

THE COMPARATIVE EFFICACY OF SOME OF THE COMMONLY  
USED URINARY ANTIBACTERIAL AGENTS IN THE  
TREATMENT OF EXPERIMENTAL CANINE  
BACTERIAL NEPHRITIS

by

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## INTRODUCTION

Nephritis in the canine patient is a basic problem in veterinary medicine and probably occurs more commonly than presently diagnosed. Veterinary pathologists have recorded that from five to ten percent of the dogs undergoing routine autopsies have characteristic lesions of nephritis (2), (10).

Clinically, nephritis may be divided into acute and chronic types. The acute type is characterized by a sudden onset, listlessness, a disinclination to move about, inappetence, vomiting, and polydipsia. The temperature is usually elevated at the onset, but may drop to normal in a few days without the benefit of treatment. Lumbar tenderness may cause an arching of the back and a stilted gait. Partial or complete anuria is frequently noted and hematuria is not uncommon.

Results of urinalysis usually reveals a high specific gravity ranging from 1.030 to 1.050 and proteinuria. Examination of the urine sediment may reveal an increased number of leukocytes and the presence of erythrocytes and urinary casts. As the disease condition progresses, the specific gravity of the urine usually decreases to what is called a point of "fixation" (1.010 to 1.012) (14).

Chronic nephritis is commonly seen in dogs over eight years of age (2). The onset is slow with a period of time passing before marked symptoms are evident. Early cases show increased thirst with occasional periods of sickness. The patient is usually dehydrated and the hair coat has an unthrifty appearance.

There may be a pronounced diarrhea in the later stages of the condition. Cardiac hypertrophy with dilatation of the left ventricle may result from the increased work load placed upon the heart (3). Copious amounts of a pale urine with low specific gravity (1.010 to 1.012) may be voided. Laboratory tests may reveal only a trace of protein or none at all. A few leukocytes and granular casts may be noted upon microscopic examination of the urinary sediment.

Uremia is a common sequel and is characterized by congestion of the conjunctiva, ulceration of the mucosa, a fetid mouth odor, a full and bounding pulse, and nervous symptoms varying from convulsions to a comatose state. Other symptoms which may be seen are muscle twitchings of a fibrillary type, constipation or diarrhea, emaciation and sometimes eczema.

Canine nephritis commonly results from an acute infection, which may initiate a lodgment of micro-organisms in the glomerular or intertubular vessels, or the damage to renal tissue from bacterial toxins and inflammatory products passing through the kidney (9). In the past, it was commonly believed that bacterial nephritis was established by bacteria ascending by way of the lumen of the ureter into the renal pelvis and parenchymal tissues of the kidney, more recently it has been assumed that unless there is an urinary obstruction or stasis that most infections are hematogenous (2). Theoretically, organisms may also reach the kidney by way of the ureteral lymphatics.

Bacterial nephritis is more commonly due to Escherichia coli and Proteus vulgaris, and less commonly to streptococci,

staphylococci, or other specific organisms (2).

In a report by Mosler and Coles (15) they found that in a total of 53 cases of clinical urinary tract infections that 22.6 percent were due to Escherichia coli, 32.1 percent were caused by Proteus sp., 20.7 percent due to streptococci, and 18.9 percent were infected with Micrococcus pyogenes.

Both human and veterinary medical literature contain numerous enthusiastic reports of the clinical efficacy of the urinary antibacterial agents in the treatment of urinary tract infections. Controlled bacteriological tests have shown that the favorable clinical effects may be only temporary with the infecting organism still present in the urinary tract following treatment (15).

It is generally agreed that the successful treatment of kidney infections will depend not only on the selection of a suitable antibacterial agent, but also obstructive lesions must be corrected and infecting foci such as pyometra, vaginal infections, peritonitis, pneumonia, prostatitis, gastro-intestinal, and other infections eliminated.

The rate of relapse and reinfection after any type of drug therapy is apparently very high, making the treatment of urinary tract infections a definite problem (12).

Some of the more common urinary antibacterial agents used in the therapy of bacterial canine nephritis are penicillin, chloramphenicol, tetracyclines, sulfonamides, nitrofurans, and streptomycin. Penicillin, streptomycin, sulfisoxazole, and

chloramphenicol were selected as representatives of this group for this study.

Penicillin is produced commercially by the culturing of the Penicillium mold strains of Penicillium notatum or of Penicillium chrysogenum (17). Penicillin has proven to be relatively specific in its action against Gram-positive bacteria, but has shown to be ineffective against most Gram-negative organisms.

Penicillin is both bactericidal and bacteriostatic. Bacterial multiplication is inhibited at low concentrations of penicillin and the bacterial cells are killed with higher concentrations. The period of the highest antibacterial action is when the multiplication of the bacteria is the greatest. Some bacteria, which are originally susceptible, develop a resistance to penicillin. This drug is considered active in the presence of blood, serum, pus, and large numbers of bacteria (11).

The mode of action of penicillin against bacteria is unknown. It is believed to inhibit the metabolic activities vital to the bacterial cell by blocking the assimilation of protein which is essential for growth and reproduction (11).

Penicillin is excreted primarily by the urinary system. It is considered a relatively nontoxic substance, and approaches the ideal therapeutic agent in relation to the antibacterial action and the wide margin of safety in which it possesses (11).

The administration of penicillin in animals is largely by the intramuscular route. The minimal dosage of penicillin for the canine is considered to be 5,000 units of penicillin per pound of body weight intramuscularly. This dosage may be

increased to 10,000 units per pound of body weight in the presence of a virulent infection (17).

Streptomycin is produced from a species of actinomyces belonging to the genus Streptomyces griseus (11). It is a valuable therapeutic agent as it is effective against Gram-negative bacteria and supplements the drugs which are active only against Gram-positive organisms. The action of streptomycin against the micro-organisms seems to be that of interference with one or more of the cellular enzyme systems essential for bacterial cell division (11). It was found that streptomycin sulfate could be converted into Dihydrostreptomycin Sulfate by reducing the carbonyl group by catalytic hydrogenation (11). Dihydrostreptomycin is a more stable, less toxic product and has an antibacterial activity comparable to that of streptomycin.

Streptomycin and dihydrostreptomycin are readily absorbed into the blood stream and distributed to the various body tissues and fluids following intramuscular injection. Streptomycin is indicated for treatment of systemic infections due to sensitive Gram-negative and acid fast Gram-positive bacteria. Streptomycin and dihydrostreptomycin are reported to be effective in the treatment of urinary infections, especially those due to Escherichia coli, Proteus vulgaris, Aerobacter aerogenes, and Pseudomonas aeruginosa (17).

Prolonged streptomycin therapy has the tendency to produce the development of resistant strains of bacteria and chronic toxicity. The most serious toxic action of streptomycin is the neurotoxic effect upon the vestibular and auditory mechanism (11).

The development of dihydrostreptomycin reduced the toxicity problem somewhat, but it still is worthy of serious consideration.

Streptomycin is excreted primarily in the urine in about one-half the concentration of the blood stream (11). This may cause unduly high concentrations of streptomycin in the blood of individuals with renal dysfunction and result in serious toxic effects. The dosage should be adjusted accordingly in the treatment of these patients (17).

The minimal therapeutic dose of streptomycin or dihydrostreptomycin for mammals is considered to be five mg. per pound of body weight, injected intramuscularly in aqueous solution at 12 to 24 hour intervals (11).

Chloramphenicol (Chloromycetin) is produced from cultures of a soil-borne actinomycete, Streptomyces venezuelae (17). It has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, rickettsia, and the larger viruses (11). Apparently, little is known about the mode of action of chloramphenicol against these pathogens.

Chloramphenicol is administered both orally and intramuscularly. When given orally in the dog, it does not cause vomiting or diarrhea, but it may induce anorexia. It is readily absorbed following oral administration in dogs, and appears in practically all tissues within one and one-half hours following administration. It reaches the highest concentration in the liver, bile, and the kidneys (11). Chloramphenicol is excreted in an active and inactive form, with only 6.3 percent of the total drug

excreted in the active form (11). The active form is excreted mainly by the renal glomeruli, the inactive form is excreted by the renal tubules and bile in the dog.

Chloramphenicol may be preferred to streptomycin in the treatment of urinary tract infections because of its lack of toxicity (17).

The oral dosage of chloramphenicol recommended for small animals is 25 to 50 mg. per pound of body weight per day, administered in two or three divided doses.

Sulfisoxazole (3,4-dimethyl-5-sulfanilamidoisoxazole) is a sulfonamide marketed under the trade name Gantrisin by Hoffmann La Roche, Inc. It is a highly soluble sulfonamide commonly used in treating urinary tract infections of man (18).

Previous studies have shown sulfisoxazole to have about the same range of bacteriostatic activity as sulfadiazine. The solubility of sulfisoxazole in pH ranges of 4.5 to 6.0 is considerably greater than that of sulfadiazine (18).

It is believed that when sulfonamides are administered, they exert a bacteriostatic action on the micro-organisms. The reticulo-endothelial system and the sulfonamide appear to combine actions, the sulfonamides exert a bacteriostatic action in vivo and aid the reticulo-endothelial system in combating and removing the invading pathogenic organisms. The exact mechanism of the antibacterial action of the sulfonamides has been postulated in several theories (11).

The excretion of the sulfonamides is primarily through the urinary tract. The sulfonamides which are not readily absorbed

by the intestinal tract are excreted by the feces. There are small amounts excreted in bile, pancreatic juice, gastric juice, intestinal juice, saliva, and in the milk (11).

Sulfisoxazole has become one of the drugs of choice in treating urinary tract infections in man (18). Its use has become popular because of its solubility and low toxicity (16).

Sulfisoxazole is administered orally to small animals, usually in a dosage range of one grain per pound of body weight per day divided into three doses.

A number of controlled tests have been made in human medicine, in which bacteriological studies have accompanied the treatment of the urinary tract infections with various urinary antibacterial agents. Most of the reports in regard to the treatment of urinary tract infections in veterinary medicine are clinical in nature, and bacteriological studies have not been done. Apparently much of the information in regard to the treatment of bacterial nephritis and infections of the urinary tract in veterinary medicine has been adapted from the human medical literature.

On this basis the following survey of the efficacy of the selected urinary antibacterial agents on experimental canine bacterial nephritis was made.

#### REVIEW OF LITERATURE

Kidney disease has been considered a problem in veterinary medicine for a number of years. Wright (23), in 1932, stated that kidney disease was such a common finding in the dog, that

it should be considered first in the diagnosis of what otherwise were obviously alimentary symptoms.

King (13), in 1937, reported that although kidney disease was a common condition seen upon autopsy of the dog, that there was much work to be done both on preventive and curative lines.

Haines (8) reported on a clinical case of bacterial nephritis which was treated with penicillin. The animal died and upon autopsy the renal tissue revealed multiple abscesses and cloudy degeneration. Escherichia coli was cultured from the renal abscesses.

Rollag (19) indicated in a clinical report the difficulty in obtaining a bacteriological cure in a case of bacterial nephritis due to Escherichia coli. In this report it was indicated that improvement of the clinical symptoms was accomplished by treatment with antibiotics and the usual urinary tract agents, but recurrence of the symptoms would arise at about two-week intervals. Euthanasia was performed and upon autopsy a diagnosis of suppurative nephritis was made.

Results of a screening survey by Mosier and Coles (15), involving approximately 300 dogs, indicated a bacterial etiology in an estimated 25 percent of the animals presented with a suspected urinary tract disorder.

In subsequent work by Mosier and Coles (15), 25 dogs, diagnosed both by clinical and laboratory means as having bacterial urinary tract infections, were used to evaluate the clinical effectiveness of Furadantin (nitrofurantoin) in urinary tract infections. Forty percent of the dogs treated in this study had

sterile urine upon post treatment bacteriological examinations. Clinical manifestations were improved in over 90 percent of the animals by treatment, but recurred in some instances after treatment was discontinued.

Coles and Mosier (7) established bacterial urinary tract infections in 27 dogs by experimental means to evaluate the effect of nitrofurantoin on experimental canine nephritis. After treatment, with relative high dosages of nitrofurantoin for periods up to 20 days, only three dogs, or 17.65 percent, had sterile urine upon a bacteriological examination at the time of necropsy.

Bloom (2) states that there is a species difference in the types of renal inflammatory disease between man and canine. With this in mind we review some of the literature pertaining to the use of antibacterial agents in the treatment of urinary infections in human medicine.

Adcock and Plumb (1) reported on 11 cases of urinary tract infections treated with streptomycin. In five patients with infection due to organisms of the *Aerobacter* group, prompt relief of symptoms occurred, pyuria disappeared and the urine became and remained sterile. Pretreatment tests had shown these organisms to be sensitive to streptomycin in vitro. *Pseudomonas aeruginosa* was isolated alone or in combination with other bacteria in five cases. Upon treatment there was relief of symptoms and pyuria diminished or disappeared. Unfortunately, the results of treatment were temporary and bacilluria persisted in each case. In vitro tests had indicated that these organisms

were fairly resistant to streptomycin. The eleventh patient was a case of chronic cystitis due to Escherichia coli, which temporarily improved from the streptomycin therapy. In three cases it was found that the strains of bacteria isolated after therapy were more resistant to streptomycin in vitro than the strains isolated prior to treatment.

In a series of 50 patients treated with Chloramphenicol by Chittenden, et al. (6), it was found that 13 (26 percent) were infected by a single invader, while in the other 37 (74 percent) the infection was caused by two or more bacilli or combinations of bacilli and cocci. In the patients with simple bacillary urinary infection the treatment usually returned the elevated temperature to normal within a few hours and grossly purulent urine became clear, free of leukocytes, and bacilli within 24 to 36 hours.

In the 50 cases treated, infection was bacteriologically controlled in 19 cases (38 percent), clinically improved in 22 (44 percent), and the infection was unimproved in nine cases (18 percent).

In this study Escherichia coli, Aerobacter aerogenes, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella schottmuelleri, and Proteus vulgaris were the common urinary tract pathogens that responded to chloramphenicol treatment.

Schweinburg and Rutenburg (20) evaluated the therapeutic activity of NU 445 (Sulfisoxazole) in 20 unselected patients which had various urinary tract infections due to Gram-negative bacilli. They received two types of responses. A clinical and

bacteriological cure was obtained in seven patients (35 percent). Thirteen patients (65 percent) were listed as clinical and bacteriological failures. Three of this group indicated temporary improvement, but had a recurrence. Twelve of the patients that were not cured had mixed infections.

On the basis of this clinical trial, these workers stated that sulfisoxazole was a safe and effective drug in the treatment of uncomplicated monovalent infections due to Escherichia coli and B. proteus and was apparently ineffective in polyvalent infections.

In a study on the antibacterial management of urinary tract infections made by Rhoads, Billings, and O'Connor (18), 325 cases were studied that were known to have bacterial urinary tract infections. The object of the study was to obtain the comparative results of different antibacterial agents commonly used in treating urinary tract infections.

A group of patients with urinary tract infections, due to Escherichia coli, were surveyed in regard to the effectiveness of treatment with various antibacterial agents. Seven patients were treated with streptomycin, three patients (43 percent) developed negative urine cultures, with a bacteriological control of the infection in only one patient. Nine patients were treated with chloramphenicol, three patients (33 percent) developed negative urine cultures, with the infection controlled permanently in two patients. Twenty-three cases were treated with Gantrisin, six patients (26 percent) developed negative urine cultures, with the infection permanently controlled in two

patients. This survey showed a remarkably low incidence of permanent cures with any type of drug therapy except in patients having cystitis without obvious obstruction. Results indicated that combined therapy of two or more agents were more effective than treatment with a single drug.

Sulfisoxazole was considered by these authors to be the sulfonamide of choice in most urinary tract infections.

Waisbren and Garr (21) reported on 23 cases of clinical urinary tract infections due to Proteus organisms which were treated with chloramphenicol, penicillin, and the combination of the two agents. Five cases responded to chloramphenicol, three cases responded to penicillin, and four cases responded to the combination of the two agents. Eight cases did not respond to chloramphenicol, 12 of the patients did not respond to penicillin, and five cases showed no response to the combination of chloramphenicol and penicillin in spite of an apparent in vitro sensitivity.

It is the opinion of this author that chloramphenicol, penicillin, gantrisin, and neomycin may be considered effective against some infections due to Proteus organisms. The combination of penicillin and chloramphenicol may cure infections that have not responded to either drug given alone.

Nesbit and Baum (16) in a report on the treatment of infections of the genitourinary tract stated that the physician today, despite the many chemotherapeutic and antibiotic agents available, continues to encounter a number of urinary infections that fail to improve under therapy or that recur. They were of

the opinion that inadequate dosage of the antibacterial agent was often the reason for the therapeutic failure. Infections of the kidney are primarily located in the tissues, therefore successful treatment of kidney infections will depend on selection of not only the proper antibacterial agent but also the maintenance of a tissue level that will be adequate to destroy the organism. Another cause of failure of treatment is the resistance of the organisms to the agent used in treatment. Resistant strains of bacteria appeared more commonly under situations where there was poor contact of the drug with the organism, either as a result of inadequate dosage or because of the nature of the tissues where the organisms are located. Also the development of cross resistance against drugs having similar bacterial spectra was considered highly significant.

These authors state that it is very important to identify the bacteria before treatment. A Gram stain of the urine sediment may be sufficient as a preliminary guide to the selection of a treatment agent. When streptococci are demonstrated the use of penicillin is indicated. If Gram-negative organisms or staphylococci are identified in the urine sediment, the use of a sulfonamide such as sulfadiazine, triple sulfonamides, or sulfisoxazole is advisable. This procedure reserves the more expensive antibiotics for instances in which penicillin or the sulfonamides are ineffective and allow time for the use of sensitivity tests in selection of the most suitable agent. It is suggested that chloramphenicol should be given for a minimum of seven days, and that it has been found to be effective against

Escherichia coli and Streptococcus faecalis, with a bacteriostatic effect on Aerobacter aerogenes, Bacillus proteus, and Klebsiella pneumoniae.

They concluded that combinations of the various antibacterial agents may eventually prove to be most effective in the treatment of urinary tract infections.

Carroll (5) maintains that because of moderate side reactions, low cost, and good tolerance the compounds Gantrisin, Elkosin, Thiosulfil, and Kynes are preferable in acute cases of urinary tract infection where the infecting organism has not been identified. He reports that Gantrisin is effective against Proteus as well as against the coccal infections. This is important in the treatment of urinary tract infections as Proteus splits the urea in the urine and causes a constant alkaline condition which renders methenamine and mandelic acids ineffective. Carroll's studies showed penicillin to be ineffective against Proteus, and streptomycin and the tetracyclines were only moderately effective.

Carroll suggests that the persistence and recurrence of urinary infections are due to failure of drainage or the presence of obstructive lesions. In chronic pyelonephritis obstructions of the tubular structures below the lesion are not usually demonstrable. It is his opinion that multiple small infected areas are transformed into colonies of organisms surrounded by fibrous tissue that makes them inaccessible to the drug. Long continuous therapy must be used to reach these organisms with an effective tissue level of the antibacterial agent. Carroll

reports the administration of Gantrisin over periods of three months with favorable effect on the infection and no deleterious effect on the patient.

The literature reviewed appears to indicate that although there is probably some species difference between man and the canine in the inflammatory lesions of urinary tract infections, the problem of treatment and control of these infections are similar.

#### MATERIAL AND METHODS

A total of 14 dogs were used in this study. The dogs were of common mixed breeds ranging in age from six months to two years, and weighing between 13 and 32 pounds. There were seven males and seven females. Urine was collected from each animal by abdominal puncture and examined bacteriologically prior to use in this study to eliminate any previously infected animals.

The 14 dogs were divided into four groups. Group I, consisting of three dogs, was inoculated with Escherichia coli. Group II, consisting of three dogs, was inoculated with Streptococcus canis. Group III, which consisted of four dogs, was inoculated with Escherichia coli. Group IV, consisting of four dogs, was inoculated with Proteus sp.

In each instance the organism used was originally isolated from a clinical case of canine urinary tract infection. After the organism was isolated and identified, it was tested for sensitivity to antibiotics by adding approximately one ml. of a 24-hour broth culture to four ml. of melted tryptose-dextrose

agar cooled to 45 degrees Centigrade. This agar mixture was poured onto the surface of a plate containing five percent sheep blood agar. After solidification, the antibiotic discs containing penicillin, streptomycin, aureomycin, chloramphenicol, tetracycline, terramycin, polymyxin, and erythromycin were placed on the surface of the plate. The results of antibiotic sensitivity were determined after the plate had been incubated for 18 hours at 37 degrees Centigrade.

The organism selected for use in the establishment of bacterial nephritis was cultured in broth for a period of 24 hours at 37 degrees Centigrade, and this culture used as the inoculum.

The technique used in establishing the infection was essentially the same as that described by earlier investigators (7), (22). The dogs were anesthetized with sodium pentobarbital and prepared for surgery in the routine manner. A longitudinal incision of about three inches in length, parallel to the thirteenth rib, was made on the left side of the animal. The external oblique, internal oblique, and transverse abdominal muscles were separated in the direction of their fibers. The peritoneum was divided with the transverse abdominal muscle and the left kidney located and elevated to the surface of the incision. The renal artery was isolated by separating the adipose tissue away from the kidney and exposing the structures at the hilus of the kidney. A forcep was placed under the renal artery thereby isolating it from the other structures. The bacterial suspension was then inoculated into the kidney by injection of 0.5 ml. of the

inoculum into the renal artery through a curved 28-gauge hypodermic needle. A forcep was immediately placed on the renal vein for a short period to insure complete spread of the bacterial suspension throughout the renal tissues. The kidney was then replaced into the abdominal cavity and the incision closed in the usual manner.

Urine samples were collected daily after the injection of the bacterial suspension to determine if the infection was established. Since specimens collected by catheterization are likely to be contaminated by the micro-organisms normally present in the external genitalia of both sexes, the urine was obtained by abdominocentesis with a 20-gauge,  $1\frac{1}{2}$ -inch hypodermic needle (4).

Examination of the urine consisted of a bacteriological examination by culture of the urine on five percent sheep blood agar media, routine urinalysis for protein, glucose, specific gravity, and pH, and a microscopic examination of the urinary sediment.

Following isolation of the organisms from the urine, a period of five to 20 days was allowed to elapse before treatment was initiated, thus enabling the bacterium to become firmly established in the renal tissues, and therefore to more closely approximate a clinical condition.

Treatment consisted of at random selection of one animal from each group for treatment with penicillin-streptomycin combination, one with sulfisoxazole, and one with chloramphenicol.

The number four dog in Groups III and IV served as a control and was not treated.

The dosage of penicillin-streptomycin used was 10,000 units of Penicillin G Procaine, crystalline, and five mgm. of Dihydrostreptomycin sulfate per pound of body weight administered intramuscular each 12 hours.

Chloramphenicol was administered orally in a dosage of 25 mgm. per pound of body weight divided into three doses daily, with the exception of Group I, in which 15 mgm. per pound of body weight was administered, and Group II, in which 10 mgm. per pound of body weight was administered.

Sulfisoxazole was used in two preparations, Renzol tablets and Gantrisin tablets. Renzol is a compound prepared by Allied Laboratories, Inc., Indianapolis, Indiana. It contains  $1\frac{1}{2}$  grains sulfisoxazole, 0.09015 mgm. of hydrocyamine hydrobromide, 0.00745 mgm. of atropine sulphate, and 0.0024 mgm. of scopolamine per tablet. The recommended dosage of one tablet per ten pounds of body weight three times a day was used in Groups I and II. Sulfisoxazole (Gantrisin), used in Groups III and IV, was administered orally at the rate of one grain per pound of body weight per day divided into three equal doses.

Groups I, II, and IV were treated for a period of five days. Group III was treated for a ten-day period. Seven to ten days following the termination of the treatment period, urine samples were collected and examined, by means of bacterial cultures, for continued presence, possible recurrence, or change of organisms.

Following euthanasia of the dogs, cultures of both kidneys and the mucosa of the urinary bladder were made.

#### RESULTS OF EXPERIMENTATION

##### Results of Penicillin-Dihydrostreptomycin Therapy

Experimental animal number 5 was a male dog of mixed breed weighing 32 pounds. This animal was injected with hemolytic Escherichia coli organisms into the left renal artery on March 22, 1958. Cultures of the urine later indicated that a urinary tract infection due to hemolytic Escherichia coli had been established. A combination of penicillin-dihydrostreptomycin was selected as the drug for treatment. Treatment was initiated eight days following the date of injection and was continued for a five-day period. Hemolytic Escherichia coli was not present on the urine culture made 24 hours post treatment. The urine was cultured ten days following treatment and hemolytic Escherichia coli was isolated. Following euthanasia, culture of the right kidney was negative for bacterial growth, but hemolytic Escherichia coli organisms were present on the culture of the left kidney.

Experimental animal number 8 was a female of mixed breed weighing 20 pounds. This animal was injected with hemolytic Streptococcus canis into the left renal artery on May 7, 1958. Cultures of the urine later indicated that a urinary tract infection due to hemolytic Streptococcus canis had been established. A combination of penicillin and dihydrostreptomycin

was selected as the drug for treatment. The treatment was started 20 days after the date of injection. Streptococcus canis was not isolated from the urine when cultured within 24 hours after the termination of treatment. The urine culture made seven days following the termination of the treatment period showed the Streptococcus canis organism present. After euthanasia was performed, cultures were made of the right and left kidneys and mucosa of the urinary bladder, all of which revealed the presence of hemolytic Streptococcus canis.

Experimental animal number 16 was a female dog of mixed breed weighing 30 pounds. The animal was injected into the left renal artery with hemolytic Escherichia coli organisms on June 21, 1958. Cultures of urine specimens later indicated that an infection, due to Escherichia coli, had been established in the urinary tract. The combination of penicillin and dihydrostreptomycin was selected for use over a period of ten days. Treatment was started six days following the date of injection. The urine culture made within 24 hours following the termination of the treatment period was negative to bacterial growth. Cultures of the urine seven days post treatment, of the right and left kidneys, and the mucosa of the urinary bladder were negative to bacterial growth.

Experimental animal number 17 was a male dog of mixed breed weighing 20 pounds. This animal was injected into the left renal artery with a culture of Proteus sp. on June 22, 1958. Urine cultures, made from specimens collected a few days after injection of the organisms, indicated the establishment of

Proteus sp. in the urinary tract. Penicillin and dihydrostreptomycin combination was used over a period of five days for treatment. The treatment was started eight days following the date of injection. Urine cultures at the termination of the treatment period were negative for bacterial growth. Cultures of the urine, right and left kidneys, and mucosa of the urinary bladder were made seven days after the termination of treatment and did not reveal a bacterial growth. (Table 1.)

#### Results of Chloramphenicol Therapy

Experimental animal number 1 was a female dog of mixed breed weighing 20 pounds. This animal was injected with a culture of hemolytic Escherichia coli organisms into the renal artery on March 22, 1958. Cultures of the urine indicated a urinary tract infection due to Escherichia coli organisms had been established. Chloramphenicol was selected as the drug to be used in treatment. Treatment was initiated eight days following the date of injection of the micro-organisms. The urine culture made within 24 hours after the termination of treatment revealed the presence of hemolytic Escherichia coli organisms. The urine was again cultured one week post treatment, this culture also revealed the presence of hemolytic Escherichia coli organisms. Following euthanasia, cultures were made of the right and left kidneys. The culture of the right kidney was negative for bacterial growth, the culture of the left kidney revealed the presence of hemolytic Escherichia coli in the tissues.

Table 1, Results of penicillin-streptomycin therapy (used simultaneously).

Experimental Animal	Organism Infection	Treatment History	Bact. Culture
No. : Weight		Duration : Dosage	24 Hr. Post : 7 Days Post Treatment : Treatment
5	<u>Escherichia coli</u>	Streptomycin 5 mg. per lb. Body wt. BID Penicillin 10,000 units Per lb. bdy. wt. BID	Urine- E. coli Left kidney- E. coli Right kidney- Negative
8	<u>Streptococcus canis</u>	Streptomycin 5 mg. per lb. Body wt. BID Penicillin 10,000 units Per lb. bdy. wt. BID	Urine- Strep. canis Left kidney- Strep. canis Right kidney- Strep. canis
16	<u>Escherichia coli</u>	Streptomycin 5 mg. per lb. Body wt. BID Penicillin 10,000 units Per lb. bdy. wt. BID	Urine- Negative Left kidney- Negative Right kidney- Negative
17	<u>Proteus sp.</u>	Streptomycin 5 mg. per lb. Body wt. BID Penicillin 10,000 units Per lb. bdy. wt. BID	Urine- Negative Left kidney- Negative Right kidney- Negative

Experimental animal number 6 was a dog of mixed breed weighing 30 pounds. This animal was injected into the renal artery with a culture of hemolytic Streptococcus canis on May 7, 1958. Urine cultures of specimens collected at later dates indicated the establishment of Streptococcus canis in the tissues of the urinary tract. Chloramphenicol was used in treatment for a period of five days. Treatment was initiated 20 days following the date of injecting the micro-organisms. The urine specimen collected and cultured within 24 hours of the termination of the treatment period revealed the presence of Streptococcus canis. Euthanasia was performed seven days following the termination of treatment, cultures of the urine, right kidney, and mucosa of the urinary bladder were positive for Streptococcus canis organisms. The culture of the left kidney was negative for bacterial growth.

Experimental animal number 14 was a female dog of mixed breed weighing 15 pounds. This animal was injected into the left artery with a culture of hemolytic Escherichia coli on June 21, 1958. Cultures of the urine indicated that Escherichia coli organisms had become established in the tissues of the urinary tract. Chloramphenicol was used in the treatment for a period of ten days. Treatment was initiated five days after injection of the organisms. Urine cultures made from specimens collected within 24 hours of the termination of the treatment period indicated the presence of Escherichia coli organisms. Euthanasia was performed seven days following termination of treatment. The cultures made of the urine, right and left

kidney, and mucosa of the urinary bladder revealed the presence of hemolytic Escherichia coli.

Experimental animal number 19 was a female dog of mixed breed weighing 13 pounds. This animal was injected with Proteus sp. culture into the renal artery on June 24, 1958. Urine cultures revealed that Proteus sp. organisms had become established in the tissues of the urinary tract. Chloramphenicol was selected for treatment. The treatment period was started six days after treatment and continued for a period of five days. The urine specimen collected and cultured within 24 hours of termination of the treatment period indicated the presence of Proteus sp. organisms. Following euthanasia, seven days after treatment, the urine culture revealed the presence of Proteus sp. organisms. The culture of the right and left kidney, and mucosa of the urinary bladder was negative for bacterial growth. (Table 2.)

#### Results of Sulfisoxazole Therapy

Experimental animal number 3 was a female dog of mixed breed weighing 25 pounds. This animal was injected with a culture of hemolytic Escherichia coli organisms into the left renal artery on March 22, 1958. The cultures of the urine indicated that Escherichia coli organisms had become established in the tissues of the urinary tract. Sulfisoxazole was selected for treatment. The treatment was initiated eight days following the injection of the organisms and continued for a period of five days. The culture of the urine collected within 24 hours after the termination of treatment revealed the presence of

Table 2. Results of chloramphenicol therapy.

Experimental Animal	Organism	Treatment History	Bact. Culture
No. : Weight	Injection	Dosage : Duration	24 Hr. Post : Treatment : Treatment
1	20	<u>Escherichia coli</u> 100 mgm. TID (15 mgm. per lb. per day)	Urine <u>E. coli</u> Left kidney- Right kidney- Negative Urine- <u>E. coli</u> Left kidney- Right kidney- Negative
6	30	<u>Streptococcus canis</u> 100 mgm. TID (10 mgm. per lb. per day)	Urine <u>Strep. canis</u> Left kidney- Negative Right kidney- <u>Strep. canis</u> Urine- <u>Strep. canis</u> Left kidney-
14	15	<u>Escherichia coli</u> 25 mgm. per lb. body wt. per day	Urine <u>E. coli</u> Left kidney- Right kidney- <u>E. coli</u> Urine- <u>E. coli</u> Left kidney- Right kidney- <u>E. coli</u>
19	13	<u>Proteus sp.</u> 25 mgm. per lb. body wt. per day	Urine <u>Proteus sp.</u> Left kidney- Negative Right kidney- Negative Bladder- Negative

Escherichia coli organisms and a Streptococci. Euthanasia was performed ten days following the termination of treatment. The cultures of the urine, right and left kidneys were absent of bacterial growth.

Experimental animal number 7 was a male dog of mixed breed weighing 25 pounds. This animal was injected with a culture of hemolytic Streptococcus canis into the left renal artery on May 7, 1958. The cultures of the urine indicated the Streptococcus canis organisms had become established in the tissues of the urinary tract. Sulfisoxazole was selected as the therapeutic agent. The treatment was initiated 20 days after injection for a period of five days. A culture of the urine within 24 hours after the termination of treatment revealed the presence of Streptococcus canis organisms. Following euthanasia, one week after the termination of treatment, the urine, left kidney, and mucosa of the urinary bladder showed the presence of Streptococcus canis on bacterial culture. The culture of the right kidney was negative for bacterial growth.

Experimental animal number 12 was a female dog of mixed breed weighing 20 pounds. This dog was injected with a culture of hemolytic Escherichia coli organisms into the left renal artery on June 14, 1958. Cultures of the urine indicated that Escherichia coli organisms had become established in the tissues of the urinary tract. Sulfisoxazole was selected as the treatment agent. The treatment period was started 13 days after injection and was continued for ten days. A culture of the urine taken within 24 hours after the termination of treatment was

negative for bacterial growth. Following euthanasia, seven days post treatment, cultures were made of the urine, left and right kidney, and mucosa of the urinary bladder. These cultures were all negative for bacterial growth.

Experimental animal number 18 was a female dog of mixed breed and weighed 15 pounds. This animal was injected with a culture of Proteus sp. into the left renal artery on June 22, 1958. Cultures of the urine indicated the Proteus sp. had become established in the tissues of the urinary tract. Sulfisoxazole was selected as the drug for treatment. Treatment was started on the eighth day following injection of the organisms and was continued for a five-day period. A culture of the urine made within 24 hours after the termination of treatment was negative for bacterial growth. Seven days after the termination of treatment, euthanasia was performed. Cultures of the urine and mucosa of the urinary bladder revealed the presence of Proteus sp. organisms. The cultures of the right and left kidneys were negative for bacterial growth. (Table 3.)

#### Results of Control Animals

Experimental animal number 15 was a male dog of mixed breed weighing 30 pounds. This animal was injected with a culture of hemolytic Escherichia coli organisms into the renal artery on June 21, 1958. Cultures of the urine later indicated that a urinary tract infection due to hemolytic Escherichia coli organisms had been established. This animal was selected to serve as a control animal. Cultures of the urine were made at the same

Table 3. Results of sulfisoxazole therapy.

Experimental Animal	Organism	Injection	Treatment History	Dosage	Duration	24 Hr. Post Treatment	7 Days Post Treatment	Bact. Culture
3	<u>Escherichia coli</u>			Renzol tablets One tablet per 10 lbs. body wt.	5 days	Urine-E. coli. (Streptococci)		Urine- Negative Left kidney- Negative Right kidney- Negative
7	<u>Streptococcus canis</u>			Renzol tablets One tablet per 10 lbs. body wt.	5 days	Urine <u>Strep. canis</u>		Urine- Strep. canis Left kidney- Strep. canis Right kidney- Negative
12	<u>Escherichia coli</u>			Gantrisin 1 Grain per lb. body wt. per day	10 days	Urine Negative		Urine- Negative Left kidney- Negative Right kidney- Negative
18	<u>Proteus sp.</u>			Gantrisin 1 Grain per lb. body wt. per day	5 days	Urine Negative		Urine- <u>Proteus sp.</u> Left kidney- Negative Right kidney- Negative Bladder- <u>Proteus sp.</u>

intervals as the animals that were treated. The urine culture made at the time of termination of treatment of the other animals indicated the presence of Escherichia coli organisms. The cultures made following euthanasia indicated Escherichia coli organisms were present in the urine, tissues of the left kidney, and mucosa of the urinary bladder. The culture of the right kidney was negative for bacterial growth.

Experimental animal number 20 was a male dog of mixed breed weighing 25 pounds. This animal was injected with a culture of Proteus sp. into the left renal artery on June 24, 1958. Urine cultures later indicated the establishment of Proteus sp. organisms in the tissues of the urinary tract. This animal was selected to serve as a control. Urine samples were taken at corresponding times with the animals being treated. The urine culture collected at the corresponding time with the termination of the treatment period of the animals being treated revealed the presence of Proteus sp. organisms. Following euthanasia cultures of the urine and mucosa of the urinary bladder indicated the presence of Proteus sp. Cultures of the right and left kidneys did not reveal bacterial growth. (Table 4.)

#### DISCUSSION

Penicillin and dihydrostreptomycin combination produced a negative culture of the urine in all four cases upon the bacteriological examination of the urine made within 24 hours after the termination of treatment. In two cases, experimental animals 5 and 8, the infecting organism, Escherichia coli or

Table 4. Results of control animals.

Experimental Animal	No.	Weight	Organism	Injection	Treatment History	Bact. Culture
					Dosage : Duration	24 Hr. Post* : Treatment
15	30		<u>Escherichia coli</u>		Control	Urine- <u>E. coli</u> Left kidney- <u>E. coli</u> Right kidney- Negative
20	25		<u>Proteus sp.</u>		Control	Urine- Proteus sp. Left kidney- Negative Right kidney- Negative

\* Urine specimens were collected at corresponding intervals with the animals that received treatment.

Streptococcus canis, were present in the urine and kidney tissues at the time of necropsy.

The duration of treatment may be of significance in comparing the results obtained in the treatment of experimental animals 5 and 16. In animal 16 the ten-day period of treatment appeared to produce a bacteriological cure, while the infecting organisms reappeared on bacteriological culture after the five-day treatment period of animal 5.

Chloramphenicol therapy, in this series, did not produce negative urine cultures in spite of the fact that the organisms used indicated a sensitivity to chloramphenicol in vitro.

Upon necropsy of experimental animal number 14, a severe suppurative pyelonephritis of the left kidney was observed. Consequently, this case was probably not a true indication of the efficacy of chloramphenicol for a ten-day period of treatment.

In the series using sulfisoxazole therapy the urine was sterile upon bacteriological examination 24 hours after the termination of the treatment in two cases, experimental animals number 12 and 18. A positive culture of the urine was obtained upon necropsy of experimental animal number 18.

The ten-day treatment of experimental animal number 12 apparently produced a bacteriological cure. The five-day treatment period of experimental animal number 3, infected with the same strain of organisms, did not produce a sterile urine specimen upon bacteriological examination within 24 hours after the treatment period. A second organism, identified as a

Streptococcus, appeared on the cultures of the urine of animal number 3. This was a common finding of Rhoads, Billings, and O'Connor (18). Sulfisoxazole is usually effective against Escherichia coli, but apparently it is ineffective against some strains of Streptococcus.

The absence of organisms upon the bacteriological examination of the urine and kidney tissues at necropsy of experimental animal number 3 can only be theorized. The treatment may have reduced the number of infecting organisms and allowed the normal body defenses to overcome the infection. Obstructive lesions may have been produced by the enlargement of the kidney tissues due to inflammation caused by the infectious organism. These inflamed tissues may have been reduced in size by treatment, in turn correcting the obstructive lesions and allowing the infected areas to be repaired by the normal body processes.

There are several factors which have a direct relation on the effectiveness of an antibacterial agent upon urinary tract infections and may be the cause of a bacteriological failure in the treatment of infections of the urinary system.

A foci of infection may be the primary lesion which continually sheds the organisms which gain entrance to the urinary tract tissues by way of the blood and lymphatics. If this condition does exist it must be eliminated before a permanent bacteriological cure of the urinary tract infection can be accomplished.

Stasis of the urine due to obstructive lesions may be a cause of urinary tract therapeutic failures. Obstructive

lesions of the urinary system may be due to neoplasms, injuries, inflammatory debris, prostatitis, urinary calculi, and disease conditions. Obstructive lesions must be corrected before bacteriological cures can be attained with antibacterial agents.

Inadequate dosage of the antibacterial agent may be a common cause of therapeutic failure. The organisms are usually situated within the tissues of the kidneys. The commonly considered dosage schedules may sterilize the urine, but the antibacterial level in the tissues may not be sufficient to be effective against the organisms.

The duration of treatment is an important factor in the treatment of urinary tract infections. In chronic infections barriers from cellular infiltration and cicatrix formation may reduce the antibacterial level reaching the infecting organisms. The maintenance of an antibacterial level for a sufficient period of time to allow infiltration into these areas is necessary for a bacteriological cure.

Another cause of therapeutic failure may be the resistance of the organisms to the antibacterial agent. An antibacterial drug has limitations in usefulness based upon its bacterial spectrum. Unfortunately, some organisms which are normally considered susceptible to a drug may not be controlled by this drug upon its use in treatment. The identification of the infecting organism and determining the drug of choice for the treatment by the use of antibiotic sensitivity testing generally increases the rate of bacteriological cures of urinary tract infections.

There is the possibility that the manner in which the antibacterial agent is excreted may have an effect upon therapeutic response. Jones (11) states that 80 percent of penicillin is excreted through the renal tubules. Organisms which are located in some areas of the kidneys may be exposed to an insufficient level of the antibacterial to create a therapeutic response.

The use of combined antibacterial agents appear to increase the number of bacteriological cures. It is reasonable to assume that two agents may attack the bacterial cell from different metabolic standpoints, both contributing to a more complete therapeutic response. Combined antibacterial agents may also be of benefit in treating urinary tract infections which are caused by more than one micro-organism.

#### SUMMARY

The results of this series indicates that chloramphenicol is not effective against urinary tract infections in the canine due to Escherichia coli, Streptococcus canis, and Proteus sp. when used in the commonly applied dosages and period of treatment.

Sulfisoxazole would appear to be of benefit in the treatment of urinary tract infections of the canine due to Gram-negative organisms. Based on this series, therapy should be maintained for a period of at least ten days to provide for maximum effectiveness. Due to the low cost of this drug, in comparison with many of the so-called broad spectrum antibacterials, the expense of effective treatment should not be

considered prohibitive.

Of the antibacterial agents used, the combination of penicillin and dihydrostreptomycin was the most effective against Escherichia coli, Streptococcus canis, and Proteus sp. In this series, the ten-day period of treatment was the most effective.

The results of this study indicate that the procedure of treatment generally administered by veterinary practitioners, using penicillin, dihydrostreptomycin, chloramphenicol, and sulfisoxazole, may not be effective in producing bacteriological cures in urinary tract infections due to Escherichia coli, Proteus sp. and Streptococcus canis.

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THE COMPARATIVE EFFICACY OF SOME OF THE COMMONLY  
USED URINARY ANTIBACTERIAL AGENTS IN THE  
TREATMENT OF EXPERIMENTAL CANINE  
BACTERIAL NEPHRITIS

by

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AN ABSTRACT OF A THESIS

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Bacterial nephritis is frequently encountered in canine urinary tract infections. It is not uncommon for this condition to recur following treatment, thus, obtaining a bacteriological cure may be a definite problem to the veterinary practitioner.

The purpose of this study was to attempt to evaluate the efficacy of the more commonly used antibacterial agents and their procedure of use as generally administered by veterinary practitioners in the treatment of canine urinary tract infections.

A total of 14 dogs of common mixed breeds, seven males and seven females, ranging in age from six months to two years, weighing between 13 and 32 pounds, were used. The dogs, after urine cultures were made and found to be negative, were divided into four groups. Group I, consisting of three dogs, was inoculated with Escherichia coli organisms. Group II, consisting of three dogs, was inoculated with Streptococcus canis. Group III, consisting of four dogs, was inoculated with Escherichia coli. Group IV, consisting of four dogs, was inoculated with Proteus sp.

The organisms used for inoculation were originally isolated from clinical cases of canine urinary tract infections. After the organism was isolated, identified, and tested for sensitivity to antibiotics, it was cultured in broth for 24 hours prior to its use as an inoculum.

The infection was established by surgically exposing the left kidney and injecting 0.5 ml. of the bacterial inoculum into the left renal artery. Following the injection of the bacterial

culture, urine specimens were collected daily to determine if a urinary tract infection had been established. The urine specimens were collected by abdominocentesis to eliminate possible contamination from the organisms normally present in the external genitalia. The urine samples were cultured on five percent sheep blood agar and a routine urinalysis for protein, glucose, specific gravity, and pH was performed. A microscopic examination was made of the urinary sediment.

Treatment was initiated five to 20 days following isolation of the organisms from the urine after injection. This period allowed the organisms to become firmly established in the tissues of the kidney. Treatment consisted of the random selection of one animal in each group for treatment with penicillin and dihydrostreptomycin combination, one with sulfisoxazole, and one with chloramphenicol. Two animals, one in Group III and one in Group IV, were selected to serve as control animals and were not treated. The recommended dosage for each drug was used for a period of five days in Groups I, II, and IV, and for ten days in Group III.

The urine specimens were collected and examined daily during the treatment period, within 24 hours after termination of treatment, and at the time of necropsy seven to ten days following termination of treatment.

Chloramphenicol, in this series, did not produce negative urine cultures in spite of the fact that the organisms used indicated a sensitivity to chloramphenicol in vitro. These results indicate that chloramphenicol is not effective against

urinary tract infections in the canine due to Escherichia coli, Streptococcus canis, and Proteus sp. when used in the commonly applied dosages and period of treatment.

In the series using sulfisoxazole therapy, the urine was sterile upon bacteriological examination within 24 hours following termination of therapy in two cases, experimental animals number 12 and 18. Only one case, experimental animal number 12, had a sterile urine culture upon necropsy seven days following termination of treatment. The ten-day period of treatment of animal number 12 apparently produced a bacteriological cure. The five-day treatment period of experimental animal number 3, infected with the same strain of organisms, did not produce a sterile urine culture. A second organism, identified as a Streptococcus, appeared on the urine cultures of animal number 3 at the termination of the treatment period. This has been reported a common finding with sulfisoxazole therapy.

Based on this series, sulfisoxazole is of benefit in the treatment of urinary tract infections of the canine due to Gram-negative organisms, and treatment with this drug should be maintained for at least ten days to obtain maximum effectiveness.

Penicillin and dihydrostreptomycin combination produced a negative urine culture in all four experimental animals on bacteriological examination made within 24 hours following treatment period. Two animals, experimental animals number 16 and 17, had sterile urine cultures at the time of necropsy. A bacteriological cure was apparently obtained in experimental animal number 16, when treated for a ten-day period. The

five-day treatment period of experimental animal 5, infected with the same strain of organisms, did not produce a sterile urine culture at the time of necropsy.

In this series the combination of penicillin and dihydrostreptomycin was effective against urinary tract infections due to Escherichia coli, Streptococcus canis, and Proteus sp., and was most effective when used for a ten-day treatment period.

The results of this study indicate that the procedures of treatment generally administered by veterinary practitioners, using penicillin, dihydrostreptomycin, chloramphenicol, and sulfisoxazole, may not be effective in producing bacteriological cures in urinary tract infections due to Escherichia coli, Proteus sp., and Streptococcus canis.