

SINGLE DOSE THERAPY OF ACUTE CYSTITIS IN  
ADULT FEMALES: DOUBLE-BLIND COMPARISON  
OF FOUR REGIMENS

---

A Thesis  
Presented to  
The Faculty of Pharmacy  
University of Manitoba

---

In Partial Fulfillment  
of the Requirements for the Degree  
Master of Science

---

by  
Patricia Elaine Ludwig, B.Sc. Pharm.

March, 1980

SINGLE DOSE THERAPY OF ACUTE CYSTITIS IN  
ADULT FEMALES: DOUBLE-BLIND COMPARISON  
OF FOUR REGIMENS

BY

PATRICIA ELAINE LUDWIG

A thesis submitted to the Faculty of Graduate Studies of  
the University of Manitoba in partial fulfillment of the requirements  
of the degree of

MASTER OF SCIENCE

©<sup>v</sup> 1980

Permission has been granted to the LIBRARY OF THE UNIVER-  
SITY OF MANITOBA to lend or sell copies of this thesis, to  
the NATIONAL LIBRARY OF CANADA to microfilm this  
thesis and to lend or sell copies of the film, and UNIVERSITY  
MICROFILMS to publish an abstract of this thesis.

The author reserves other publication rights, and neither the  
thesis nor extensive extracts from it may be printed or other-  
wise reproduced without the author's written permission.

## ACKNOWLEDGEMENTS

I would like to express gratitude for the help and guidance given by my advisors, Drs. Allan R. Ronald and John Shaw. Special thanks is extended to Drs. Frederick J. Buckwold and Fred J. Aoki for their comments and constructive criticisms. In addition, I gratefully acknowledge the technical assistance given by Shirley Hoban and Linda Fox.

A special acknowledgement is given to my husband, Jim Ludwig, for his encouragement and understanding during the completion of this work.

A B S T R A C T

A prospective blind randomized study was done to assess the treatment of acute cystitis with four single dose regimens. We compared sulfisoxazole (SSX), 1 g, sulfisoxazole 2 g, trimethoprim-sulfamethoxazole (TMP/SMX), 160 mg/800 mg (two tablets) and TMP/SMX, 320 mg/1600 mg (four tablets). The site of infection was determined by the antibody-coated bacteria (ACB) test. Eighty-three patients entered the study. Seventeen patients had negative initial urine cultures and seven were lost to follow-up. The 59 evaluable patients ranged in age from 18 to 61 years. The infecting pathogen was Escherichia coli in 46, Staphylococcus epidermidis in 8, Proteus mirabilis in 4, Enterobacter spp. in 2, and Enterococcus in 1. One patient had a mixed infection with E. coli, P. mirabilis and Enterococcus. The infecting pathogens in 12 of the patients were positive for ACB. Of the 59 patients, 11 had sulfonamide resistant organisms.

Fourteen of the 17 patients who received SSX 1 g and 10 of 11 patients who received SSX 2 g were cured. There were four relapses, three in the SSX 1 g group and one in the SSX 2 g group. In the SSX 1 g group, the ACB test was positive in five patients and three patients were infected with a sulfonamide-resistant E. coli. In the SSX 2 g group, one patient had a sulfonamide-resistant E. coli and one patient had a sulfonamide and trimethoprim resistant Enterococcus. Fourteen of 15 patients who received TMP/SMX two tablets (0.96 g) were cured. The ACB test was positive in six patients and two patients had sulfonamide resistant E. coli. In the TMP/SMX four tablet group

(1.92 g), a reinfection occurred in one patient at one week; therefore, 15 of 16 patients were cured. The ACB test was positive in one patient, four had sulfonamide resistant organisms and one patient had a TMP resistant E. coli.

Adult females with acute cystitis can be effectively treated with single low doses of SSX or TMP/SMX.

## TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. LITERATURE REVIEW	8
- Epidemiology	9
Uncomplicated Urinary Infection	9
Acute Urethral Syndrome	11
Acute Cystitis with Spontaneous Remission	13
- Etiology	16
Bacterial Urinary Infection	16
Acute Urethral Syndrome	19
- Lower Tract Defense Mechanisms: Physico-chemical Properties of Urine and Their Effect on Bacterial Growth	22
- Localization of the Site of Infection	27
- The Relevance of Urine Antibacterial Activity to the Treatment of Urinary Tract Infections	33
- Antimicrobials Commonly Used for Acute Urinary Tract Infection	37
Sulfonamides	37
(i) Sulfisoxazole	39
(ii) Trimethoprim-Sulfamethoxazole	41
- Single Dose Studies	48
III. MATERIALS AND METHODS	52
- Clinical Material	53
- Laboratory Methods	54

Examination of Urine	54
Antibiotic Sensitivities	54
Vaginal Swabs	54
ACB Test	55
Determination of Urine Inhibitory and Bactericidal Titers	55
Mini Kill Curves	57
To Test the Effect of Inoculum and Medium on Sulfisoxazole Minimum Inhibitory Concentration	58
- Definition of Clinical Results	59
IV. RESULTS	61
- Clinical	62
- Relation of Urinary Antibiotic Activity to Eradication of Bacteriuria	74
V. DISCUSSION	93
- Introduction	94
- Comparison of Four Single Dose Regimens	97
- Relationship of ACB Positivity with Response to Treatment	99
- Significance of Dysuria and Pyuria with Bacteriuria and Abacteriuria	102
- Relation of <u>In Vitro</u> Sensitivities with Outcome of Therapy	106
- Distinction Between Persistence and Reinfection	109
- Relationship of Urinary Inhibitory and Bactericidal Titers with Clinical Outcome	113
- Urinary Analgesics	118



VI. SUMMARY	119
VII. BIBLIOGRAPHY	121

## LIST OF TABLES

<u>Table</u>		<u>Page</u>
I	Methods Available for Localization of Infection in the Urinary Tract	32
II	Summary of Single Dose Studies	51
III	An Outline of Population Characteristics with Treatment Regimens	67
IV	The Bacterial Etiology and Sulfonamide/Trimethoprim Susceptibility in the Study Group	68
V	Relationship of Vaginal Infection to Urinary Tract Infection	69
VI	Clinical Outcome of Patients with Negative Midstream Urine and Negative Vaginal Cultures	70
VII	Results of Therapy of Acute Cystitis to Sulfisoxazole (SSX) and Trimethoprim-Sulfamethoxazole (TMP-SMX) Single Dose Regimens	71
VIII	Response of Patients with Positive Antibody-Coated Bacteria Assay	72
IX	Correlation of Treatment Outcome to Specific Gravity and pH of Spot Urines Collected 4, 6, 12 and 24 hour Post Treatment	73
X	Antibacterial Effect of the Urine of Patients who have been Treated with a Single Dose of Sulfisoxazole 1 g	77
XI	Antibacterial Effect of the Urine of Patients who have been Treated with a Single Dose of Sulfisoxazole 2 g	80
XII	Antibacterial Effect of the Urine of Patients who have been Treated with a Single Dose of TMP-SMX (160 mg/800 mg)	82
XIII	Antibacterial Effect of the Urine of Patients who have been Treated with a Single Dose of TMP-SMX (320 mg/1600 mg)	85

- |     |  |    |
|-----|--|----|
| XIV | Effect of Inoculum Size and Medium on Varying Two-fold Sulfisoxazole Concentrations Using Microtiter "U" Plates                            | 88 |
| XV  | Geometric Means of Inhibitory Titers of Urine at Time After the Single Dose Hours and Relation to Clinical Effectiveness and Drug Regimens | 90 |

## LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
1	Prevalence of Bacteriuria According to Age and Sex	10
2	Sites of Enzyme Blockade in Purine Synthesis Produced by Sulfamethoxazole (SMX) and Trimethoprim (TMP)	47
3	Representative Mini Kill Curve Colony Counts of Pre- and Post-Treatment Urines from Four Cured Patients each Representing a Single Dose Regimen	89
4	Sulfisoxazole Inhibitory Titers and Geometric Means	91
5	Trimethoprim-Sulfamethoxazole Inhibitory Titers and Geometric Means	92
6	Representative Examples of Reinfection of the Urinary Tract by a Different Organism from that Originally Isolated, and Relapse due to Persistence of the Same Organism as Indicated by Biotype Number	112

I. INTRODUCTION

Recent progress in the prevention and control of many infectious diseases has brought to the fore those infections which are caused primarily by the indigenous bacterial flora and/or hospital-associated infections. Infections of the urinary tract occupy a major position among these types of infection.

The sensation of discomfort on passing urine (dysuria) is experienced during the life of most women (Fry, 1962; Waters, 1969; Steensberg, 1969). There is no doubt that acute uncomplicated urinary tract infection (cystitis) is the most common reason for treatment of bacteriuria, and in almost 40% of females will recur within one year following an acute infection. This infection predominantly is a disease of women of childbearing age. Why infection is more frequent in women than in men is not known. Conceivably, the crux of the problem resides merely in the shorter urethra present in the female and its increased opportunity to be exposed to, and colonized successfully by, the perineal enteric flora.

Urinary tract infection may involve only the lower urinary tract (bladder and/or urethra) or may involve both the upper (kidney) and lower tracts.

The term "acute cystitis" is used to describe the symptom complex of dysuria, frequency, urgency, and suprapubic tenderness with laboratory confirmation of bacteriuria. Bacteriuria refers to the presence of significant numbers of bacteria (100,000 or more organisms per millilitre) in a cleanly voided urine and as such, is the only accurate indicator of infection. Although temporarily distressing,

cystitis is a superficial mucosal infection of the bladder and a benign self-limiting disease in most instances.

The organisms involved are primarily enteric Gram-negative bacilli and are those commonly present in the lower bowel and on the perineum (Stamey et al, 1973). Of these, Escherichia coli is the most frequently isolated causative agent. Staphylococcus epidermidis is the second most frequent pathogen. The remaining incidents are caused by Proteus mirabilis, Klebsiella aerogenes, and Streptococcus faecalis. Other genera or species are rare.

Furthermore, it has been long recognized that many patients with complaints of frequency and dysuria have "negative" urine cultures. This clinical entity is termed as the "acute urethral syndrome". Other synonyms include trigonitis, symptomatic abacteriuria and non-specific urethritis. The acute urethral syndrome is a common clinical problem whose etiology and pathogenesis are poorly defined. About half the symptomatic women seen in general practice fall into this category (Gallagher et al, 1965; Mond et al, 1965). In some women it has been attributed to periurethral disease, but it also has been associated with trauma, vaginitis, gynecologic surgery, and birth control pills. A few individuals may have infection caused by mycoplasma, chlamydia, gonococci or viruses (Kunin, 1974; Dans and Klaus, 1975).

The overall goal in management of acute urinary infection is, whenever possible, to eradicate the invading organism from the urinary tract and to leave no persisters and, if possible, to prevent the next recurrence.

The traditional non-specific oral therapy of forcing fluids is important. It results in more frequent bladder emptying, thus removing infected urine. Many women with cystitis have learned the value of forcing fluids and manage their symptoms without additional medical aid. At one time, manipulation of pH of urine was a part of the management of acute cystitis. It is known that an acid pH inhibits bacterial multiplication and can augment host defenses (Brumfitt and Percival, 1962; Kaye, 1968).

Other adjuncts to therapy include drugs that act as local urinary analgesics. Phenazopyridine may relieve some dysuria. At present antibacterial therapy is the mainstay of the management of acute urinary tract infection. E. coli strains cultured from patients are generally sensitive to all antimicrobials effective against Gram-negative organisms, including sulfonamides.

There has been much controversy as to how vigorously chemotherapy should be pursued (Levenson and Kaye, 1972). A rational approach to the treatment of urinary tract infection depends on the prognosis of the untreated infection and the long-term results to be expected from therapy. The side effects, cost, and inconvenience of therapy must also be considered. Although no one chemotherapeutic agent is unequivocally the drug of choice, a short-acting oral sulfonamide, such as sulfisoxazole (Gantrisin<sup>®</sup>) is preferred by many authorities. When taken with proper precautions, short-acting sulfonamides have few side effects, are inexpensive, and high concentrations are achieved in the urine. Equally effective



alternative oral chemotherapeutic agents are ampicillin, amoxicillin, nitrofurantoin, tetracycline, and trimethoprim-sulfamethoxazole (Santoro and Kaye, 1978).

Disappearance of bacteriuria is closely correlated with the sensitivity of the microorganism to the concentration of the antimicrobial agent achieved in the urine (McCabe and Jackson, 1965; Stamey et al, 1974; Klastersky et al, 1974). In fact, in the presence of normal renal function, most of the urinary antimicrobial agents provide an excess of antibacterial activity in urine by a factor of ten or more. Moreover, there is little information that chemotherapeutics that are considered primarily bactericidal in vitro perform better than those that merely are inhibitory.

The cure rate will vary, depending on the type of patient and the infecting organism. Failure of therapy is more likely to occur in the presence of urological abnormalities, such as stones, renal parenchymal involvement (in contrast to only lower tract involvement), poor patient cooperation in taking the drug, and antibiotic resistance of the infecting organism.

The site of infection in the urinary tract has been shown in a number of studies to be an important determinant of the outcome of therapy. Symptoms and signs, radiographic findings, antibody studies and renal function studies are all inadequate to predict the site of infection in the majority of females with bacteriuria. Most of these methods are not clinically applicable because they are cumbersome, are not sensitive, or are not specific. Although no

single test completely meets all the requirements as a clinically useful means of localizing urinary tract infections, the detection of antibody coated bacteria in the urine sediment (ACB test) is now a feasible in vitro non-invasive test. Organisms that originate in renal tissue are coated with immunoglobulins, whereas organisms that have multiplied in the bladder do not have antibody on their surface. Since 1974 this test has been useful for a number of therapeutic studies of urinary infection but it requires further standardization and clinical trials before it can be made available as a routine test for localization of infection (Ronald, 1979).

The optimal duration of therapy for patients with infection confined to the bladder is unknown. The usual recommended course of therapy consists of three or four daily doses of a given antimicrobial agent for periods of seven to 14 days. A number of studies (Gruneberg and Brumfitt, 1967; Ronald et al, 1976; Fang et al, 1978; and Bailey and Abbott, 1978) have suggested that single dose treatment is suitable for acute lower urinary tract infections in individuals with no renal abnormalities.

Single dose therapy decreases the possibility of drug toxicity, reduces the selective pressure on the normal GI flora and is inexpensive. Also, a patient cured with single dose therapy usually does not require further investigation. General adoption of this treatment regimen depends on further evidence and the approval of the Health Protection Branch.

The objectives of this study were as follows:

- (1) to delineate a possible therapeutic role for a low single oral dose for therapy of acute cystitis,
- (2) to compare the efficacy of a bacteriostatic short-acting sulfonamide, sulfisoxazole (SSX) with a bactericidal, longer acting combination of trimethoprim-sulfamethoxazole (TMP-SMX),
- (3) to study the relationship between ACB positivity and response to treatment, and
- (4) to study the relationship between urine inhibitory and bactericidal titers with microbiologic response and clinical success.

## II. L I T E R A T U R E   R E V I E W

## EPIDEMIOLOGY

(a) Uncomplicated Urinary Infection

Infections of the urinary tract are among the most frequent of all infections, especially in women (Kass, 1956).

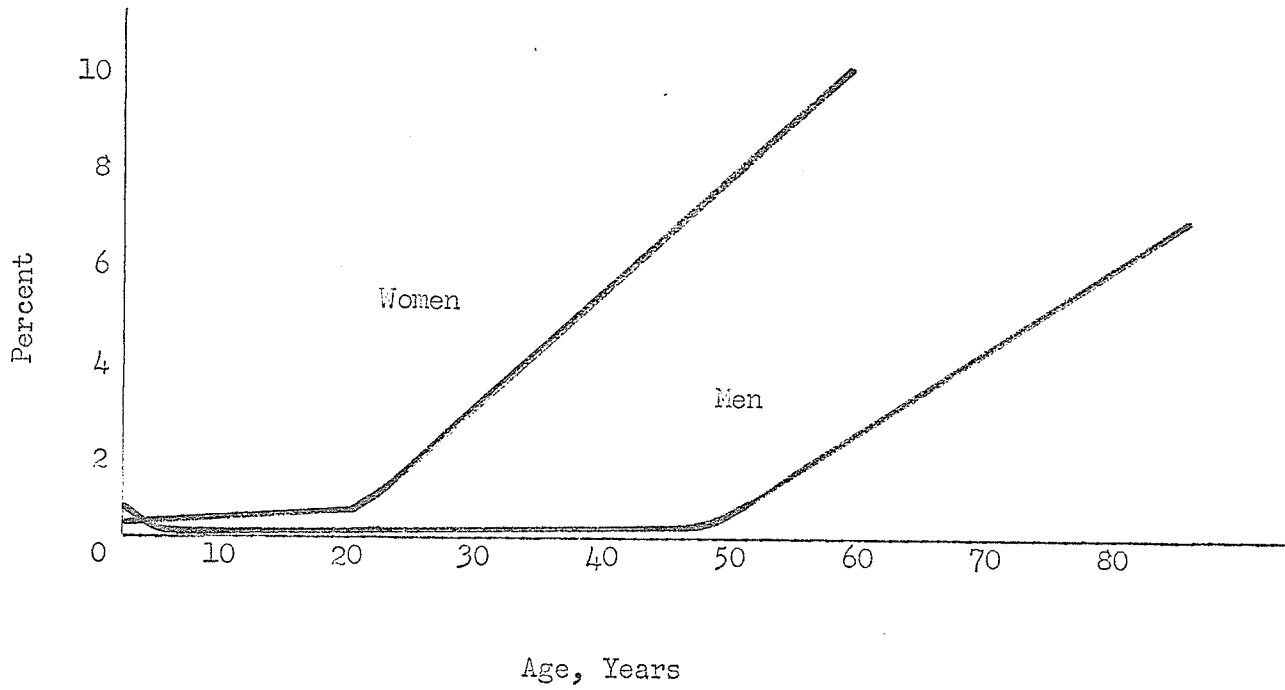
Urinary tract infections are of importance in themselves as a troublesome cause of discomfort and sometimes of ill-health (Waters, 1969).

The problem of urinary tract infection spans all age groups beginning with neonates, as found by Fass and co-workers (1973) (Figure 1). Routine suprapubic puncture in over 1,000 infants showed the prevalence of bacteriuria to be about 1% and it was more common in boys (Shannon, 1970). During the preschool years, urinary tract infection is more common in girls than in boys. Much information on the natural history and epidemiology of urinary tract infection comes from Kunin's studies on school children in Central Virginia. He found that the prevalence of bacteriuria in school-age and adolescent girls was consistently between 1 and 2% (Kunin, 1970, 1972). Bacteriuria was rare in school-boys (prevalence 0.03%).

Once adulthood is reached the prevalence of bacteriuria increases in the female but not the male population. The prevalence of bacteriuria in young, non-pregnant women is about 1 to 3%; after marriage it increases to about 4 to 6% and then rises to about 10 to 15% in elderly women (Kunin, 1974).

In house-to-house population surveys in Wales and Jamaica,

Figure 1.



Prevalence of Bacteriuria According to Age  
and Sex (Fass *et al.*, 1973)

about 2% of adult women were found to be bacteriuric in the 15 to 24 year old age group, increasing 1 to 2% per decade to a prevalence rate of 10% in the 55 to 64 year decade (Kass et al, 1965). It was also reported that 0.5% of 1,515 males had bacteriuria. In a survey of 1,037 young women, there were 1.3% with urinary tract infection, as compared with only one out of 1,735 males (Teles and Rocha, 1969). Freedman and co-workers (1965) in a general practice found an overall prevalence of bacteriuria of 1 to 3% in young and middle-aged women. Bacteriuria was not observed in males until ages 50 to 59.

In Great Britain, Fry et al, (1962) and Waters (1969) showed that the proportion of women who sought medical attention was significantly higher in the younger age group (up to 30 or 35 years) and also acute cystitis was significantly more common in the married than in the single women. Mond and co-workers (1965) found in a single-handed general practice in Britain, that urinary tract infections were four times as common in married women as in single. Interestingly, Kunin and McCormack (1968) reported that the frequency of bacteriuria in nuns is strikingly less (0.4 to 1.6% in the four decades 15 to 54 years), clearly suggesting that child-bearing or sexual intercourse or both, play a significant role in urinary infections. Steensberg (1969) and his colleagues in Denmark, found the prevalence of urinary tract infections in females (20 patients per 1,000 per year) to correspond fairly well with British results, though the latter showed lower frequencies in elderly women than those found in his study.

It has been estimated that about 10 to 20% of the female population will experience a urinary tract infection sometime during their lifetime (Kass et al, 1965; Sanford, 1975). The age variations in the prevalence of urinary tract infection in women indicate that it is a question of fundamentally different entities in younger women of child-bearing age and in elderly women after the menopause. The frequent acute infections in young women are, most likely, correlated with sexual activity, pregnancies, and deliveries. From a minimum at about the time of the menopause, the prevalence rises steadily with age, a result which might depend on the increasing frequency of degenerative and obstructing disorders of the urinary tract (Kunin, 1974).

Morbidity data collected in general practices will never provide a complete picture of the morbidity of the population. On the other hand, general practice studies provide a suitable outline of the disease entities.

(b) Acute Urethral Syndrome

The epidemiologic dynamics of urinary tract infections in adult women is complex as prevalence rates alone do not reveal the true extent of the overall risk of infection in a population. It has long been recognized that many patients seen with complaints of frequency and dysuria have "negative" urine cultures (Sanford, 1975). In the now classical study, Gallagher et al, (1965) studied a group of patients seen in the offices of eight physicians in Auckland, New...



Zealand. During eight months, 130 patients were studied. Only 77 (59%) of the 130 patients had infected urine. The striking finding was "insignificant" bacteriuria ( $<10,000$  organisms/ml) in 53 persons (41%). Of greater importance was the demonstration that 41 of the 53 individuals (32%) had sterile urine cultures. These patients were regarded as having the "urethral syndrome". Subsequently, O'Grady and associates have suggested the term "symptomatic abacteriuria" (O'Grady et al, 1973). Gallagher et al (1965) recorded the presenting symptoms and showed only minor differences between the infected and uninfected (acute urethral syndrome) patients. Loin pain and costovertebral tenderness occurred with comparable frequency in both groups. Thus, distinction between bacteriuria infections and the acute urethral syndrome cannot be solely on clinical characteristics. Bacteriological confirmation of infection is important. These overall observations have been confirmed in subsequent studies; Mond et al (1965) found that 45 of 83 women with symptoms suggestive of urinary tract infection were non-infected; Steensberg et al (1969) found that 23% of the women with symptoms of urinary tract infection did not have bacteriuria; Fairley et al (1971) found that 23 of 66 (35%) women presenting to general practitioners with symptoms of acute urinary tract infection had  $\leq 10,000$  bacteria/ml of urine. In the group of 45 patients studied by Mond, 47% had an excess of white cells in urine and in the groups of 23 patients studied by Fairley, nine had pyuria ( $>2,000$  WBC/ $\text{mm}^3$  of urine) (39%) and five had gross pyuria ( $>15,000$  WBC/ $\text{mm}^3$  of urine). O'Grady et al (1973) have shown that

patients with frequency and dysuria in the absence of bacteriuria fall into two groups: those who were symptomatic and always abacteriuric, and those who were symptomatic but sometimes bacteriuric. Urinary leukocyte excretion also fell into two patterns: patients who never had pyuria or had  $< 20 \text{ WBC/mm}^3$  and those who had higher levels of pyuria.

(c) Acute Cystitis with Spontaneous Remission

It appears that symptoms of uncomplicated urinary tract infection in women without specific antibacterial treatment show a tendency towards spontaneous remission within 48 hours (Kunin, 1974). Kass et al (1965), working in Jamaica and Wales, found, on re-examination of women with asymptomatic bacteriuria detected in population surveys, that each year, in about one-fourth of the adult female population, the infection clears spontaneously. Asscher et al (1969), in a one-year follow-up of 45 women with asymptomatic bacteriuria, found that one-third of the women developed acute symptoms, one-third lost their infection spontaneously without treatment, and one-third remained infected and became asymptomatic at the end of 12 months. Similar results have been reported by Freedman et al (1965). Mabeck (1972), working in Denmark, did a double-blind therapeutic trial of acute symptomatic urinary tract infection of women and showed that about 80% of women treated with placebo produced sterile urine spontaneously within five months. About one-half of these had recurrent infection within a year.

These reports are important, not only for our understanding the epidemiology and dynamics of urinary infection, but also because they have obvious significance, particularly for trials of new therapeutic agents (Kunin, 1974).

## ETIOLOGY

(a) Bacterial Urinary Infection

In most medical practices, bacterial urinary infection is responsible for the symptoms of dysuria, frequency, suprapubic pain in the majority of women. Almost 90% are due to the Gram-negative aerobic bacilli found in the gut, and only 10% are due to Gram-positive cocci. About 5% of urinary infections are mixed, i.e. two urinary pathogens are present together (Ronald, 1978). The Enterobacteriaceae family contains the most common organisms found in uncomplicated infections with the exception of Pseudomonas species.

Close to 80% of acute urinary tract infections, independent of age and sex, are caused by a single bacterium, Escherichia coli. In many instances, the infection has been shown by serologic typing to be autogenous, that is, to originate from the patient's own gut flora, vaginal or urethral mucous membranes (Mond et al, 1965; McGeachie, 1966; Grunenburg et al, 1968; Schwarz et al, 1969; Turck et al, 1969; Steensberg et al, 1969; O'Grady et al, 1970; O'Keefe et al, 1973). E. coli contains three major antigens that can be used to further characterize the organism. The most researched antigen is the O or somatic cell wall antigen. It is the lipopolysaccharide component of the organism and contains the endotoxic activity. Over 150 serotypes have been described. The K or capsular antigen and the H or flagella antigen are both proteins; there are over 100 serotypes of K antigen and over 50 of H antigen. Other organisms of the