

A Preliminary Clinical Evaluation of Kibow Biotics,[®] a Probiotic Agent, on Feline Azotemia.

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Abstract

A clinician, curious about the manufacturer's claims, examined the results of a probiotic combination marketed as Kibow Biotics[®] on azotemia in cats. Results indicate a decrease in creatinine levels in six out of seven patients treated (86%) even though dosing was less than the recommended amount in most cats. This study suggests that probiotic therapy is safe and effective and indicates a place for such products in management of renal failure in cats. Further study is indicated to determine optimal dosing and potential adverse side effects, and to assess which cases are most and least responsive.

Introduction

Feline renal failure is a significant cause of morbidity and mortality in cats in the United States.¹ Reducing morbidity and mortality associated with renal failure is an important goal in companion animal veterinary medicine. Regular screening of geriatric cats can assist in early diagnosis.² Ascertaining the cause of renal damage may greatly assist in formulating a therapeutic plan. Sadly, many cases present in more advanced conditions. Therapy involves reducing uremic toxins, normalizing renal blood flow and blood pressure, maintaining hydration and electrolyte balance, and supporting tissue repair when possible.

Regardless of cause, it is considered desirable to reduce levels of blood urea nitrogen (BUN) and serum creatinine in renal failure patients.⁴ Feeding reduced levels of high biological value protein in advanced failure has been the staple treatment of chronic renal failure in cats.³ Dietary therapy has been shown to increase survival of feline renal failure patients.^{4,5} Use of other agents such as phosphorus binding substances and parathyroid hormone modulation are also utilized.^{5,6} There are divergent opinions regarding the make up of an optimal diet for feline renal failure and more data is needed to answer these questions. Feline patients may be difficult to medicate orally over long periods of time, which creates a challenge when designing clinically useful programs for chronic use. Products selected must be well tolerated as well as effective.

A novel, biological therapeutic approach involving use of probiotic bacteria is reported to decrease BUN and serum creatinine levels in pigs and rats.^{7,8} No feline studies are currently available. Kibow Biotics[®] is produced by Kibow Biotech and contains a patented mixture of probiotic bacteria consisting of *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterium longum*. When these probiotic bacteria are combined with prebiotics, they form functional compositions known as *symbiotics*. *In vivo* studies show that these bacteria have an affinity for many uremic toxins. Theoretically the use of such products may support healthy bowel function, break down toxic substances, eliminate excess waste materials, and enhance the patient's immune system. In animal studies involving rats with surgically induced renal insufficiency, use of this product lead to increased survival rates of 66% and 83% in treated groups compared to 33% survival rates in placebo treated rats.^{7,8}

The author decided to challenge the company advertising and see if positive results were obtained. This study documents those findings.

Materials and Methods

Patients with elevated BUN and serum creatinine were selected as they came into the office. No attempt to screen patients was made. Clients were advised about the product and its potential benefits. No risks were

known. Clients voluntarily bore the expense of the product and of testing monthly for three months. The manufacturer provided the product at a discount for those undertaking the study. Values of BUN, serum creatinine, body mass, diet, and general comments were collected before, and at each subsequent visit. These were recorded on an individual work sheet and graphed for evaluation. All laboratory testing was performed by Antech laboratories in the standard way.⁹ Body weights were determined using a single digital scale for all cats.

Results

All clients presented with the manufacturer's product data elected to be included in the study. Eight cats were enrolled over a thirty-day period. One case (number 8) dropped out after one month as the owner did not wish to have testing done monthly, was not certain that the treatment would be beneficial, and had difficulty medicating his cat. This cat was extremely uncooperative and it was agreed that dropping the treatment until more positive results were known was a good idea. All other cats completed the study. All clients have elected to continue therapy at their expense following their participation in this study. Each case response is summarized in the Table one below.

Case No.	BUN Pretx	BUN 30d	BUN 60d	% Decrease	Cr PreTx	Cr 30d	Cr 60d	% Decrease	Diet	Comments
1	43	33	30	30.2	3.2	3.1	2.1	34.4	3	Hi Protein Diet, Active
2	41	37	36	12.2	2.6	2.1	2.2	19.2	2	Difficult to dose
3	64	61	61	4.7	5.0	3.9	3.8	24.0	1	Higher vitality
4	41	ND	34	17.7	2.9	ND	2.5	13.8	2	Vomiting at whole capsule dose
5	74	51	47	36.5	7.9	4.4	3.8	51.9	1	Fibrosarcoma, Adenocarcinoma hospice; Higher vitality
6	55	45	51	7.3	3.3	3.1	3.0	10.0	1,2	Dysbiosis?, Better at ending
7	61	86*	57	6.6	2.9	3.9*	2.9	0	4	Hospitalized twice in three months ⁺

Table 1. Case Response Summaries.

Legend of Abbreviations—BUN (blood urea nitrogen level reported in mg%; normal values 14-36), Cr (creatinine reported in mg%; normal values 0.6-2.4), Diet 1 (Prescription kidney diet; IVD Modified or Hill's K/D), Diet 2 (Commercial cat food), Diet 3 (Innova EVO), Diet 4 (home prepared meat), * Dehydration (heat or diarrhea), ⁺ Dosing not regular.

A graphic representation of the percentage change illustrates the results below in Figure One.

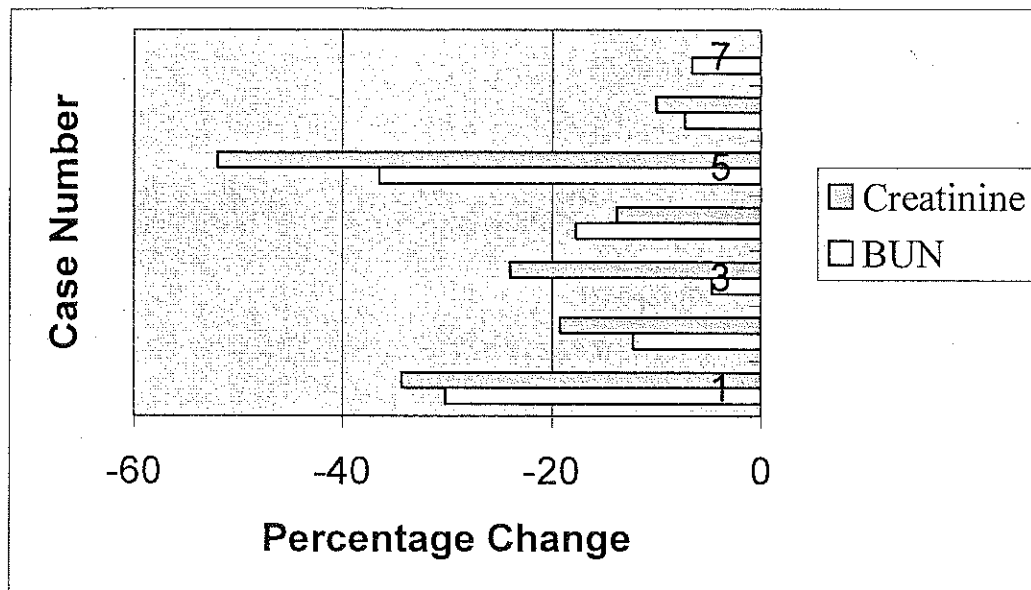


Figure 1. A Comparison of BUN and Serum Creatinine Decreases as Expressed in Percentages.

This was a diverse group of patients. Table two summarizes other known pertinent patient factors. No attempt to alter therapy plans was made. Treatment plans were programmed based upon best therapy for that individual, and Kibow Biotic[®] was simply added to the cat's program.

Case No.	Sex	Age Yrs	Wt (kg) 1	Wt (kg) 2	Wt (kg) 3	Renal Disease/ Since	Culture Urine?	Fluid Therapy	Nutritional Therapy	Homotox
1	MN	13	4.77	4.77	4.77	CGN 5 mos	No	No	No	Yes
2	MN	15	6.68	6.51	6.16	CGN	Neg	No	Yes, 2	No
3	FN	18	3.13	2.93	2.93	CGN 3 yrs	Neg	No	Yes, 1,2,3	No
4	MN	13	5.68	ND	5.65	FUS related Post-renal Blockage 1.5 yrs	No	No	Yes 1	No
5	FN	17	8.44	8.81	9.31	CGN Paraneoplastic Tubular dz? 1.5 yrs	Neg	Yes SQ	Yes 1, 2	Yes
6	MN	10	4.95	4.83	4.94	CGN 4 mos	Neg	Yes SQ	Yes 2	No
7	FN	19	2.59	2.81	3.1	Recurrent Pyelonephritis 3 yrs	No	Yes IV I/P SQ O/P	Yes 1, 2	Yes

Table 2. Patient Factors.

Legend of Abbreviations—Kg (kilogram), M (male), N (neutered), F (female), CGN (chronic generalized nephropathy), dz (disease), FUS (feline urologic syndrome), IV I/P (intravenous fluids in-patient), SQ O/P (subcutaneous fluids out-patient), Nutritional therapy 1 (diet), Nutritional therapy 2 (Standard Process Feline Renal Support), Nutritional therapy 3 (Renagen[®], a Chinese herbal by Thorne Labs), Homotox (Homotoxicology, a specialized form of homeopathic therapy).

Cats received either one-half capsule twice daily or one capsule daily. Clients admitted to varying this dosage so a valid comparison based upon dose or route could not be made.

Weight, Kg	Morning Dose	Evening Dose
< 1 kg	1	0
1-2 kg	1	1
2-4 kg	2	1
4-8 kg	2	1-2

Table 4. Kibow Biotech's Company Recommendations for Dosing of Veterinary Patients.

Most patients in this study took one capsule daily or half capsule twice daily mixed with food. This is in disagreement with the company's advise to give the capsule whole or with liquid food.¹⁰

Discussion

Examination of the limited data above shows a very clear relationship between use of the probiotic and decreasing azotemia. 7/7 (100%) of cases showed a decrease in BUN, which varied from 4.7% to 36.5%. Creatinine also showed improvement with 6/7 (85.7%) showing decreases ranging from 10% to 51.9%. Such a decline must originate from altered blood flow, reduced toxin presentation, increased toxin excretion/conversion, or other unknown issues. Kibow Biotech coined and trademarked the term, Enteric Dialysis™ to describe the removal of uremic toxins by bacterial action in the colon.^{10, 11} This study supports that theory, even though the dosing was lower than that recommended by the company.

It would have been interesting to monitor other parameters such as packed cell volume, and phosphorus, but finances limited the scope of this particular study. Body weights generally fell in 4/7 (57.1%) over the 60-day period of this study. The exceptions to this were three cases that either maintained weight, 1/7 (14.3%), or that gained weight, 2/7 (28.6%). These three cats all received homotoxicology support for their kidneys in addition to their other treatments, which raises an interesting opportunity for further study in attempting to determine the best protocols for renal failure in cats. Reports of homotoxicology benefiting renal disease in veterinary patients exist.^{12,13,14,15}

Case number seven deserves comment. This is a very aged cat that was hospitalized three times in the last year for chronic renal failure, dehydration and recurring bacterial pyelonephritis. She has very advanced oral cavity disease, the owner is reluctant to do dental prophylaxis and she had received antibiotics for long periods of time. Chronic antibiotic therapy can damage intestinal flora and may affect negatively the immune system of the patient.^{16, 17} During a three-month period of time her serum creatinine varied from 3.9 mg/dl to 2.6 mg/dl and back up again. Her pre-hospitalization serum creatinine was 3.9 mg/dl and she completed her study period with a serum creatinine of 2.9 mg/dl, which represents a substantial improvement in a case this severe. Her serum creatinine and BUN did show declines but the study overlapped one of her decompensations and hospitalizations, so it appears that little actually happened. However, the cat has shown amazing increases in appetite and energy per the owner's report as well as experiencing weight gain when it was not expected. This cat did experience some diarrhea that resolved and may be related to intestinal dysbiosis and/or gastrointestinal cleansing resulting from improved intestinal floral health. During periods of bacterial die-offs toxins may be released as the body flushes these toxins out the gastrointestinal system. The diarrhea seemed to be associated with antibiotic therapy and worsening of the azotemia. The exact reasons for this cannot be known for certain.

Case number five has been diagnosed with vaccine-related-fibrosarcoma and adenocarcinoma for a year-and- a-half. This client has elected modified hospice for this patient, and per her caregiver, her quality of life has improved markedly since taking the probiotic. She is very active and feels well even though her tumor is relatively large. This case has not had kidney biopsies but it is likely that she has some issues associated with the advanced state of her tumor involving glomerular/tubular function.

All cats in this study have palpably small kidneys indicating chronic disease. Case four suffered a rather bad case of FUS blockage several years ago and it is suspected that this contributed to his present renal failure. All cats in this study received vaccinations. Our clinic utilizes a reduced vaccination protocol. We vaccinate for FVRCP only every three years, and we cease vaccinations in indoor cats with other disease states in support of vaccine label recommendations.

Patient tolerance of the product was good, but it was difficult to give the recommended amounts without mixing it with food. No cats would accept it as a capsule and several clients balked at the cost. We attempted to put it in water and drench these patients but this was not accepted. Finally, all cats ingested it easily from canned cat food. There is some concern that giving probiotics with food may decrease their numbers, but judging from the above results there is a clinically significant effect from ingesting adequate numbers of these bacteria. Higher dosing may give even better results. Only one cat suffered any discomfort, and that was case number four. This cat experienced vomiting soon after receiving the oral product mixed with water. The owner ceased the product for three days and began mixing it with food and the cat did fine after this.

Veterinarians practicing Complementary and Alternative Veterinary Medicine (CAVM) have long proposed and advocated the use of probiotics in aging veterinary patients. The alternative movement has frequently been criticized for use of such nonvalidated procedures but they frequently turn out to be very useful. CAVM has reported a wide number of benefits observed clinically. This study demonstrates another value to this practice and validates those clinical opinions. Hopefully, other practitioners will do similar small clinical reports that can be used to target more precisely those modalities that are particularly promising for treatment of feline azotemia and renal failure. Immediate opportunities exist in comparing various probiotic products for activity in reducing azotemia. Kibow Biotech states that the specific strains of bacteria used in Kibow Biotic[®] are more effective than other products currently on the market. It would be very useful to compare various other CAVM practices as part of a protocol to treat chronic renal failure in cats.

The author has personally seen many remarkable improvements in cats suffering from renal disease after administering nutraceuticals, whole food and glandular supplementation, Traditional Oriental Medicine, homotoxicology, biopuncture, and homeopathy. Other approaches exist using western herbs as well. Integrative Veterinary Medicine is gaining momentum and this would seem a very fruitful area for research and validation of modalities potentially helpful to feline medicine. Of even greater interest is the possibility of reducing renal failure, prolonging the period of normalcy, and even potential life extension by early intervention with probiotic formulas as medicants or food additives. The biological therapy movement would receive such research data with great excitement.

In conclusion, Kibow Biotics[®] seems to have benefited these cases. The manufacturer's promise of decreasing azotemia appears to be verified, and these patients did experience improved health and vitality. This data does not refute or substantiate improved immune status or longevity. The cats generally did have good stools and only one case of vomiting occurred. Clients were happy to use the product and have been pleased to reorder indicating client satisfaction and ease of use. The single case of diarrhea resolved and did not recur. The author would like to see more involved placebo-controlled, double-blind trials comparing this product to other probiotic formulations.

References

1. Hughes, K, Slater, M, Geller, S, Burkholder, W, and Fitzgerald, C. Diet and Lifestyle Variables as Risk Factors for Chronic Renal Failure in Pet Cats. *Preventive Veterinary Medicine*, (2002). (55): 1-15.

2. Grauer, G. Early detection of renal damage and disease in dogs and cats. *Vet Clin North Am Small Anim Pract*, (2005). 35(3): 581-596.
3. Polzin DJ, Osborne CA, Adams LD, O'Brien TD. Dietary management of canine and feline chronic renal failure. *Vet Clin North Am Small Anim Pract*, (1989). 19(3): 539-60.
4. Plantinga EA, Everts H, Kastelein AM, Beynen AC. Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets. *Vet Rec*, (2005). Oct 8; 157(15): 455-6.
5. Adams LG, Polzin DJ, Osborne CA, O'Brien TD. Effects of dietary protein and calorie restriction in clinically normal cats and in cats with surgically induced chronic renal failure. *Am J Vet Res*, (1994). Feb; 55(2): 308.
6. Elliott J, Rawlings JM, Markwell PJ, Barber PJ. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. *J Small Anim Pract*, (2000). Jun; 41(6): 235-42.
7. Natarajan Ranganathan, Beena Patel, Pari Ranganathan, Joseph Marczely, Rahul Dheer, Tushar Chordia, and Zhigang Yang, Eli A Friedman. *Probiotic Reduces Azotemia in Gottingen Minipig*. 3rd World Congress Of Nephrology (WCN), 2005.
8. Ranganathan, Natarajan ; Patel, Beena ; Ranganathan, Pari ; Marczely, Joseph ; Dheer, Rahul ; Chordia, Tushar ; Dunn, Stephen R. ; Friedman, Eli A. Probiotic amelioration of azotemia in 5/6th nephrectomized Sprague-Dawley rats. *The Scientific World Journal*, (2005). (5): 652-660.
9. Antech Diagnostics, Inc. 17672-A Cowan Avenue, Irvine, California, 92614, 800-745-4725.
10. A Probiotic Approach for Uremic Toxin Removal: Kibow Biotics.® Product brochure. www.kibow.com. Website.
11. Beena Patel, Rahul Dheer, Joseph Marczely, and Natarajan Ranganathan. *Comparative microbial viability analysis in two delivery formats- gelcaps or admixed with food/diet*. 12th International Congress on Nutrition and Metabolism in Renal Disease (ICNMR) poster #P-A49, 2004.
12. Heel. 2000. *Biotherapeutic Index: Ordinatio Antihomotoxica et Materia Medica*, 5th Edition. Biologische Heilmittel Heel GMBH, Baden-Baden, Germany, p 279.
13. Martin Goldstein. 1997. Personal communication.
14. Paula Broadfoot, Demers J, Palmquist R. Personal communication of benefits of homotoxicology and future research directions during AHVMA Homotoxicology Seminar in Denver, CO. 2004.
15. Brad Roach. Personal communication via email. 2005.
16. Bongaerts G, Severijnen R, Timmerman H. Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy. *Med Hypotheses*, (2005). 64(1): 64-68.
17. Rial D. Rolfe. The role of probiotic cultures in the control of gastrointestinal health. *Journal of Nutrition*, (2000), 130: 396S-402S.