

Where is the Evidence? Efficacy of L-Lysine to Prevent and Treat Feline Herpesvirus-1 Infection

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Abstract

Question: Does L-lysine dietary supplementation in shelter cats reduce upper respiratory disease incidence?

Hypothesis: L-Lysine supplementation in shelter cats does not effect a reduced upper respiratory disease incidence.

Objectives: To summarize the extant research on L-lysine and feline herpesvirus-1. To obtain information on feline upper respiratory disease incidence in animal shelters across Iowa. To analyze survey results for evidence of L-lysine efficacy in the shelter environment for reducing upper respiratory disease incidence.

Background: Feline upper respiratory infection (URI) and conjunctivitis are a significant health threat in animal shelters. As one causal pathogen, feline herpesvirus-1 (FHV-1) has been shown to be inhibited by L-lysine under certain conditions.

Methods: A quality-based evaluation of the current literature using the American Dietetic Association's Quality Analysis Manual was conducted after searching PubMed, Commonwealth Agricultural Bureau, and Veterinary Information Network databases. A survey instrument for evaluating L-lysine usage in Iowa animal shelters was developed by the authors and completed by participating shelter managers.

Results: Twenty-two articles were retrieved and four articles were selected for quality evaluation after screening for primary research and relevance. All articles received an ADA score of positive. From 15 completed surveys, there was no statistical significance between L-lysine usage and decreased URI incidence.

Conclusions: Maggs et al. 2007 represents the current best evidence with regard to the efficacy of L-lysine in treating URI in animal shelters. Results do not support dietary supplementation with L-lysine. Survey results further do not support shelter usage of L-lysine in controlling URI.

Introduction

Feline upper respiratory infection (URI) is a well recognized and ubiquitous disease complex that in multi-cat environments such as animal shelters represents a significant health threat to the population. Feline herpesvirus-1 (FHV-1) is one virus known to be involved in the disease⁵. FHV-1 is widespread, with up to 97 % of cats showing serologic exposure evidence, and persists in a latent state within the trigeminal nerve after primary infection. Recrudescence infection and viral shedding is estimated to occur in about half of infected cats, thus providing a reservoir for FHV-1 spread to naive cats^{7,8}. Conditions associated with animal shelters promote viral reactivation resulting in acute infection, viral shedding for up to three weeks, and primary infection of susceptible cats^{6,7}. With primary infection of FHV-1, kitten morbidity in multi-cat environments approaches ~ 100%⁷.

Owing to low environmental persistence, extreme susceptibility to disinfection and transmission mainly by direct contact or fomites, URI can be controlled where shelter management includes quarantine and isolation facilities, low cat density, ideal sanitation, good air flow, and quality care¹². However, most shelters experience a departure from the ideal and URI outbreaks occur, with continuous infection and depopulation as possible consequences. After overcrowding, URI is the second leading cause of euthanasia in animal shelters⁵.

Adjunctive therapies for the treatment of FHV-1 infection are an appealing approach for reasons including cost, ease of administration, availability, and safety. L-lysine is known to antagonize arginine in herpesvirus protein synthesis and is used to treat infections in humans and cats. Research findings suggest that oral administration of 500 mg lysine q12h is effective in reducing severity of FHV-1 conjunctivitis and amount of viral shedding, but does not seem to reduce incidence. *In vitro* studies demonstrate L-lysine inhibition of viral replication in low-arginine media. Anecdotal reports suggest some clinical improvement when cats are treated with L-lysine^{3,4,8,10,11,14}.

Shelters are adding L-lysine to cat diets in an attempt to prevent and treat URI. A search of the Association of Shelter Veterinarians list serve entries over the last four years revealed that 2% of the 10,000 postings related specifically to the availability, dosage, and use of L-lysine. At a range of \$0.05 to 0.50 per dose, the affordability of this approach depends on cat numbers and shelter funding. Is there an evidence based clinical justification for treating URI or conjunctivitis with L-lysine in shelters?

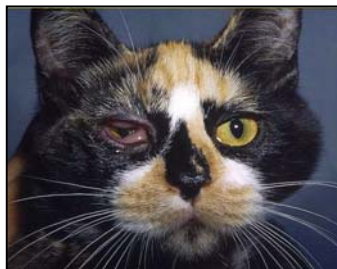


Figure 1 Courtesy Dr. C.J. Baldwin



Figure 2 Courtesy Dr. C.J. Baldwin

Figures 1 & 2 Examples of FHV-1 ocular infections; note the conjunctivitis and edema.

Author	ADA score	Dependent Variables Studied	Outcome
Stiles et al. 2002	Positive	Disease score, plasma lysine and arginine, viral shedding	Plasma lysine did not antagonize arginine; lysine treatment decreased disease symptoms.
Maggs et al. 2000	Positive	Viral titer and CRFK cell growth	Lysine inhibits FHV growth in low-arginine media. Arginine promotes FHV replication.
Maggs et al. 2003	Positive	Disease score, plasma lysine and arginine, viral shedding	Lysine treatment decreased viral shedding. No adverse arginine effects.
Maggs et al. 2007	Positive	Lysine intake, disease score, plasma lysine and arginine, viral shedding	Inconclusive; higher disease score and viral shedding in the treatment group, plasma arginine declined in both groups.

Table 1 Summary of the reviewed articles.

Materials and Methods

A search of PubMed, Commonwealth Agricultural Bureau (CAB) and Veterinary Information Network (VIN) using the search terms "lysinine," "FHV" and "herpes" was conducted. Abstracts were screened for primary research and relevance. Selected articles were read in full and analyzed for quality using the American Dietetic Association's Evidence Analysis Manual, which considers study design, controls, blinding, relevance, methodology, statistics and research funding. Through this evaluation a Quality Rating of positive, neutral, or negative was assigned.

Sixty Iowa shelters received a survey instrument that was developed to determine use of L-lysine and incidence of URI. Other parameters such as vaccination and deworming programs, diet, cat admissions per month and year, cat housing type, cat density, source and dosage of L-lysine were also requested. A student's *t* test and Chi square test were done through the JMP 6.0.0 statistical package to determine the probability of lysine effecting URI incidence.

References

1. American Dietetic Association, ADA Evidence Analysis Manual, April 2007.
2. Barnasch MJ, Foley JE. Epidemiologic evaluation of multiple respiratory pathogens in cats in animal shelters. *Journal of Feline Medicine and Surgery* 2005; 7: 109-118.
3. Becker V, Olschensky U, Levitt J. The role of arginine in the replication of herpes simplex virus. *Journal of General Virology* 1987; 1: 471-478.
4. Czarnocki GL, Hirakawa DA, Baker DH. Antagonism of arginine by excess dietary lysine in the growing dog. *Journal of Nutrition* 1985; 115: 743-752.
5. Foley JE, Barnasch MJ. Infectious diseases of dogs and cats. In: Miller L, Zawistowski S (eds). *Shelter Medicine for Veterinarians and Staff*. 2004; Ames, IA: Iowa University Press, pp. 235-294.
6. Gaskell RM, Povey RC. Re-activation of feline viral rhinotracheitis virus following corticosteroid treatment. *Vet Rec* 1973; 93:204-205.
7. Gaskell RM, Povey RC. Experimental induction of feline viral rhinotracheitis virus re-activation in FVR-recovered cats. *Vet Rec* 1977; 100: 128-133.
8. Griffith RS, DeLiang DC, Nelson JD. Relation of arginine-lysine antagonism to herpes simplex growth in tissue culture. *Chemotherapy* 1981; 27 (3): 209-213.
9. Maggs DJ, Lappin MK, Reef JS, et al. Evaluation of serologic and viral detection methods for diagnosing feline herpesvirus-1 infection in cats with acute respiratory tract or chronic ocular disease. *J Am Vet Med Assoc* 1999; 214: 502-509.
10. Maggs DJ, Collins BK, Thorne JG, Nassef MP. Effects of L-lysine and L-arginine on *in vitro* replication of feline herpesvirus type-1. *American Journal of Veterinary Research* 2000; 61: 1474-1478.
11. Maggs DJ, Nassef MP, Koss PH. Efficacy of oral supplementation with lysine in cats latently infected with feline herpesvirus. *American Journal of Veterinary Research* 2003; 64: 37-42.
12. Maggs DJ. Update on pathogenesis, diagnosis, and treatment of feline herpesvirus type 1. *Clinical Techniques in Small Animal Practice* 2005; 20:94-101.
13. Maggs DJ, Sykes JE, Clarke HE, Yoo SH et al. Effects of dietary lysine supplementation in cats with enzootic upper respiratory disease. *Journal of Feline Medicine and Surgery* 2007; 9: 99-106.
14. Stiles J, et al. Effect of oral administration of L-lysine on conjunctivitis caused by feline herpesvirus in cats. *American Journal of Veterinary Research* 2002; 63: 98-103.

Results

The search of PubMed, CAB and VIN revealed 4, 13, and 5 titles, respectively. Upon screening the abstracts for primary research and relevance 4 articles were identified for review. Table 1 demonstrates the Quality Ratings and key features of each study. All received positive ADA scores and were randomized controlled trials. Maggs et al. 2000 and 2003 were not blinded. Small sample size was present in all but Maggs et al. 2007. Stiles et al. 2002 used specific pathogen-free (SPF) cats that had been vaccinated for FHV-1 6 months previously and then inoculated to produce primary infection. Maggs et al. 2003 used SPF cats in group housing fed *ad libitum* and challenged with a steroid-induced latent infection. Maggs et al. 2000 examined L-lysine and L-arginine effects on *in vitro* FHV-1 growth. Maggs et al. 2007 supplemented dietary lysine in group-housed and group-fed cats with enzootic URI.

Out of 20 responding shelters:

5 have been using L-lysine over a range of 6 months to 7 years.

3 administer 250 mg once daily and 1 gives 500 mg once daily.

1 gives 322 mg at a veterinarian recommended frequency.

4 give lysine "as needed", while one gives for the first week or the entire stay.

Formulations include powdered and tablet form.

3 give to all cats, and 2 give only to symptomatic cats.

Only those giving L-lysine to all cats report a decreased disease incidence; this was not statistically significant with the Chi square or the student's *t* tests.

Other variables such as diet, vaccination, housing, cat density, and length of stay vary and are difficult to correlate to disease incidence.

17 report greater incidence of URI within the first 2 weeks of entering the shelter compared to incidence of recurrent or chronic infection.

Conclusions

Despite positive ADA scores, small sample size and lack of researcher blinding can be sources of error. Using SPF cats eliminates some disease variables, but compromises reality. *In vitro* studies lend support to L-lysine's inhibition of FHV replication but do not represent an *in vivo* environment. Conflicting results between the studies may represent the divergence of treatment results from stricter, less variable and artificial populations to the more realistic and variable clinical environment of Maggs et al. 2007. Maggs et al. 2007 presents the current best evidence regarding efficacy of L-lysine in a multi-cat environment with unknown or varied health and disease history, such as that encountered in shelters. This study contained unexpected detractors including in-group fighting; this stress may further represent the shelter environment. The authors failed to draw a definitive conclusion; their results did not support efficacy of dietary L-lysine in controlling enzootic URI.

Survey assessment of disease incidence and variables is difficult. Survey return rate (33%) may be due to the busy summer months. Given the small sample size, our results do not suggest strong conclusions. The efficacy of lysine in the shelter environment seems to depend most on receiving population; those shelters administering to all cats for their entire stay reported decreased disease incidence. However, given the small sample size this result was not statistically significant. Assessment of chronic URI incidence can be hindered by euthanasia. Earlier studies demonstrating lack of arginine antagonism may support cats receiving lysine upon admission to the shelter, as this may prevent recrudescence or establishment of disease, but further evidence is needed to warrant this as a shelter management recommendation. Shelters may have greatest success in disease management through strict sanitation, disinfection and population control protocols.

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