaccinated against *B. bronchiseptica* or toxigenic *P. multocida*.

Upon arrival, the recipient pigs were allowed a 7-day acclimation period prior to the trial. For the first 3 days of this acclimation period, the pigs were treated with 4 mg per kg IM of ceftiofur hydrochloride (Excenel® Pharmacia & Upjohn Animal Health, Kalamazoo, Michigan) to minimize respiratory infections at the start of the trial. Also, recipient pigs were fed a commercial diet containing 140 g/ton Neomycin and 100 g/ton Terramycin (Land O' Lakes, Inc., Minneapolis, Minnesota) for the entire 7 days, until the trial

began. All 72 pigs were negative for *B. bronchiseptica* and *P. multocida* by culture at day 0 of the trial.

At the start of the trial (study day 0), each of the 21-day-old recipient pigs was allotted to one of three treatment groups:

- an "NME" group (n = 24) that was exposed to the donor pigs and was not medicated with tilmicosin,
- an "ME" group that was exposed to the donor pigs and medicated with tilmicosin, or
- a Control group that was neither exposed to the donor pigs nor medicated with tilmicosin.

Facilities

All pigs used in this study were housed in isolation rooms at the University of Wisconsin Animal Research Center. The donor pigs were randomly distributed to pens in six rooms (two pens per room) with four pigs per pen. The second pen in each room housed eight 3-week-old recipient pigs. A randomized design of treatments to rooms was used to eliminate room differences. The pen dividers allowed nose-to-nose contact. In addition, the gate doors were opened for approximately 1 hour each day to maximize the contact between donor and recipient pigs. Three groups of eight recipient pigs were housed in the remaining two rooms as the nonexposed Controls.

Nutrition

Diets were formulated to meet or exceed NRC 98 requirements for nursery pigs. The Control and NME groups were fed the same diet. The diet for the ME pigs included an addition of 363 g per ton of tilmicosin. At the start of the trial, diets were sampled and analyzed to ensure drug concentrations were within target concentrations. Feed consumption was monitored during the entire trial, and all recipient pigs were weighed on study days 0, 21, and 42.

Bacterial culture

During the trial, nasal swab cultures were collected on days 0, 21, and 42. Control animals were sampled first, after which the NME and ME groups were sampled. Strict biosecurity was maintained to prevent cross-contamination between rooms.

All swabs were cultured for *B. bronchiseptica* and *P. multocida* types A and D. *Pasteurella multocida* type D isolates were toxin tested using the standard protocol at the Bayer

Veterinary Diagnostic Center using a fetal feline lung cell line, previously described by Rutter and Luther.[10] Toxin testing was conducted only for *P. multocida* type D isolates because they are more commonly found than are the type A isolates.[1–3]

Postmortem examination

On study day 21, all donor pigs were slaughtered and examined for AR and other lesions. From each room, three of the recipient pigs were randomly selected and euthanized, and postmortem data was collected on study day 21. The remaining five recipient pigs, regardless of treatment group, were maintained on the nonmedicated diet for an additional 21 days. On day 42, the remaining recipient pigs were euthanized and necropsied.

Visual snout scores, pneumonia lesions, and any other postmortem findings were recorded.[11,12] Pneumonia was scored from 0–3 based on an estimate of the total percentage of lungs showing gross pneumonic consolidation, as previously described.[12]

Pleuritis was scored 0–3 where:

1= mild, local pleuritis with no adhesions to the chest or pericardium;
2= moderate adhesions to the chest or pericardium;
3= widespread pleuritis with severe adhesions

as previously described.[11,12]

Snouts were cut transversely between the first and second premolars. After gently cleaning the turbinates with water, the visual gross scores for atrophy and deviation were recorded. The visual atrophic rhinitis score (0–9: 0 = no lesions, 9 = severe lesions) puts twice the weight on atrophy as it does on deviation.[9,13]

Snouts were then photographed with a 35-mm camera and the photographs used to measure the turbinate perimeter ratio (TPR) according to the scoring system described by Collins, et al.[14] (a ratio of ≥1.4 = no lesions, a ratio of <1.0 = severe lesions). Measurements were performed using a digital image processing and analysis program (NIH Image version 1.59, National Institute of Health, Bethesda, Maryland).

Statistical analysis

Total feed intake (FI) and average daily gain (ADG) were calculated for each

treatment group and for the different time periods. ADG (g per day) and F:G was calculated on a pen basis. Descriptive statistical analysis of the continuous variables (ADG, Feed efficiency [FE], FI, TPR) were determined using an univariate ANOVA in SAS (PC/SAS Version 7–1, SAS Institute, Cary, North Carolina). Categorical data including culture results, pneumonia, pleuritis, and visual snout scores were analyzed using the CATMOD procedure in SAS. Data were considered to be significantly different if the *P* value was <.05.

Results

Growth performance

All of the treatment groups had similar average starting weights (5.74 ± 0.99 kg).

Among all three treatment groups, FI did not differ (*P* > 0.1) over the first 21 days (Figure 1). From day 21 to day 42, FI was significantly higher for Control pigs than ME or NME pigs (*P*<.05), and was significantly higher for ME pigs than NME pigs (*P*<.05).

During the first 21 days of the trial, ADG for NME pigs tended to be less (*P*=.06) than the Control and ME pigs (Figure 1). There were no significant differences between Control and ME pigs.

From days 21 to 42, ADG in the Control pigs was significantly higher (*P*<.05) than in the NME and ME pigs. When overall ADG was calculated for the entire 6-week trial, ADG differed significantly among all three treatment groups (Figure 1).

FE did not differ significantly among the three treatment groups throughout the trial (Figure 1).
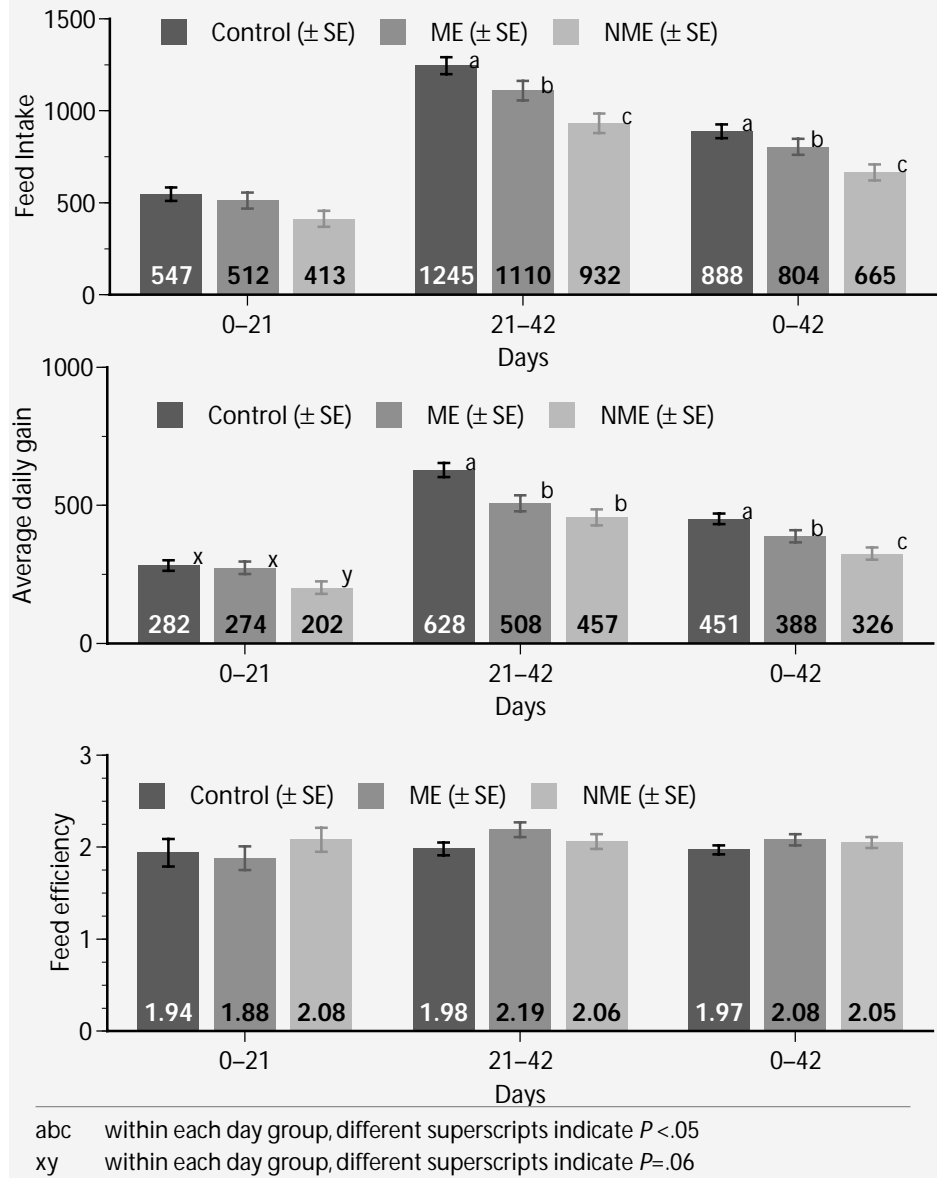
Serologic testing of donor pigs

Donor pigs had antibody titers for *A. pleuropneumoniae* (10 of 24), *Mycoplasma hyopneumonia* (13 of 24) *H. parasuis* (2 of 24), SIV (6 of 24), and *S. suis* (7 of 24).

Bacterial culture

On day 0, six of eight of the donor pigs were culture positive for *P. multocida* type A, and two of the eight were culture positive for toxigenic *P. multocida* type D. All recipient pigs were culture negative for *B. bronchiseptica* and *P. multocida* types A and D (Figure 2).

The Control pigs remained culture negative for *P. multocida* types A and D

Figure 1: Growth performance of recipient pigs

abc within each day group, different superscripts indicate *P*<.05
xy within each day group, different superscripts indicate *P*=.06

throughout the entire study, although one Control pig was culture positive for *B. bronchiseptica* on day 42 (Figure 2).

By day 21, most of the donor pigs were culture positive for *B. bronchiseptica* and *P. multocida* type A (Figure 2). Only two of the 24 donor pigs were culture positive for toxigenic *P. multocida* type D. Significantly more of the NME pigs were culture positive for *P. multocida* type A compared to ME pigs (*P*<.05) (Figure 2). However, culture results for *P. multocida* type D (toxigenic or nontoxigenic) and for *B. bronchiseptica* did not differ between the NME and ME groups.

By day 42, the percentage of pigs culture positive for *B. bronchiseptica* and *P. multo-*

cida type D (toxigenic or nontoxigenic) did not differ between the ME and NME groups. However, there were still significantly more pigs in the NME group than in the ME group that were culture positive for *P. multocida* type A (*P*<.05).

Postmortem examination and snout scores

Most donor pigs had pneumonia and pleuritis lesions, and also had a median visual AR score of 5 (Table 1). At necropsy, no pneumonia or gross pleuritis lesions were observed in any of the Control pigs (Figure 3). Both pneumonia and pleuritis scores were significantly (*P*<.05) higher in the NME pigs than in the ME or in the Control pigs; ME and Control groups did not

Figure 2: Percent positive *Bordetella bronchiseptica* and *Pasteurella multocida* cultures from recipient pigs

Bordetella bronchiseptica

Pasteurella multocida type A

Pasteurella multocida type D (non-toxigenic)

Pasteurella multocida type D (toxigenic)
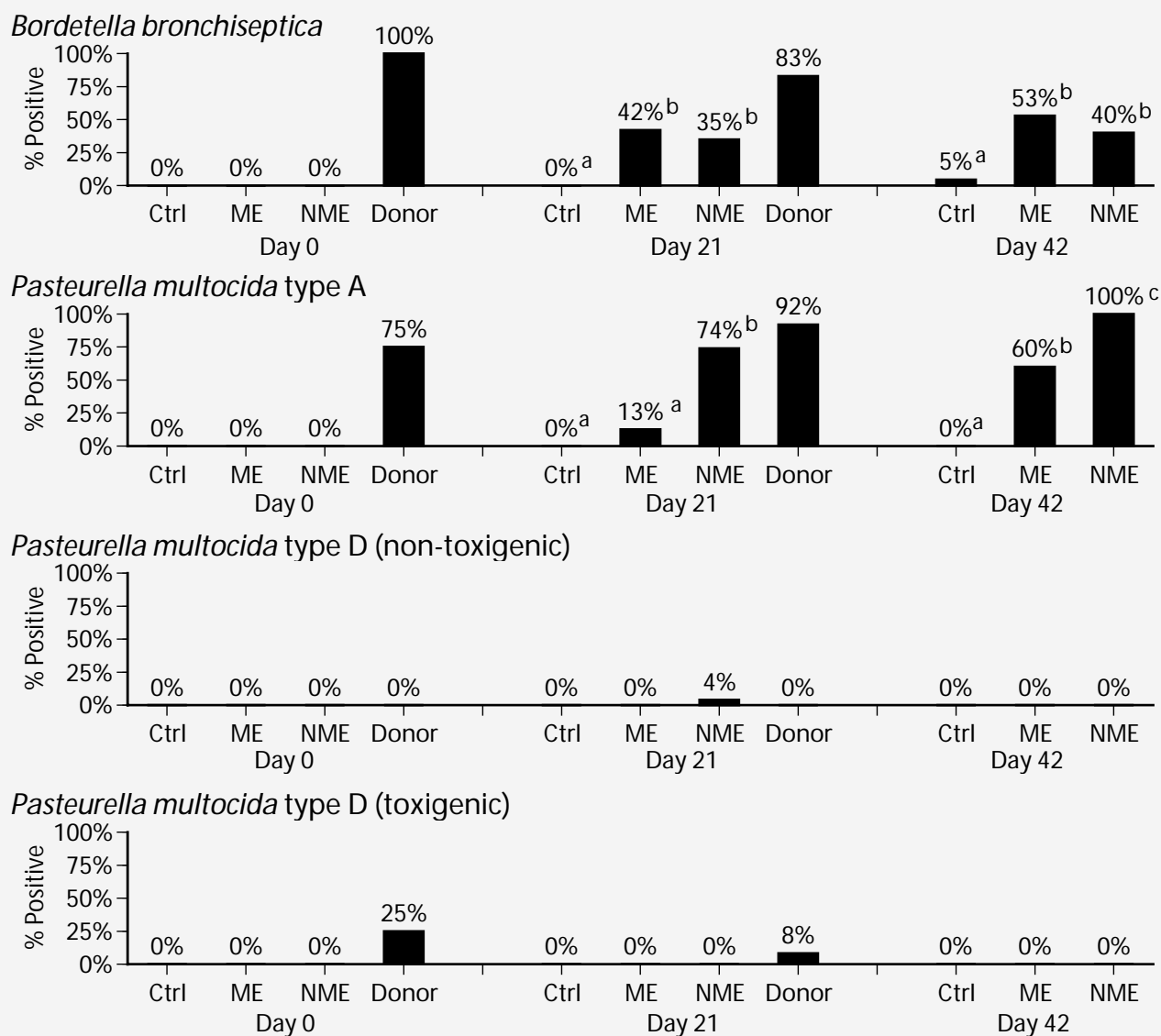
abc   within each day group, different superscripts indicate *P* <.05

Table 1: Donor pig results at day 21

Measurement	Value
Positive for *P. multocida* type A or D	96% (23 of 24)
Turbinate perimeter ratio	0.87 ± 0.07
Median gross visual AR score	5
Pneumonia score	79% (19 of 24)
Pleuritis score	37.5% (9 of 24)

differ.

The median visual snout score for both the Control pigs and the ME pigs was zero (0). However, the median visual snout score of the NME pigs (3) was significantly worse (*P* <.05) than in the other two treatment groups.

TPR measurements of the donor pigs at day 21 showed evidence of PAR (Table 1). Whether recipient pigs were euthanized at day 21 or 42, the TPR measurement differed significantly among groups (*P* < .05) (Figure 4).

Discussion

The study's primary focus was to determine what effect tilmicosin would have on transmission of progressive atrophic rhinitis. The model was designed to simulate the natural transmission of disease via animal contact similar to what would occur in a commercial herd, where animals can be simultaneously exposed to different pathogens.

In our study, disease characterized by turbinate atrophy, pneumonia, and pleuritis appeared to be effectively transmitted from 12-week-old donor pigs with clinical signs of PAR to healthy 3-week-old recipient pigs. Our biosecurity and isolation methods were also effective in preventing transmission of *P. multocida* to the Control pigs. However, we could not verify that toxigenic *P. multocida* type D had been transmitted from donor pigs to recipient pigs, since only two of the 24 donor pigs cultured positive for toxigenic *P. multocida* type D at any point in the trial. Although by day 21, 22 of the 24 donor pigs were

Figure 3: Percentage of recipient pigs with any lesions
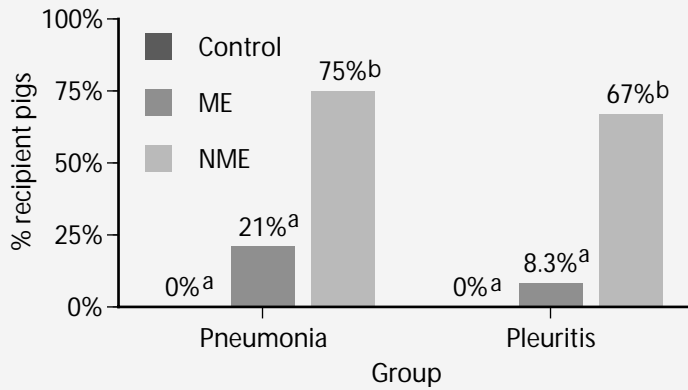
ab   within each day group, different superscripts indicate *P* <.05

Figure 4: Turbinate perimeter ratios (TPR) for recipient pigs
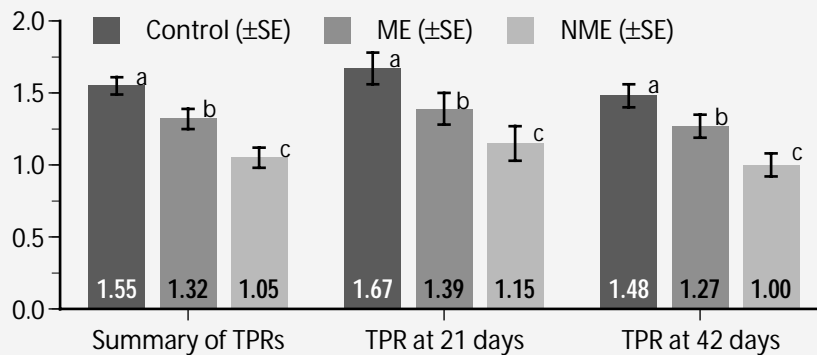
abc   within each day group, different superscripts indicate *P* <.05

culture positive for *P. multocida* type A, toxin testing on this serotype was never performed. Therefore, we lack the bacterial evidence that would allow us to definitively differentiate between progressive or nonprogressive atrophic rhinitis in the recipient pigs.

The significant differences in ADG and FI between the ME and NME pigs, and the significantly more severe lesions observed at necropsy in the NME pigs compared to the ME pigs, are highly suggestive of progressive atrophic rhinitis. Growth and lesion data were not consistent, however, with the bacterial results. No toxigenic *P. multocida* type D was ever cultured from any of the ME or NME pigs, and nontoxigenic *P. multocida* type D was cultured from only one of the NME pigs. It is possible that the discrepancy between the culture results and growth rate and necropsy data could be explained by a failure to detect *P. multocida* type D and its toxins. However, two donor pigs were found to be culture positive for toxigenic *P. multocida* type D on day 21, suggesting that the tests used were adequate.

We based our standard laboratory protocol to test only the *P. multocida* type D isolates for toxin on reports that toxigenic *P. multocida* type A is rarely cultured in cases of progressive atrophic rhinitis.[1–3] In retrospect, it would have been more informative to test all *P. multocida* isolates for toxin production.

Although ADG differed significantly among all three treatment groups when calculated for the overall study period, it was only during the 21–42 day period, when no tilmicosin was administered, that all three groups became significantly different. It seems likely that the Control pigs, because they had been isolated, maintained maximum health and continued to grow well from days 21–42. After the tilmicosin was withdrawn from the feed of the ME pigs, their growth differed significantly from the Control pigs (*P* <.05) and not from the NME pigs.

Tilmicosin appeared to limit the number of pigs testing positive for *P. multocida* types A and D in the ME group. After tilmicosin was discontinued and all of the donor pigs were removed from the study, the number of pigs testing positive for *P. multocida* continued to increase (Figure 2). This is another indication that the drug may not be 100% protective against infection, but is able to minimize the effects of disease and to improve the growth performance of exposed treated pigs compared to exposed nontreated pigs. Our findings were consistent with those of a study that evaluated tilmicosin's effectiveness against respiratory disease in 12- and 21-day-old weaned pigs, in which it was observed that the clinical expression of mycoplasmal pneumonia was delayed in treated pigs.[15] Two other studies examined tilmicosin's efficacy against *A. pleuropneumoniae* and observed that treated pigs had an increase in ADG and a decrease in the severity of *A. pleuropneumoniae* pneumonia.[16,17]

TPR has been shown to be an effective tool in evaluating AR in pigs.[14] The TPR values we observed in the Control pigs were consistent with the findings of Collins, et al.[14] The TPRs of the NME pigs at day 42 were similar to the TPRs of the donor pigs that were euthanized at day 21. The TPR measurements in our study further support the likelihood that the donor pigs had transmitted progressive atrophic rhinitis to the exposed recipients.

It is important to keep in mind that our donor pigs came from a commercial herd and had been exposed to a variety of other pathogens typical for such operations. Therefore, the role of the few respiratory pathogens identified in this study should not be overstated. The possibility remains that the other respiratory pathogens present in the donor pigs may have influenced the outcome of the study.

Implications
- When determining the role of *P. multocida* in atrophic rhinitis (progressive and nonprogressive), it is important to test for toxin production regardless of serotype.
- Tilmicosin, used as a feed additive at 363 g per ton for 3 weeks in a pig starter diet, appeared to minimize the lesions and improve the growth performance of pigs exposed to various respiratory pathogens.

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