Comparison of Common Antibiotic Therapies for *Haemophilus* Pleuropneumonia in Pigs

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ABSTRACT

Three experiments were done to evaluate some antibiotic therapies that are used commonly to treat pigs infected with *Haemophilus pleuropneumoniae*. Haemophilus-free piglets, 12 weeks of age, were challenged in a chamber with an aerosol of *H. pleuropneumoniae* serotype 1 and were medicated with antibiotics at various times before or after challenge. Antibiotic formulations which are commonly used to treat pneumonia in swine were used. They were chloramphenicol, penicillin, and a long-acting formulation of oxytetracycline given intramuscularly; and oxytetracycline, chloramphenicol and spiromycin (investigated as a potentially useful antibiotic) given in solution as the sole source of drinking water. Infection, disease (death, fever, gross lung lesions) and growth rate were measured in pigs following experimental challenge.

The therapeutic effect of these antibiotic formulations was evaluated for prevention of the disease (52 pigs), treatment of acute disease (36 pigs), and treatment of chronic pneumonia (45 pigs). Injectable, long-acting oxytetracycline prevented all manifestations of disease ($P < 0.05$) when given 24 hours before challenge. When treatment commenced immediately after the first signs of disease, each of the injected antibiotics reduced death rate ($P < 0.05$), but they neither improved average daily gain nor reduced the incidence of infection and lung lesions. Chronically infected carrier pigs were produced by first immunizing them with a *Haemophilus* vaccine and then challenging them three weeks later. None of the treatments reduced the proportion of carriers of *H. pleuropneumoniae*.

Key words: *Haemophilus pleuropneumoniae*, pigs, antibiotics.

RÉSUMÉ

Comparaison des antibiothérapies usuelles pour la pleuro-pneumonie porcine à *Haemophilus*

Trois expériences permirent d'évaluer certaines antibiothérapies communément utilisées pour traiter les porcs infectés par *Haemophilus pleuropneumoniae*. Les auteurs soumirent des porcelets sains et âgés de 12 semaines à une infection expérimentale, au moyen d'aérosols du sérotype #1 d'*H. pleuropneumoniae*; ils leur administrèrent aussi, à divers intervalles, avant et après cette infection, des antibiotiques qu'on emploie ordinairement pour traiter la pneumonie porcine, entre autres: du chloramphénicol, de la pénicilline et de l'oxytétracycline à longue action, par la voie intramusculaire; de l'oxytétracycline, du chloramphénicol et de la spiromycine, testée comme antibiotique éventuellement utile, donnés en solution comme la seule source d'eau de boisson. Les auteurs analysèrent aussi leurs observations relatives à l'infection et aux manifestations de la maladie, i.e. la fièvre, les lésions pulmonaires macroscopiques et la mort, ainsi qu'au taux de croissance.

Ils évaluèrent en outre l'efficacité des antibiotiques expérimentaux pour la prévention de la maladie et le traitement de ses manifestations aiguës et chroniques, chez respectivement 52, 36 et 45 porcs. L'oxytétracycline à longue action réussit à prévenir toutes les manifestations de la maladie ($P < 0,05$), lorsqu'on l'injectait 24 heures avant l'infection expérimentale. Quand on commenca l'antibiothérapie immédiatement après l'apparition des premiers signes de la maladie, chacun des antibiotiques injectés réduisit le taux de mortalité ($P < 0,05$), mais aucun n'améliora le gain de poids quotidien moyen ni ne réduisit l'incidence de l'infection et des lésions pulmonaires. Le fait de vacciner des porcs contre *Haemophilus* et de les soumettre à une infection de défi, trois semaines plus tard, se solda par la production de sujets porteurs, atteints de la forme chronique de la maladie. Aucun des traitements ne contribua à réduire la proportion de porteurs d'*H. pleuropneumoniae*.

Mots clés: *Haemophilus pleuropneumoniae*, porcs, antibiotiques.

INTRODUCTION

Haemophilus was first isolated from a pneumonic pig lung in 1957 and was identified from a Saskatchewan pig in 1971 (1,2). Porcine *Haemophilus* pleuropneumonia (PHP), caused by *H. pleuropneumoniae*, occurs in acute, chronic and subclinical forms and many epizootics have been reported in Canada and throughout the world (3). All three forms of the disease are now widely distributed in North America

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and nearly 70% of swine herds are seropositive in some regions (4).

Producers and veterinarians find chronic PHP difficult to control and often medicate pigs on an empirical basis (5). Antibiotic therapy is commonly used to control acute, chronic and subclinical PHP, because currently marketed vaccines do not prevent infection or the development of chronic carrier pigs (6). Nicolet and Scholl recommend that treatment of pigs with clinical, acute PHP begin as soon as possible after disease is detected with an injectable antibiotic (7). In at least one case, medication in feed and water was not effective for treating PHP (8).

Three experiments were done to compare the therapeutic efficacy of various commonly used treatments given at the recommended antibiotic dosage. In the first experiment, intramuscular or peroral antibiotics were given to pigs prior to challenge exposure to determine whether these treatments would prevent infection and disease. Second, because pigs with acute disease need high levels of antibiotic quickly, only intramuscularly administered antibiotics were compared for treatment of acute PHP. Third, in pigs with chronic PHP which may benefit from prolonged medication, oxytetracycline given intramuscularly as a long-acting formulation, oxytetracycline given orally in drinking water and spiromycin, a new antibiotic given orally, were compared.

MATERIALS AND METHODS

Bacteria

A strain of *Haemophilus pleuropneumoniae* serotype 1 originally isolated from the lung of a pig which died of PHP was used for challenge as previously described (9). This strain, designated 79-9, was susceptible to tetracycline (30 μg disc), penicillin (10 μg disc), and chloramphenicol (30 μg disc) but was resistant to spiromycin (10 μg disc) using the Kirby-Bauer technique on chocolate agar. After 24 h of growth at 37°C in an atmosphere of 5% CO_2 the bacteria were washed from chocolate agar plates with 0.85% NaCl and the bacterial suspension was diluted to contain approximately 10^5 colony-forming units/mL based on optical density.

Experimental Animals and Challenge Exposure with H. pleuropneumoniae

Landrace x Yorkshire x Lacombe pigs of both sexes were obtained from a *Haemophilus*-free herd and housed in metal pens in an isolation room. They had negligible antibody titers against *H. pleuropneumoniae* as measured by both serum agglutination and enzyme-linked immunosorbent assays. When they were 11 to 12 weeks of age, a group of five to seven piglets were selected randomly and exposed to the aerosol for ten minutes in the chamber. The chamber was constructed of galvanized steel and acrylic plastic and had a volume of 1.6 m^3 (9). An aerosol of *H. pleuropneumoniae* was generated from the bacterial suspension and blown into the chamber using a nebulizer (DeVilbiss ultrasonic nebulizer, Model 65, The DeVilbiss Co., Somerset, Pennsylvania) as previously described (10).

Recovery of Haemophilus

For isolation of *H. pleuropneumoniae*, samples of lung tissue were streaked onto sheep blood agar (5%) and *Staphylococcus aureus* was streaked perpendicularly. The plates were incubated at 37°C in 5% CO_2 and examined after 24 and 48 h. Haemolytic colonies exhibiting satellitism were identified as *H. pleuropneumoniae*.

Evaluation of Disease

Clinical signs of disease were monitored daily. Pigs that died after challenge and had gross lesions characteristic of PHP were deemed to have died from *H. pleuropneumoniae* infection. Haemorrhagic necrosis of the lung with pleuritis was considered to be a gross lesion characteristic of PHP. Body temperature was measured daily for at least five days after challenge and only pigs which had a body temperature greater than or equal to 41.0°C at least once during the five days after challenge were considered febrile. After death or humane euthanasia using a captive bolt pistol (Temple Cox Development Co. Ltd., Kent, England) and exsanguination, the entire lung of the pig was removed and palpated to detect lesions. A sample for bacteriological culture was taken aseptically from a lesion or from the dorsal portion of the right diaphragmatic lobe if no lesion was present. A pig was considered to be a chronic carrier if *H. pleuropneumoniae* was isolated from its lung one week or longer after challenge. Body weights were measured periodically throughout the experiments, and the average daily gains (ADG) were calculated.

Statistical Analysis

The significance of average daily gains among treatments was evaluated using one way analysis of variance. If that statistic was significant Student's t-test was used to determine which group differed from which other group (11). The significance of proportions was evaluated using chi-square analysis (11). The minimum significant confidence interval was set at 94% ($P < 0.06$).

Experiment I: Prevention

Methods

Fifty-two piglets were divided into one group of seven (controls) and three treatment groups of 15 (principals). Antibiotic therapy of all principals was started 24 h before challenge (Day −1) using the dosage recommended on the label. Group 1 (controls) were not treated. Pigs in group 2 received long-acting oxytetracycline (Liquamycin/LA, Rogar/STB, Edmonton, Alberta) (LAOT) intramuscularly at a dose of 20 mg/kg on two occasions (Day −1 and Day 2). Group 3 received chloramphenicol (Rogarmycine soluble powder, Rogar/STB, Edmonton, Alberta) in the drinking water for seven days at a concentration of 147 mg/L. Group 4 received oxytetracycline (Liquamycin soluble powder, Rogar/STB, Edmonton, Alberta) in the drinking water for seven days at a concentration of 222 mg/L. On Day 0, pigs were challenged using a suspension containing 1.7×10^5 CFU/mL. In each group of principals, three to six pigs were sacrificed two and four weeks after challenge and the remaining pigs were slaughtered ten weeks after challenge at approximately 90 kg of body weight. Two of the seven pigs in the control group survived challenge and were also slaughtered at approximately 90 kg of body weight.

TABLE I
DISEASE AND LESIONS OF PIGS GIVEN ANTIBIOTICS TO PREVENT ACUTE *HAEMOPHILUS* PNEUMONIA

Treatment Group	Route of Administration	Death	Fever	Lung Lesions in Survivors (Weeks After Challenge) 2	4	10
1 Unmedicated	None	5/7[a]	5/7	none	none	2/2
2 LAOT[c]	IM[b]	0/15[c]	0/15[c]	0/7	0/4	0/4
3 Chloramphenicol	oral	5/15	9/15	2/3	1/3	2/4
4 Oxtetracycline	oral	3/15[c]	5/15	0/4	1/4	1/4[d]

[a]Positive pigs/pigs in group.
[b]IM = intramuscular.
[c]Less than unmedicated group ($P < 0.05$).
[d]*H. pleuropneumoniae* was not isolated from the lung of this pig.
[e]Long-acting formulation of oxytetracycline.

TABLE II
AVERAGE DAILY GAIN (g/d) OF PIGS GROWN TO 90 kg GIVEN ANTIBIOTICS TO PREVENT ACUTE *HAEMOPHILUS* PNEUMONIA

Treatment Group (Route)	Phase of Experiment (Day of Experiment)[a] Pretreatment (-28 to -5)	Treatment (-5 to 9)	Total (-28 to 69)
1 Unmedicated	498 ± 77[b] (n=7)	182 ± 32 (n=2)	642 ± 7 (n=2)
2 LAOT[e] (IM)	637 ± 161 (n=15)	384 ± 272 (n=15)	781 ± 66[c] (n=4)
3 Chloramphenicol (oral)	577 ± 98 (n=15)	-261 ± 232[d] (n=10)	632 ± 73 (n=4)
4 Oxytetracycline (oral)	531 ± 136 (n=15)	193 ± 378 (n=12)	699 ± 49 (n=4)

[a]During the pretreatment (days -28 to -5) phase all groups were treated alike. During the treatment (days -5 to -9) phase all pigs were challenged, but each group was treated with a different antibiotic or none. The total (days -25 to 69) represents the average daily gain during the entire experiment.
[b]Mean ± SD.
[c]Long-acting formulation of oxytetracycline.
[d]Less than unmedicated ($P < 0.05$).
[e]Greater than unmedicated ($P < 0.05$).

TABLE III
DISEASE AND LESIONS IN PIGS WITH ACUTE *HAEMOPHILUS* PNEUMONIA TREATED WITH ANTIBIOTICS INTRAMUSCULARLY

Group	Death	Fever	Survivors[a] Lung Lesions	Isolation of *Haemophilus*
1 Unmedicated	8/9[b]	6/9	1/1	1/1
2 LAOT[e]	3/9[c]	7/9	6/6	4/6
3 Chloramphenicol	3/9[c]	8/9	4/6	3/4[d]
4 Penicillin	3/9[c]	7/9	4/6	0/5[d]

[a]Pigs sacrificed one to four weeks after challenge.
[b]Positive pigs/pigs in group.
[c]Significantly ($P < 0.05$) less than unmedicated group.
[d]Some lungs without lesions were not cultured for bacteria.
[e]Long-acting formulation of oxytetracycline.

Results

Intramuscular injection of LAOT 24 h before challenge prevented death and fever (Table I). When given in the drinking water, oxytetracycline reduced mortality ($P < 0.05$), but not the occurrence of fever compared to the untreated group. The proportion of pigs which had lung lesions at two, four and ten weeks after challenge also appeared to be reduced for the groups treated with either intramuscular or oral oxytetracycline, but statistical significance could not be determined because too few control pigs survived. Chloramphenicol in the drinking water did not significantly reduce disease compared to the untreated, challenged group.

After survivors were sacrificed, *H. pleuropneumoniae* was isolated from all lungs with lesions except from one pig treated with oral oxytetracycline and slaughtered ten weeks after challenge. In addition, there were lungs without gross lesions which were not cultured for bacteria.

The ADG for the periods preceding treatment (days -28 to -5), during treatment (days -5 to 9), and for the total duration of the experiment (days -28 to 69) are shown in Table II. The ADG was significantly reduced after challenge in all groups ($P < 0.05$). The group that received intramuscular LAOT demonstrated a greater ADG during treatment ($P = 0.24$), and over the entire period of the experiment ($P = 0.04$) than did pigs in the other three groups (Table II). The pigs given chloramphenicol lost weight during treatment ($P < 0.05$) even though they continued to eat.

Experiment II: Treatment of Acute *Haemophilus* Pneumonia

Method

Thirty-six piglets were divided into four groups of nine pigs/group. The pigs were challenged on day 0 with a suspension of 2.5×10^6 CFU/mL. Antibiotic treatment was begun 18 h postchallenge as soon as signs of clinical disease (listless and anorexic pigs) were noticed. Group 1 received no treatment (controls). Long-acting oxytetracycline was administered intramuscularly to group 2 at a dose of 20 mg/kg on days 1 and 4. Intramuscular injections were given twice daily on days 1 through 7 to group 3 (chloramphenicol (Rogar-mycine '200', Rogar/STB, Edmonton, Alberta) 22 mg/kg/day) and group 4 (procaine penicillin G (Ethacilin, Rogar/STB, Edmonton, Alberta), 80,000 international units/kg/day). Two surviving pigs from each medicated group were sacrificed on days 7, 14 and 28. The single surviving control pig was sacrificed on day 14.

Results

When treatment was started as soon as clinical signs were observed, the death rate from acute pneumonia was

significantly reduced ($P < 0.05$) in all three groups given antibiotics (Table III). There were no differences among treatment groups in the proportion of pigs which became febrile or which had lung lesions. The proportion of pigs which became chronic carriers of *Haemophilus* was least in the group treated with penicillin (Table III). All untreated pigs which died after challenge had lung lesions typical of pleuropneumonia from which *H. pleuropneumoniae* was isolated. *Haemophilus pleuropneumoniae* was not isolated from lungs of euthanized pigs which did not have lesions. There was no difference in ADG of survivors among groups (data not shown).

Experiment III: Treatment of Chronic Disease

Method

Previous experiments indicated that pigs could be chronically (more than two weeks) infected with *H. pleuropneumoniae* by first immunizing them and then exposing them to an aerosol challenge with strain 79-9 (unpublished observations). Hence, 45 piglets between five and six weeks of age were moved to an isolation room and randomly divided into five groups of nine pigs/group. Group 1 was not vaccinated and served as a control group to confirm that the challenge was virulent. Pigs in groups 2 through 5 were vaccinated with a commercial *Haemophilus* bacterin (Pleurinord, Nordisk Droge, Copenhagen, Denmark) twice at an interval of 28 days (Days -47 and -19). Pigs were challenged on day 0 with a suspension containing 3×10^5 CFU/mL. On day 2 when clinical signs of PHP were evident (listless, anorexic), one pig in each of the five groups was sacrificed for postmortem examination. On day 14 an additional pig from each group was sacrificed and lungs were cultured to verify that they were chronically infected with *H. pleuropneumoniae*. Antibiotic treatment was started on day 20 at a dosage recommended by the manufacturer. Pigs in group 1 and group 2 did not receive any antibiotic treatment. Pigs in the other three groups were treated for two weeks as follows: Group 3 — LAOT intramuscularly at a dose of 20 mg/kg every three days; Group 4 —oxytetracycline in the drinking water at a concentration of 222 mg/L; Group 5 — spiromycin (Spirasol, May & Baker Canada, Inc., Toronto, Ontario) in the drinking water at a concentration of 440 mg/L. At the end of the treatment period, two or three pigs in each group were sacrificed and examined. The body weight and clinical signs in the remaining pigs were monitored until they were slaughtered at 90 kg body weight.

Results

The challenge was virulent because two pigs (one each in Groups 1 and 4) died within 48 hours, three of five pigs (Groups 1, 3 and 4) killed after 48 hours had lung lesions and *H. pleuropneumoniae* was isolated from two of these lesions (Groups 1 and 4). All untreated pigs which died after challenge had lung lesions typical of pleuropneumonia (hemorrhagic necrosis and pleuritis) from which *H. pleuropneumoniae* was isolated. *Haemophilus pleuropneumoniae* was not isolated from lungs of euthanized pigs which did not have lesions. The other pigs became chronically infected and all five that were killed 14 days after challenge had lung lesions from which *H. pleuropneumoniae* was isolated. After challenge, there was no difference in mortality rate, incidence of fever, lung lesions, or isolation of *H. pleuropneumoniae* among the five groups (data not shown).

During the 67 day interval between vaccination and treatment, the ADG of vaccinated pigs (Groups 2-5) was less ($P < 0.05$) than the ADG of the unvaccinated pigs (Table IV). For each group, the ADG was less between days 0 and 20 after challenge than during the 47 days before challenge. The group given oxytetracycline intramuscularly had a greater ($P < 0.05$) average daily gain during the 24 day period following the onset of treatment (Table IV) than the vaccinated, unmedicated group. However, by five weeks after treatment and continuing until pigs were slaughtered at approximately 90 kg, there was no significant difference in the ADG among groups (data not shown).

DISCUSSION

The strain of *H. pleuropneumoniae* used in these experiments was susceptible *in vitro* to chloramphenicol, penicillin and tetracycline; however, the chloramphenicol formulations used (22 mg/kg/day IM or 147 mg/L in drinking water) were least effective for reducing clinical disease. Death, fever and development of gross lung lesions did not occur among pigs given intramuscular injection of LAOT (6.7 mg/kg/day) beginning 24 h prior to challenge with *H. pleuropneumoniae*. On the other hand, pigs offered drinking water containing oxytetracycline (222 mg/L) for seven days beginning

TABLE IV
AVERAGE DAILY GAIN (g/d) OF PIGS WITH CHRONIC *HAEMOPHILUS* PNEUMONIA TREATED WITH VARIOUS ANTIBIOTICS

Group	Vaccinated	ADG Between Vaccination and Treatment[a]	Antibiotic (route)	ADG After Treatment[b]
1	no	602 ± 64 (n = 6)	none	656 ± 99 (n = 4)
2	yes	560 ± 39 (n = 7)	none	646 ± 108 (n = 4)
3	yes	484 ± 51[c] (n = 7)	Oxytetracycline (oral)	688 ± 47 (n = 4)
4	yes	560 ± 81 (n = 6)	LAOT[e] (IM)	812 ± 112[d] (n = 4)
5	yes	557 ± 67 (n = 7)	Spiromycin (oral)	520 ± 86 (n = 4)
All Vaccinated Groups		539 ± 69[c]		

[a] Mean ± SD for the 67 d period from vaccination until treatment was started.
[b] Mean ± SD for the period from the onset of treatment until 24 d later.
[c] Significantly ($P < 0.05$) lower than unvaccinated group (Group 1).
[d] Significantly ($P < 0.05$) greater than vaccinated, unmedicated group (Group 2).
[e] Long-acting formulation of oxytetracycline.

24 h prior to challenge had reduced rate of death, lung lesions and isolation of *H. pleuropneumoniae* as compared to the unmedicated group. Hence, it appears that a total dose of 40 mg/kg of injectable LAOT during one week provided more prophylactic value to the pig than medicated drinking water containing 222 mg/L of oxytetracycline even though the water provided a greater dose.

In recent studies, the proportion of *H. pleuropneumoniae* isolates susceptible to tetracycline *in vitro* ranged from 43% to 86% (12,13,14). The degree of resistance to this antibiotic may be increasing in some areas as suggested by the finding in Quebec that only 43% of isolates were susceptible to tetracycline in 1982 as compared to 74% in 1980. In herd outbreaks of acute PHP an antibiotic must be selected and used before antibiotic susceptibility can be determined. Based on our experiments, a long acting preparation of oxytetracycline given intramuscularly is likely to be more effective than chloramphenicol in the drinking water for preventing spread in the face of an outbreak. The effect of penicillin or chloramphenicol given intramuscularly was not investigated for prevention.

Intramuscular treatment of acutely ill pigs with LAOT, chloramphenicol, or procaine penicillin-G reduced the death rate, but none reduced the proportion of pigs which became febrile or developed lung lesions. Because some of the treated pigs died before the antibiotic could have taken effect, timely treatment of infected pigs could reduce mortality even more than we observed. Perhaps any injectable antibiotic to which the strain of *Haemophilus* is susceptible would have a similar beneficial effect. The proportion of pigs from which *H. pleuropneumoniae* could be isolated more than two weeks after challenge was reduced only in the group treated with high doses (80,000 iu/kg/day) of penicillin. We did not observe any adverse reactions to this treatment; however, high doses of procaine penicillin (approximately 30,000 iu/kg) have caused apparent procaine toxicity (15).

For chronically infected pigs, none of the antibiotic treatments reduced the proportion of infected pigs or improved the ADG of pigs fed to 90 kg. Intramuscular injection of LAOT temporarily improved ADG for about three weeks, but pigs in other groups gained weight slightly faster during the period from five weeks after treatment until slaughter. Thus, the early weight gains of the pigs given LAOT were matched by later "compensatory growth" of the control pigs and this transitory effect is probably not significant in most situations. We tested the new antibiotic spiromycin, before antibiotic sensitivity discs were available. Hence, we were not aware that the strain of *H. pleuropneumoniae* we used was resistant to that antibiotic prior to the time of the trial.

Vaccination and challenge were used to produce chronically infected pigs. It should be noted that vaccinated pigs had lower ADG than unvaccinated pigs during the 67 day interval following vaccination (Table IV). One of three naturally infected herds studied in Denmark also had lower ADG after vaccination whereas ADG increased following vaccination in two other herds (16).

This information may be useful to veterinary practitioners and swine producers because it suggests that injection of pigs with a long-acting antibiotic preparation to which the strain of *Haemophilus* is susceptible, prior to exposure to the organism (challenge) will prevent infection and disease. In a practical situation, this means that clinically normal pigs in pens adjacent to pigs with *Haemophilus* pneumonia should be treated in order to prevent infection, disease and economic loss. Treatment of acutely ill pigs early in the course of disease will reduce death rate; however, treatment of chronically infected pigs will neither improve rate of gain to 90 kg nor eliminate infections. Vaccination with this *Haemophilus* bacterin reduced ADG and would cause an economic loss to producers. The effect of commonly used *Haemophilus* bacterins on growth rate should be investigated further.

Other long-acting formulations of antibiotics would be desirable for medicating pigs that need effective medication, but are difficult to restrain for frequent injection.

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