Antiplatelet effects and pharmacodynamics of clopidogrel in cats

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Objective—To evaluate antiplatelet effects and pharmacodynamics of clopidogrel in cats.

Design—Original study.

Animals—5 purpose-bred domestic cats.

Procedure—Clopidogrel was administered at dosages of 75 mg, PO, every 24 hours for 10 days; 37.5 mg, PO, every 24 hours for 10 days; and 18.75 mg, PO, every 24 hours for 7 days. In all cats, treatments were administered in this order, with at least 2 weeks between treatments. Platelet aggregation in response to ADP and collagen and oral mucosal bleeding times (OMBTs) were measured before and during drug administration. Serotonin concentration in plasma following stimulation of platelets with ADP or collagen was measured before and on the last day of drug administration. Platelet aggregation, OMBT, and serotonin concentration were evaluated at various times after drug administration was discontinued to determine when drug effects were lost.

Results—For all 3 dosages, platelet aggregation in response to ADP platelet aggregation in response to collagen, and serotonin concentration were significantly reduced and OMBT was significantly increased at all measurement times during drug administration periods. All values returned to baseline values by 7 days after drug administration was discontinued. No significant differences were identified between doses. None of the cats developed adverse effects associated with drug administration.

Conclusions and Clinical Relevance—Results suggest that administration of clopidogrel at dosages ranging from 18.75 to 75 mg, PO, every 24 hours, results in significant antiplatelet effects in cats. (J Am Vet Med Assoc 2004;225:1406–1411)

Cardiogenic arterial thromboembolism (CATE) is common in cats and is usually associated with some form of underlying myocardial disease.13 Intracardiac thrombus formation is believed to result from endocardial injury and blood stasis, followed by platelet adhesion and aggregation and subsequent activation of the coagulation cascade. Emboli that originate from the thrombus are primarily composed of a fibrin network with interspersed platelets, illustrating the role that platelets play in the pathogenesis of CATE. Furthermore, platelet aggregation is altered in cats with cardiac disease, and collateral blood flow around a site of embolization is reduced in response to platelet release products such as serotonin.14

Antiplatelet drugs such as aspirin would appear to be an attractive choice for the prevention of CATE in cats. However, aspirin treatment has not been reported to result in dramatic reductions in the prevalence of CATE.9,10 The thienopyridines ticlopidine and clopidogrel are newer antiplatelet drugs that exert their effects through irreversible inhibition of ADP receptors on the platelet membrane; this is uniquely different from the cyclooxygenase inhibiting effect of aspirin. Following administration, the thienopyridines must undergo hepatic transformation to 1 or more active metabolites.11 Therefore, in vivo and ex vivo studies, such as bleeding times and platelet aggregation studies, respectively, are required to demonstrate their antiplatelet effects. In addition, plasma concentration of the parent drug does not correlate with antiplatelet effect, so pharmacodynamic instead of pharmacokinetic studies are typically used to determine dose and dosing intervals in the species of interest.12,13 In humans, the thienopyridines have been shown to significantly reduce the risk of stroke, myocardial infarction, and vascular death, compared with aspirin therapy.13,14

Ticlopidine has been shown to impair platelet function in cats, but its use was associated with adverse effects that precluded use of the drug in clinical patients.13 In addition, clopidogrel has supplanted ticlopidine in human medicine because of its equal or better clinical efficacy and more favorable safety profile.15 To our knowledge, the effects of clopidogrel in cats have not been determined. The purpose of the study reported here was to determine antiplatelet effects and pharmacodynamics of clopidogrel in cats. In addition, we wanted to determine whether there were any acute adverse effects associated with clopidogrel administration in cats.

Materials and Methods

Cats—Five purpose-bred, approximately 1-year-old, domestic cats (3 castrated males and 2 sexually intact females) were used in the study.

Experimental protocol—Cats were treated with clopidogrel at 3 dosages: 75 mg (mean ± SD, 19.2 ± 4.6 mg/kg [8.7 ± 2.1 mg/lb]), PO, every 24 hours for 10 days; 37.5 mg (9.3 ± 2.5 mg/kg [4.2 ± 1.1 mg/lb]), PO, every 24 hours for 10 days; and 18.75 mg (4.4 ± 1.3 mg/kg [2.0 ± 0.6 mg/lb]), PO, every 24 hours for 7 days. In all cats, treatments were administered in this order, with at least 2 weeks between treatments. The initial dosage (75 mg, PO, q 24 h) was chosen because it is equipotent with a dosage of 250 mg of ticlo-
platelet aggregation in response to ADP at a concentration of 5 or 10 mM and collagen at a concentration of 1 mg/mL were determined to be the minimum concentrations necessary for maximal platelet aggregation.

Measurement of OMBTs—Because of the anatomic limitations of the oral cavity in cats, the OMBT was determined, rather than the buccal mucosal bleeding time. This technique has been found to be accurate and repeatable in cats. Briefly, cats were anesthetized and placed in lateral recumbency, and the lip was reflected back and held in place by gauze that was tightly tied around the head. Spring-loaded blade cassettes were used to create 1-mm-deep and 5-mm-long oral mucosal incisions above the premolars or molars. The OMBT was the time from creation of the incisions until bleeding ceased.

Measurement of platelet secretion of serotonin—To evaluate platelet dense granule secretion, blood used for aggregometry was recovered after platelet aggregation and centrifuged at 5,000 × g for 5 minutes at 4°C to separate the cellular elements from plasma enriched with serotonin released from platelets stimulated by ADP or collagen. The platelet-free plasma was snap frozen in liquid nitrogen and stored at −80°C until analyzed. Serotonin concentrations were measured with a commercially available ELISA test kit.

Statistical analyses—Descriptive statistics (mean and SD) or mean and 95% confidence interval (CI) were calculated. Maximal inhibition of platelet aggregation was calculated by use of the following formula: (baseline percentage platelet aggregation − lowest percentage platelet aggregation during drug administration) × 100. Similarly, maximal inhibition of serotonin release was calculated by use of the following formula: (baseline serotonin release − lowest serotonin release during drug administration) × 100. Mean platelet aggregation and OMBTs were compared within each dosage group over time and between dosage groups by means of ANOVA for repeated measures with a Bonferroni correction (overall type I error, 0.05). Pairwise comparisons were performed with the least-significant difference method. Standard software was used; values of P ≤ 0.05 were considered significant.

Serotonin concentrations, body weight, and results of clinicopathologic testing obtained prior to drug administration (baseline) were compared with values obtained on the last day of drug administration with paired t tests. Standard software was used; and values of P ≤ 0.05 were considered significant.

Results—High dosage—During administration of clopidogrel at the highest dosage (75 mg, PO, q 24 h), platelet aggregation in response to ADP was significantly reduced, compared with baseline aggregation prior to drug administration (Table 1). Mean ± SD maximal inhibition of platelet aggregation was 93.3 ± 1.9%, and mean values for platelet aggregation on days 3, 7, and 10 of drug administration were not significantly different from each other. Platelet aggregation was still significantly reduced 3 days after drug administration was discontinued, but was no longer significantly different from baseline aggregation 7 days after drug administration was discontinued. Similar results were seen for platelet aggregation in response to collagen, although mean maximal inhibition was lower (65.9 ± 3.9%). Oral mucosal bleeding times were significantly prolonged on all days during drug administration (Table 1), with OMBTs on days 3, 7, and 10 of drug administration being significantly prolonged compared with baseline values. These results are consistent with previous findings in dogs and humans, in which maximal inhibition of platelet aggregation achieved with clopidogrel therapy was observed 7 days after administration was discontinued.
Table 1—Results of platelet function studies in 5 cats treated with clopidogrel.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Baseline</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Baseline</th>
<th>Day 10</th>
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<th>Day 10</th>
<th>Baseline</th>
<th>Day 10</th>
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<td>ADP</td>
<td>Collagen</td>
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<td></td>
<td>34.0 ± 15.4</td>
<td>43.6 ± 17.9</td>
<td>66.0 ± 18.6</td>
<td>534.7 ± 417.7</td>
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<td></td>
<td>3.0 ± 3.7*</td>
<td>16.6 ± 6.2i</td>
<td>333.4 ± 182.1</td>
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<td>2.0 ± 2.3</td>
<td>14.8 ± 6.7i</td>
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<td></td>
<td>1.8 ± 2.5</td>
<td>13.2 ± 5.3i</td>
<td>250.9 ± 74.7</td>
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<td>10.0 ± 7.6*</td>
<td>19.8 ± 11.9i</td>
<td>189.4 ± 129.8</td>
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<td>24.4 ± 18.4</td>
<td>40.2 ± 23.4</td>
<td>66.0 ± 17.2</td>
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<td>35.0 ± 4.6</td>
<td>49.0 ± 14.6</td>
<td>63.8 ± 18.3</td>
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<td>0.6 ± 1.3</td>
<td>12.6 ± 2.5i</td>
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<td>0.8 ± 0.8*</td>
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<td>230.4 ± 116.7</td>
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<td>13.8 ± 12.3</td>
<td>23.0 ± 17.5</td>
<td>116.0 ± 32.8</td>
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<td>22.6 ± 15.0</td>
<td>45.4 ± 3.0</td>
<td>62.0 ± 9.2</td>
<td>411.6 ± 366.5</td>
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<td>25.5 ± 13.1</td>
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<td>27.2 ± 2.9</td>
<td>47.8 ± 6.2</td>
<td>59.6 ± 10.8</td>
<td>544.1 ± 163.6</td>
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<td>1.8 ± 2.5*</td>
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<td>25.8 ± 12.8</td>
<td>43.4 ± 2.1</td>
<td>67.4 ± 14.8</td>
<td>378.1 ± 333.6</td>
<td>1,153.1 ± 316.8</td>
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</table>

Data are given as mean ± SD. Cats were treated with clopidogrel at a dosage of 75 mg, PO, every 24 hours for 10 days (high); 37.5 mg, PO, every 24 hours for 10 days (moderate); and 18.75 mg, PO, every 24 hours for 7 days (low). In all cats, treatments were administered in this order, with at least 2 weeks between treatments.

*Concentration of serotonin in plasma obtained after stimulation of platelets with ADP or collagen.

OMBT = Oral mucosal bleeding time. ND = Not done.

**Significantly (P < 0.001) different from baseline value. **Significantly (P < 0.05) different from baseline value. **Significantly (P < 0.005) different from baseline value. **Significantly (P < 0.001) different from baseline value.

Table 2—Results of clinopathologic testing in 5 cats treated with clopidogrel.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low dosage</th>
<th>Moderate dosage</th>
<th>High dosage</th>
<th>Reference range</th>
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<tbody>
<tr>
<td></td>
<td>Day 7</td>
<td>Day 10</td>
<td>Day 10</td>
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<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td>Baseline</td>
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<tr>
<td>Hematocrit (%)</td>
<td>35.4 ± 1.7</td>
<td>25.5 ± 2.6</td>
<td>27.9 ± 3.4</td>
<td>30–45</td>
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<tr>
<td>WBC (&lt;10³/mL)</td>
<td>8.96 ± 2.87</td>
<td>6.72 ± 1.40</td>
<td>6.92 ± 2.38</td>
<td>6.72 ± 1.40</td>
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<tr>
<td>Neutrophils (&lt;10³/mL)</td>
<td>4.84 ± 1.57</td>
<td>4.34 ± 1.24</td>
<td>4.27 ± 1.57</td>
<td>4.34 ± 1.24</td>
</tr>
<tr>
<td>Platelets (&lt;10³/mL)</td>
<td>350.0 ± 32.3</td>
<td>393.6 ± 62.8</td>
<td>393.6 ± 62.8</td>
<td>386.8 ± 88.1</td>
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<tr>
<td>ALT (U/L)</td>
<td>88.8 ± 62.5</td>
<td>51.4 ± 17.5</td>
<td>51.8 ± 9.4</td>
<td>51.4 ± 17.5</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>52.0 ± 4.7</td>
<td>34.4 ± 9.4</td>
<td>36.5 ± 10.2</td>
<td>34.4 ± 9.4</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.22 ± 0.04</td>
<td>0.20 ± 0.00</td>
<td>0.39 ± 0.00</td>
<td>0.20 ± 0.00</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>4.6 ± 1.3</td>
<td>4.2 ± 1.1</td>
<td>4.1 ± 1.0</td>
<td>4.1 ± 1.0</td>
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</tbody>
</table>

ALT = Alanine aminotransferase. ALP = Alkaline phosphatase.

**Significantly (P < 0.05) different from baseline value. **See Table 1 for remainder of key.

administration being a mean of 5.35, 4.58, and 3.92 times baseline times, respectively. However, OMBTs on days 3, 7, and 10 were not significantly different from each other. Oral mucosal bleeding times were no longer significantly different from baseline times 7 days after drug administration was discontinued.

Serotonin release from platelets activated with ADP or collagen was significantly reduced (mean ± SD maximal inhibition, 92.4 ± 5.5% and 84.9 ± 17.1%, respectively) after 10 days of drug administration (Table 1), but was no longer significantly different from baseline release 7 days after drug administration had been discontinued.

No adverse effects were identified during drug administration. There was a significant decrease in total bilirubin concentration, compared with baseline concentration, after 10 days of administration, but concentrations for all cats were within reference limits (Table 2).

Moderate dosage—Platelet aggregation responses during administration of clopidogrel at the moderate dosage (37.5 mg, PO, q 24 h) were similar to those seen with administration at the high dosage (Table 1). Platelet aggregation in response to ADP or collagen was significantly decreased during drug administration (mean ± SD maximal inhibition, 97.7 ± 0.6% and 72.0 ± 3.0%, respectively), with no significant differences in platelet aggregation on days 3, 7, and 10 of drug administration. Aggregation had returned to baseline values by 7 days after administration was discontinued. Oral mucosal bleeding times were significantly prolonged on all days during drug administration (OMBTs on days 3, 7, and 10 of drug administration were a mean of 3.94, 4.20, and 3.50 times baseline times, respectively), with no significant differences among values obtained on days 3, 7, and 10 of drug administration. Oral mucosal bleeding time was no longer significantly different from baseline time 7 days after drug
administration was discontinued. Serotonin release from platelets activated with ADP or collagen was significantly reduced (mean maximal inhibition, 94.1 ± 4.0% and 88.4 ± 12.6%, respectively) on day 10 of drug administration (Table 1), but was no longer significantly different from baseline release 7 days after drug administration had been discontinued. None of the cats developed any adverse effects associated with drug administration, and results of clinicopathologic tests performed after 10 days of drug administration were not significantly different from baseline values except for a significant decrease in mean total bilirubin concentration (Table 2). However, for all cats, total bilirubin concentration was within reference limits. Platelet function test results when cats were treated with clopidogrel at the moderate dosage were not significantly different from results obtained when cats were treated with clopidogrel at the high dosage.

**Low dosage**—Platelet function test results during administration of clopidogrel at the low dosage (18.75 mg, PO, q 24 h) were comparable to those obtained during administration at the high and moderate dosages. Platelet aggregation (mean ± SD maximal inhibition of platelet aggregation in response to ADP or collagen, 93.4 ± 9.2% and 60.3 ± 15.9%, respectively) and serotonin release (mean maximal inhibition of serotonin release from platelets activated with ADP or collagen, 90.4 ± 7.3% and 86.7 ± 22.3%, respectively) were significantly decreased, and OMBT was significantly increased (mean of 3.95 times baseline time) after clopidogrel had been administered for 7 days, but values were no longer significantly different from baseline values 7 days after drug administration was discontinued (Table 1). None of the cats had any adverse effects associated with drug administration, and results of clinicopathologic tests performed after clopidogrel had been administered for 7 days were not significantly different from baseline values (Table 2). Platelet function test results when cats were treated with clopidogrel at the low dosage were not significantly different from results obtained when cats were treated with clopidogrel at the high or moderate dosage.

**Discussion**

The thienopyridines ticlopidine and clopidogrel induce irreversible inhibition of ADP 

These compounds do not exert any direct antiplatelet effects but must undergo hepatic metabolism to 1 or more active metabolites. In humans administered clopidogrel long-term, the parent compound and primary metabolite are excreted in the urine (41% to 46%) and feces (35% to 57%).

Results of the present study indicated that administration of clopidogrel caused significant impairment of platelet function in cats. When cats were given clopidogrel at the moderate (37.5 mg, PO, q 24 h) or high (75 mg, PO, q 24 h) dosage, platelet aggregation in response to ADP or collagen was significantly reduced and the OMBT was significantly increased after 3 days of drug administration, and these alterations continued throughout the 10-day drug administration period. Serotonin release from platelets was significantly suppressed after 10 days of drug administration. Similarly, when cats were given clopidogrel at the low dosage (18.75 mg, PO, q 24 h), platelet aggregation and serotonin release were significantly decreased and OMBT was significantly increased after 7 days of drug administration. At all dosages, values for platelet aggregation, OMBT, and serotonin release were no longer significantly different from baseline values 7 days after drug administration had been discontinued. No significant difference in results of platelet function tests was found among dosages.

Platelet release products, specifically serotonin, appear to play a primary role in the clinical signs associated with CATE, and in the present study, clopidogrel administration resulted in significant reductions in serotonin secretion from activated platelets. Previous studies have found that clopidogrel reduces the contractile response of pulmonary and femoral arterial ring preparations to multiple vasoconstrictive agents, including serotonin. Thus, it is possible that administration of clopidogrel, through its anti-serotonin effects, could result in less severe clinical signs of CATE, even if thromboembolization itself were not prevented.

Adverse effects associated with clopidogrel administration in humans have been identified. In a study of 9,599 patients, the discontinuation rate among those taking clopidogrel was 11.94%; however, this was not significantly different from the discontinuation rate for those taking aspirin (11.92%). Clopidogrel was associated with a significantly lower prevalence of adverse gastrointestinal tract events than was aspirin (27.14% vs 29.82%) but with a significantly higher prevalence of adverse dermatologic events (15.81% vs 13.08%), including pruritus and rash. In subgroup analyses of adverse gastrointestinal tract events, only diarrhea was more common with clopidogrel than with aspirin (4.46% vs 3.36%). There was no significant difference in prevalence of hemorrhagic events (9.27% vs 9.28%), and gastrointestinal tract bleeding was significantly less common with clopidogrel (1.99% vs 2.66%). Neutropenia and thrombocytopenia, both of which have been identified in patients treated with ticlopidine, were rare in patients treated with clopidogrel (0.10% and 0.26%, respectively), and their prevalence in patients taking clopidogrel was not significantly different from prevalence in patients taking aspirin.
Thrombotic thrombocytopenic purpura is a severe and often fatal adverse event that has been associated with ticlopidine administration, but only 11 cases have been reported (out of >3 million patients treated), and there is some debate whether all of these cases were actually caused by clopidogrel, as some patients had clinical conditions or were receiving other drugs known to cause thrombotic thrombocytopenic purpura. Additionally, the expected incidence of idiopathic thrombotic thrombocytopenic purpura in the general population is 3.7 per million persons. Hepatocellular injury and cholestasis in cats with heart disease.

None of the cats in the present study had any adverse clinical effects, bleeding tendencies, or alterations in clinicopathologic data during any of the dosing periods. However, the period of drug administration was short in this study; and a longer clinical safety trial is needed to determine the safety of long-term clopidogrel administration in cats.

We were unable to determine the minimum effective dose of clopidogrel in the present study. In humans, the recommended maintenance dosage for clopidogrel is 75 mg, PO, every 24 hours. At this dosage, maximal inhibition of ADP-induced platelet aggregation ranges from 40% to 60% and maximal prolongation of bleeding time is 1.5 to 2.0 times the baseline value. There were no significant differences seen between dosages in this study, and the lowest dosage (18.75 mg, PO, q 24 hr) resulted in mean maximal inhibition of ADP-induced platelet aggregation of 93.4% and a 3.9-fold prolongation of OMBT. Thus, it appears that a lower dosage could be used to provide adequate platelet inhibition. However, clopidogrel is currently only available in the United States as 75-mg tablets. Although these tablets are not exceedingly small, splitting tablets into fractions smaller than quarters was not realistic, and administration of smaller dosages would have required compounding of the drug. Currently, 30 tablets of the commercially available form of clopidogrel cost approximately $120. Therefore, administration to a cat at a dosage of 18.75 mg, PO, every 24 hours, would cost approximately $30/mo. Even given the additional cost associated with compounding, administration of smaller dosages may be less expensive. Thus, additional studies to determine the minimum effective dosage of clopidogrel in cats are warranted.

Results of the present study suggest that it may be reasonable to administer clopidogrel at a dosage of 18.75 mg, PO, every 24 hours, in cats to prevent CATE. However, further studies are needed to determine whether clopidogrel is safe and efficacious in cats predisposed to CATE and to determine the minimum effective dosage.

References

**Selected abstract for JAVMA readers from the American Journal of Veterinary Research**

**Microbiologic findings in feedlot cattle with acute interstitial pneumonia**

Amelia R. Woolums et al

**Objective**—To test the hypothesis that feedlot cattle with acute interstitial pneumonia (AIP) have bacterial infection of the lung or liver and concurrent bovine respiratory syncytial virus (BRSV) infection significantly more often than penmates without AIP.

**Animals**—39 feedlot cattle with signs consistent with AIP and no history of treatment with antimicrobials and 32 healthy control cattle from the same pens.

**Procedures**—Postmortem, lung, and liver specimens were obtained for bacterial or mycoplasmal culture and histologic examination; lung tissue was assessed for BRSV infection immunohistochemically.

**Results**—Of the 39 affected cattle, 26 had AIP confirmed histologically. Lung tissue from 11 cattle with AIP yielded microbial respiratory tract pathogens on culture; tissues from control animals yielded no microbial growth. In 4 cattle with AIP and 2 control animals, liver abscesses were detected; bacteria were isolated from abscessed tissue in 3 and 1 of those animals, respectively. Immunohistochemically, 9 cattle with AIP and no control animals were BRSV-positive. Histologically, 9 AIP-affected cattle had only acute alveolar damage with exudation, and the other 17 had acute exudation with type II pneumocyte hyperplasia. No lesions of AIP were detected in control animals. Only 4 AIP-affected cattle had bacterial infection of the lung with concurrent BRSV infection.

**Conclusions and Clinical Relevance**—Results indicated that microbial respiratory tract pathogens are more common in cattle with AIP than in healthy penmates. Control of bacterial pneumonia late in the feeding period may reduce the incidence of AIP at feedlots where AIP is a problem. (Am J Vet Res 2004;65:1525–1532)