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Current Trends in Urinary Tract Infections: Is Cipro Really Necessary?

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Abstract

Urinary tract infections are one of the most common causes of ambulatory care visits, physician-office visits and hospitalization each year in the US. Sexual activity primarily contributes to acquisition of UTI in women; nearly half of adult women have had a UTI at least once. The most common causative agent is *E. coli*, followed by *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa, Proteus mirabilis*, other Gram-negative rods and Group B streptococci, depending on geographical location. Until the late 1990's, trimethoprim-sulfamethoxazole (TMP-SMX) was the most commonly prescribed and effective treatment option, but the rampant development of resistance to this drug has caused the IDSA to mandate a switch to Cipro as the first-line empiric treatment. This study was designed to compare Cipro's efficacy to that of TMP-SMX and nitrofurantoin, comparing two samples in the greater Chattanooga area. The samples were used to study the relationship between various factors, such as age, sex, previous UTI, previous antimicrobial treatment, sexual activity and chronic illness, and UTI incidence and resistance. Total resistance to TMP-SMX was 17%, to nitrofurantoin, 20%, and to Cipro, 8%. UTI incidence occurred in the order: *Escherichia coli> Klebsiella pneumoniae> Pseudomonas aeruginosa> Proteus mirabilis> Enterobacter* spp, *Citrobacter* spp., and other Gram negative bacilli. Age was not found to be related to antimicrobial resistance in women, but may link to resistance in men. Sexual activity and menopause may be related to UTI incidence in both samples, while previous UTI, previous antimicrobial treatment and chronic illness may correlate with resistance. The Collegedale sample was too small to substantiate results. A study over a longer time period is needed to confirm these preliminary findings.

Introduction:

Urinary tract infections (UTI) account for approximately 4 million ambulatory-care visits, 8 million physician-office visits, and 100,000 hospitalizations annually in the United States (CDC, 2000; O'Donnell et al., 2002). Sexually active women are at highest risk for the disease; about 40% to 50% of adult women report that they have had a UTI at least once in their life (Hooten, 1997). Conditions commonly associated with complicated urinary tract infections include kidney stones, urethral or prostatic obstructions, urethral stents, circumcision, micturation disorders, bowel disorders, immunosuppressive therapy, diabetes, pregnancy, age and sex (Gupta et al., 1999; Mangiarotti et al., 2000; O'Donnell et al., 2002). Symptoms range from painful urination and minor discomfort to abdominal and/or back pain, fever, decreased kidney function or

sepsis, which can become fatal in immunocompromised individuals (CDC, 2000). Infections may be minor (urethritis, cystitis, prostatitis), or "uncomplicated" infections of the lower urinary tract, or develop into more serious forms of disease, which may become systemic. Acute cystitis (bladder infection) and acute pyelonephritis (infection of the renal pelvis) are the most significant in terms of morbidity (Price and Wilson, 1997).

Transmission usually occurs through fecal contamination of the urinary tract. *E. coli,* a normal inhabitant of the colon, is the most common causative agent in UTI, accounting for approximately 80% of reported cases (Price and Wilson 1997; Mangiarotti et al., 2000; Bukharie and Saeed, 2001). Other organisms commonly associated with UTI include *Klebsiella* spp., *Staphylococcus saprophyticus, Proteus* spp., *Enterobacter* spp., *Citrobacter* spp., *Enterococcus* spp., *Candida* spp., and *Staphylococcus aureus* (Gupta et al., 1999; Talan et al., 2000; Bukharie and Saeed, 2001). Rare cases of UTI have also been associated with the genera *Hafnia, Serratia, Providencia, Morganella, Pseudomonas, Xanthomonas*, and *Alcaligenes*, several of which exhibit alarming resistance to antimicrobial treatment (Thomson et al., 1994).

Etiologic agents responsible for UTI seem to vary by location both in occurrence and prevalence. Mathai et al. (2001) collected thirty-two UTI pathogens from 1,510 patients in 31 locations in the United States to determine national incidence rates in 1997 and 1998. The species and rank order of specific agents identified during the study were slightly different than that obtained in a similar study by Bukharie and Saeed (2001) in Saudi Arabia, and Table 1 compares the results of both.

Most UTI cases may be cured with outpatient oral antimicrobial therapy. Until recently, ampicillin, amoxicillin, tetracycline, amikacin, and trimethoprim-

sulfamethoxazole were the most common therapeutic agents prescribed for both uncomplicated and complicated UTI infections (Gupta et al. 1999; Bukharie and Saeed, 2001). However, though studies reiterate the geographic variation in incidence of causative agents, one fact has become increasingly clear. Antimicrobial resistance in UTI pathogens is dramatically increasing. In the same study by Mathai et al. (2001) co-resistance was elevated, though pathogen incidence did not change, for aminoglycosides, tetracyclines, sulfonamides, and fluoroquinolones. Bukharie et al., (2001) documented resistance for all isolates combined of more than 50% for ampicillin and tetracycline, and *E. coli* resistance of 39% for trimethoprim-sulfamethoxazole (TMP-SMX). In another study conducted over a four-year period, resistance to trimethoprim and TMP-SMX rose from 9% to 18% in *E. coli* and from 8% to 16% in all isolates combined (Gupta et al., 1999). But even resistance varies geographically. In a recent study of acute uncomplicated pyelonephritis in women, 32% of isolates from Western states were resistant to TMP-SMX, compared to 14% of Midwestern isolates and 7% of Eastern isolates (Talan et al., 2000).

The above data have led to the general feeling that trimethoprim and TMP-SMX are no longer acceptable choices for empirical therapy of UTI (Gupta et al., 1999). Ampicillin is no longer used since at least 30% of causative *E. coli* strains are ampicillin-resistant (Talan et al., 2000).

Due to this increased resistance to common antimicrobial treatments, a turn has been made from the prescription of these commonly empiric antimicrobial treatments, to a more potent cure. Enter the fluoroquinolones, whose low resistance rates have made them the operative therapeutic agents in UTI treatment. Fluoroquinolones are successful

agents against Gram-negative bacilli, and their usage as antimicrobial agents has exploded, since their introduction in the 1980's. The most popular drug in this class, ciprofloxacin (Cipro), is the second most common antimicrobial prescribed in Spain and the fourth in the US (Ena et al., 1998). Its popularity stems primarily from its high success rates. In the aforementioned study by Talan et al. (2000), 47 of 255 uropathogens were resistant to TMP-SMX while only one strain was resistant to Cipro, and none of the *E. coli* isolates exhibited Cipro resistance. Gupta et al. (1999) reported prevalence of resistance to Cipro of 0% to 2% in *E. coli* and less than 10% among all isolates combined.

In the last year Infectious Disease Society of America (IDSA) mandates have recommended that the older fluoroquinolones—norfloxacin, ciprofloxacin and ofloxacin—become the standard empiric agent for UTI. But they are not without their faults. Fluoroquinolones in general are much more expensive than TMP-SMX, costing three to five dollars more per day (Talan et al., 2000; Bukharie and Saeed, 2001; O'Donnell et al., 2002). Furthermore, many in the scientific community are concerned that use of fluoroquinolones as first-line therapeutic agents is contributing to the development of resistance to this valuable class of antimicrobials. In a study in Spain, where fluoroquinolones are used as first-line antimicrobials for community-acquired UTI, Ena et al. (1998) attributed ciprofloxacin-resistance in UTI *E. coli* isolates to prior treatment with fluoroquinolones. In that country, from 1990 to 1996 prescriptions for Cipro increased from 1392 grams to 3203 grams per year and *E. coli* resistance increased from 3% to 20%. In previous studies, there were significant increases in both in ciprofloxacin-resistant *E. coli* isolated from urine samples, and from bloodstream

infections, which were attributed to regions with greater consumption of fluoroquinolones (Pena et al. 1995). O'Donnell et al. (2002), citing previous studies by Kresken et al. (1994) and Thompson et al. (1994), claim that there has been a progressive decrease in fluoroquinolone activity against clinical isolates in Europe. In the past 10 years in the US, increasing numbers of reports of strains of *E. coli, Klebsiella* spp., and *Enterobacter* spp., with MIC's at or above the susceptibility breakpoints for the fluoroquinolones have caused increasing concern over their continued potency. In addition to the threat of resistance, ciprofloxacin, the most popular of the fluoroquinolones, causes drowsiness, increases theophylline levels, and is contraindicated for pregnant women. Ingestion of divalent and trivalent cations must be avoided during therapy.

There is an alternative to TMP-SMX and Cipro in nitrofurantoin, a urinary-specific treatment with high bacterial efficacy against many enteric gram-negative rods, except *Pseudomonas aeruginosa* and *Proteus* species (Gupta et al., 1999; O'Donnell et al., 2002). A UK study also found this antibacterial drug particularly effective against staphylococci and enterococci, species completely impervious to Cipro (Spencer et al., 1994; Gupta et al., 1999; Bukharie and Saeed, 2001). Nitrofurantoin was originally introduced in 1968 and has been used as an antibacterial agent for over 35 years, with very low resistance development in target pathogens (Pelletier et al., 1992). In addition, nitrofurantoin is not as costly as Cipro. However, it must be taken 4 times daily (100 mg) for a 7-day time period as compared to Cipro's bi-daily (250mg) dose for three days. This difference raises issues of patient compliance and convenience (Gupta et al., 1999; O'Donnell et al., 2002). However, nitrofurantoin monohydrate/macrocrystals is a

relatively new formulation and may be taken twice daily, thereby addressing possible compliance problems (Spencer et al., 1994).

Nitrofurantoin is not without its side effects. With long term use, it is a documented cause of pulmonary fibrosis and may cause intrahepatic cholestasis and hepatitis, and should be avoided in patients with creatinine clearance of less than 60 mL/min (O'Donnell et al., 2002). But in clinical trials patients appear to experience less discomfort or adverse events with nitrofurantoin than trimethoprim or its derivatives (Spencer et al., 1994).

Through overuse and misuse, resistance has emerged rapidly in some centers, necessitating, at the very least, a revision of current prescribing practices. Many physicians hold that to preserve their value as strong antimicrobial agents, fluoroquinolones should not be used as an empiric therapy for UTI. Many more are of the opinion that Cipro is altogether unnecessary, that nitrofurantoin and TMP SMX are usually effective, and since cases are followed by bacterial analysis and culture to identify the infecting organism and its antimicrobial susceptibility, patients with resistant organisms may be identified and their prescriptions changed to a more powerful drug as needed.

The purpose of this study was to evaluate the efficacy of TMP-SMX, ciprofloxacin and nitrofurantoin on etiologic agents of urinary tract infections in the greater Chattanooga, Tennessee area. For comparison, cefazolin (a cephalosporin) and ampicillin (penicillin-derivative) resistance rates were also compared as representatives of the other major drug families. We also attempted to correlate resistance data to various parameters of the patient and infection, such as gender, age, previous UTI infection,

sexual activity, etc. It was hoped that a rubric could be created which would allow physicians to determine treatment success using various antimicrobials.

Materials and Methods:

Population

The population for this study consisted of patients with community-acquired urinary tract infections, during February and March 2002, visiting various medical clinics in Hamilton and Bradley Counties, surrounding Chattanooga, Tennessee. A specific group of samples was obtained from Collegedale Medical Center, along with patient histories that might be used to study trends in uropathogen resistance patterns.

Sample Collection

At the Collegedale clinic, patients were advised on proper procedure to obtain a "clean catch" urine sample, and patients then collected urine into a sterile cup. The office lab technician then examined the samples under a microscope to confirm infection. Samples were refrigerated for up to four hours prior to transport to Memorial Microbiological Labs at Memorial Hospital in Chattanooga, for identification of etiologic agent and antimicrobial profiling.

Bacterial Culture and Identification

Upon arrival at the lab, specimens were subjected to urinalysis in IRIS (International Remote Imaging System, Chatsworth, GA), to confirm infection and rule out cross-contamination by improper sample collection. IRIS is a digital microscope that

shows images of bacteria, WBC's, pH, fungi and other contaminants of urine. Cross-contamination was usually indicated by Gram-positive cocci or diptheroids in the urine. Infection was confirmed by a leukocyte count greater than five WBC/cc.

After urinalysis, samples suspected of infection were plated on both blood agar and MacConkey media and incubated for 18 hours at 37 degrees Celsius. Since it is an enriched medium, blood agar encourages the growth of a wide variety of possible bacterial pathogens whereas MacConkey media selects for Gram-negative bacteria, the most common agents of UTI infection.

Colony growth was examined after 18 hours of incubation. UTI was confirmed by a colony count greater than 10,000 colonies/mL. The most common causative agent of UTI, *E. coli*, is Gram-negative and therefore grows on both media types. In presumptive identification, a suspected *E. coli* colony on the MacConkey plates was tested for indole production using Endol reagent (Remel, Lenexa, KS). All suspected *E. coli* colonies were confirmed with the Bacticard Test (Remel) for indole (IND: p-Dimethylaminobenzaldehyde) and MUG (4-methylumbelliferyl-β-D-glucuronide), which both yield positive results with *E. coli* by fluorescence under UV light. *Pseudomonas* also grows on both plates, so to confirm infection suspected colonies were tested for oxidase production (DIFCO, Grayson, GA). Streptococcal colonies appear only on the blood agar plate because they are Gram-positive. Suspected streptococci were strain typed by the Meritec Card Agglutination Test (Meridian Diagnostics, Cincinnatti, OH), because Group-B infections can cause miscarriages, and must be treated with immediacy and accuracy.

Antimicrobial Susceptibility

After diptheroid and yeast contamination or infection were ruled out by plate examination, suspensions of the suspected pathogens were prepared from colonies on the initial isolation plates, adjusted for proper turbidity (50 μλ for Gram-negative growth and 200 μλ for Gram positive), and then loaded into individual cards for bacterial identification and antimicrobial susceptibility testing using the VITEK automated microbiology system (BioMerieux, Inc., Hazelwood, MO). The VITEK read each individual card, identifying etiologic agents and antimicrobial profiles, which the computer then printed out for each patient.

Survey Instrument

Patient history data was obtained for samples collected in Collegedale, in an attempt to examine the correlation between various UTI patient parameters and bacterial resistance. Patient histories were compiled with regard to age, sex, sexual activity, previous UTI and antimicrobial treatment, previous pelvic surgery, chronic illness and recent (within six months) antimicrobial treatment for each of the samples collected from patients visiting that clinic.

Results

A total of 108 samples were obtained from medical clinics in Hamilton and Bradley Counties, and microbial screening and antimicrobial susceptibility testing were performed according to the above-mentioned procedures at Memorial Hospital Labs. In

our study, eleven different etiologic agents were identified, the most common of which were *Escherichia coli* (54.6%), *Klebsiella pneumoniae* (13.9%), *Pseudomonas aeruginosa* (5.6%), and *Proteus mirabilis* (3.7%). Table 2 shows the percent composition of the most common isolates, comparing the data from the greater Chattanooga area to the smaller Collegedale sample. Other causative uropathogens included *Citrobacter* spp, *Enterobacter* spp, *Klebsiella oxytoca, Providencia rettgerii,* and *Morganella morganii*, each of which was responsible for less than 2% of the collected samples.

Of the 108 isolates, 80 (74%) were from women. The mean age of the women in the sample was 52.4 years with a standard deviation of 27.8 years. Incidence was highest for women between the ages of 70 and 89, with almost 40% (31) of the 80 isolates coming from this age range. There were 28 men (26%) in the sample. The mean age for men was 66.3 years with a standard deviation of 16.0 years. Incidence was highest in men in the 80-89 age group, with 29% (8) of the 28 isolates occurring in men in this age category. Approximately 7.4% of the UTI isolates obtained were from children under age 10. Figure 1 illustrates the difference in UTI incidence between men and women, and between different age groups.

Resistance was determined for each of the top four bacterial agents against five selected antimicrobials: ampicillin, cefazolin, ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole (Table 3). One hundred percent of the *K. pneumoniae* isolates were resistant to ampicillin, and 100% of the *P. mirabilis* were resistant to nitrofurantoin. One hundred percent of the *P. aeruginosa* isolates were resistant to all antimicrobial agents except Cipro. Together, these three bacterial species comprised 23% of the total sample. Two of the *E. coli* isolates (1.7%) were resistant to Cipro and

none showed resistance to nitrofurantoin, but 10.3% were resistant to TMP-SMX. These rates were compared to those calculated for the same geographical region by Sharp in 2000 (Table 4). Overall, the efficacy of ampicillin and cefazolin rose by 4.2% and 2.3%, respectively, for *E. coli*. *P. mirabilis* showed no resistance to these drugs in 2002, whereas in 2000, this bacterium exhibited a 9% ampicillin and 3% cefazolin resistance rate. Nitrofurantoin was virtually ineffective on *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis* in both studies, while resistance to TMP-SMX increased more than two-fold in *K. pneumoniae* and *P. mirabilis*, but did not change significantly for *E. coli* and *P. aeruginosa*. Resistance to Cipro decreased by 0.3% for *E. coli* and by 2% for *K. pneumoniae*, but increased by 17% for *P. aeruginosa* and by 14% for *P. mirabilis*.

In addition to calculating separate resistance rates for the most common bacteria, total resistance, regardless of infectious agent, for each of the five antimicrobials was also determined (Table 5). Resistance to ampicillin was 50%, to nitrofurantoin 20% and to TMP-SMX 17%. Resistance to Cipro was the lowest, at 8%. Eleven isolates were obtained from children under eleven years of age; four were multi-resistant organisms and one of these was susceptible only to Cipro.

Resistance data was also correlated, irrespective of etiologic agent, to gender (females—Table 6, Figure 2; males—Table 7, Figure 3) according to age. The mean resistance rate in females was calculated at 27.4% (Table 6). Ampicillin resistance was high in all groups (Table 6), peaking in the 20-29 age group (89%) and 60-69 (75%)age group (Figure 2). TMP-SMX resistance was present in all but the 50-59 and 90-99 age groups, peaking at 25% in the 60-69 year-olds. Cipro was the only antimicrobial whose resistance remained below 20% in all categories, but even this agent incurred 17%

resistance in the 40-49 year-olds. Nitrofurantoin resistance was present in all but the 30-39 and 50-59 year-olds and reaches or exceeds 20% in half the categories, peaking at 27%, in the 70-79 age group (Figure 2).

In the males, mean resistance was calculated at 42.4% (Table 7). No resistance was observed in the 20-29 or 30-39 age groups, and only ampicillin resistance was present in the 40-49 age group (Table 7). Ampicillin resistance was 100% in 60-69 year-olds, and remained high in all over-50 patients. No Cipro, cefazolin or nitrofurantoin resistance was present in any patient under 60 year of age. TMP-SMX resistance appeared in the 50-59 age group and steadily increased to its peak (38%) in patients between 80 and 89 years of age (Figure 3). Resistance to all five antimicrobials was observed in the last three age groups (60-69, 70-79 and 80-89), commonly reaching 30-40%, 10% higher than the mean resistance rate in women (Figure 2). Isolates from the 60-69 age category exhibited the second highest resistance rates; 50% were resistant to nitrofurantoin. Again, Cipro resistance was the lowest over all, but its lowest value, in the 70-79 age group, was still 14%.

The Collegedale Medical Center yielded a very small sample size. 32 UTI patients were identified during the study and of these, 15 were excluded due to contamination or lack of growth. Of the 17 remaining samples, 13 were from women and four were from men. The mean age of the women was 52.7 years with a standard deviation of 18.4 years, and the mean age for men was 64.5 years with a standard deviation of 15.9 years. Figure 4 illustrates the difference in UTI incidence between men and women and between age groups from the Collegedale sample.

Eleven (65%) in the sample were sexually active, eleven (65%) had been diagnosed with a previous UTI, six (35%) had undergone pelvic surgery at some point prior to infection, four (24%) were classified as "chronically ill" and ten (59%) had taken an antimicrobial in the last six months. All the antimicrobials taken by these ten patients were either ampicillin or quinolone derivatives.

Nine (53%) of the 17 Collegedale samples showed resistance, but only to nitrofurantoin (29%) and ampicillin (41%), with one exception in the single *Pseudomonas aeruginosa* isolate in the sample, which was only susceptible to Cipro. Of the nine resistant isolates, 77% had had a previous UTI, and 67% had received antibiotic therapy in the last six months.

As with the Chattanooga sample, resistance rates for the top four uropathogens were calculated for each of the five selected antimicrobials (Table 8). All *P. aeruginosa* isolates were resistant to every antimicrobial drug except Cipro. *P. mirabilis* was resistant only to nitrofurantoin (100%) and *K. pneumoniae* to ampicillin (100%) and nitrofurantoin (67%). These isolates amounted to five of the 17 samples. *E. coli* was only resistant to ampicillin (33%) and no pathogens were resistant to Cipro.

The Collegedale sample was also divided by sex, for comparison of UTI incidence between sexes and according to age groups (Figure 4). Only four of the 17 isolates were from men, and each one was from a different age group. Incidence was highest in women between the ages of 40 and 59, with half (8) of the 17 isolates falling into this age range.

Discussion

The Chattanooga and Collegedale samples were similar in composition, yielding *E. coli, K. pneumoniae, P. aeruginosa* and *P. mirabilis* as the top four causative agents (Table 2). However, the very small sample size of the Collegedale group makes comparison difficult. Similar to the previous year's studies by Mathai et al. (2001) and Bukharie and Saeed (2001), *E. coli* was the most common etiologic agent in both of our samples, while the order and incidence of other common uropathogens seems to vary from study to study (Tables 1 and 2).

The Chattanooga sample was primarily used to relate sex and age to UTI incidence as well as to antibiotic resistance. Examination reveals definite differences not only in incidence between the sexes, but between age groups within the sexes (Figure 1). Women are much more susceptible to urinary tract infection because of a much shorter urethra, which enables bacteria to invade and infect more easily. As would be expected, the sample of women with UTI is more than twice that of the male sample. It is interesting to examine the UTI incidence in children in our study. Urinary tract infections typically occur in as many as 5% of female and 1% to 2% of male children (Porth, 1998). Our sample yielded only female children, but incidence in this age group was quite high, at 7.4%. The increase in UTI incidence in women in their twenties can be attributed to sexual activity, as studies mentioned previously and the results from the Collegedale clinic (65% were sexually active) have substantiated. Women in their thirties and forties are typically married, have fewer sexual partners, or are simply more responsible about gynecologic hygiene, which may explain the lower UTI incidence in these groups. But it must be noted that from the forties on, our study shows a steady

increase of UTI in both males and females (Figure 1). This may be attributed to menopause, during which time the vaginal area becomes less acidic, and thus more susceptible to bacterial infection. Fewer UTI's occur in men due to the longer urethra and more difficult access to the urinary tract, reducing the chance of infection. In both men and women, UTI incidence steadily increased with age (Figure 1). More study is needed to determine the factors responsible for this trend.

At first glance, the antimicrobial resistance to the five selected therapeutic agents in this study exhibits several differences from that obtained by Sharp (2000) for the Chattanooga area. Initially, rates appear to be higher in 2002 than they were two years ago (Tables 3 and 4). *K. pneumoniae, P. aeruginosa* and *P. mirabilis* exhibit alarmingly high resistance (100 %) to all antimicrobials but Cipro. Fortunately, these bacteria comprise only 23% of uropathogens in this study, but these are still disturbing results. *E. coli* is sufficiently susceptible to Cipro and nitrofurantoin, but shows higher resistance to TMP-SMX, a trend that has caused the IDSA to switch to Cipro as the first-line empiric agent in UTI treatment. Ampicillin's and Cefazolin's efficacy seems to have improved for *E. coli* and *P. mirabilis*, while that of TMP-SMX has decreased, in some cases by more than 14 percent. Nitrofurantoin appears to have lost its effectiveness in both studies (only *E. coli* is susceptible), but resistance to Cipro was zero in both studies, except in *Pseudomonas*. However, once the sample size is taken into account, the results do not appear to be significantly different. The data compiled in the 2000 study comprised all of the resistance data for all of the bacterial isolates obtained in the Chattanooga area in 2000, which included, but were not limited to, urinary tract infections. Our study looked only at UTI's occurring during February and March of 2002. Despite this difference in

sample type, the resistance rates in these two studies are comparable. The difference between the efficacy of Cipro and the other antimicrobials is noteworthy. In both studies, Cipro was undoubtedly the more powerful antimicrobial agent, especially against *Pseudomonas*, which is virtually impervious to anything else.

Part of our purpose in this study was to create a rubric, if possible, for local physicians to estimate a given drug's success, regardless of the infectious agent. Calculations revealed that irrespective of gender, age group and other factors, there was considerably less resistance to Cipro (8%) than the other therapeutic agents. Even resistance to nitrofurantoin (20%) is disappointing and ampicillin (50%) is virtually useless (Table 5).

The analysis of resistance patterns with regard to the age group of the patient in the Chattanooga sample of women (Table 6, Figure 2) yielded a mean resistance rate of approximately 27.4%, which is higher than a desirable value for effective antimicrobial treatment. Age does appear to be a factor in UTI incidence, but does not seem to affect the development of resistance in women. All the antimicrobials experience varying degrees of resistance in all age groups, but Cipro is generally more powerful against the common uropathogens.

The mean resistance rate in men with UTI's was 42.4%, which is considerably higher (approx. 15%) than that of women. Unlike women, only bacteria from older men exhibit resistance. Age does appear to be a factor in resistance development, as exhibited by the lack thereof in the younger age groups. This might be attributed to a lower anti-infective drug exposure. Young men are typically healthy, and require antibiotic treatment only very rarely, therefore they are less likely to acquire or develop resistant

bacteria. But herein lies an anomaly. In theory, younger women ought to need less antibiotic treatment than older women as well. However, the sample size was too small (28) to draw any firm conclusions.

Generally, resistance seems to be more prevalent in older patients, which might be expected, since the older a patient is, the more he/she has been exposed to antimicrobial agents, and the more chance he/she has had to develop resistance. But the Chattanooga sample presented another alarming anomaly. Of the eleven isolates obtained from children under 11 years of age, four were resistant organisms, and one of those was susceptible only to Cipro. Since the samples were obtained from outpatient facilities or physician offices, it is safe to assume these are not critically ill children with nosocomial infections. However, without patient history, it is impossible to delineate the avenues through which these children have already acquired such alarmingly resistant organisms. Still, the spread of resistance in such young patients is a warning sign of the widespread resistance and the continual danger that commonly prescribed antimicrobials will soon be rendered insignificant.

The Collegedale sample seemed to have a lower incidence of resistant organisms. Isolates were resistant only to nitrofurantoin and ampicillin, except the single *P. aeruginosa* isolate, which was susceptible only to Cipro. Due to the small sample size, however, this conclusion is misleading. A larger study must be done to confirm the elevated uropathogen susceptibility in this area.

The difference between UTI incidence in males and females and within certain age groups also slightly varied between the Collegedale and Chattanooga samples (Figures 1 and 4). Only four (24%) of the 17 isolates were from men, and each one was

from a different age group, thus, no firm conclusions may be drawn from this group. In Collegedale, the women with the highest UTI incidence were those between the ages of 40 and 59; half of the isolates fell into this age range. This differs from the Chattanooga sample, in which the highest incidence of UTI's in women occurred between the ages of 70 and 89, and comprised only 40% of the entire sample. Here again, the difference may simply be to the small sample size obtained in Collegedale. Without further study, it is impossible to determine otherwise.

Though the clinic sample was very small and the results statistically insignificant because of this, it is sufficient to draw some preliminary conclusions. Sexual activity does appear to correlate with the contraction of a UTI, but not to antibiotic resistance. Chronic illness and pelvic surgery may be linked to resistance development, since all isolates from patients in both of these categories were resistant to at least one antimicrobial. In either case, a patient would receive antibiotic therapy, whether to cure infection (chronic) or to prevent it (surgery), thereby exposing normal flora and opportunistic pathogens to antibiotics without eliminating them, and thus spreading resistance. Similarly, over two-thirds of the patients with resistant organisms had also had a previous UTI and/or antibiotic therapy within the last six months. This too may point to a link between previous UTI infection and resistance development. Diagnosis with a previous UTI would result in antibiotic therapy, thereby increasing the possibility of drug resistance. The same would follow for any other infection and treatment the patient acquired in the previous six months.

Conclusion

Though sample sizes were not ideal, several important conclusions may be drawn from this study about the general trends in resistance in the greater Chattanooga area to the five anti-infective drugs studied. Ampicillin is virtually useless in treating UTI's. Resistance is present, to varying degrees, in virtually all bacterial UTI agents, in nearly all age groups. Cefazolin may still be useful in some areas, but its efficacy has been reduced to comparison purposes in this region. There is neither high resistance nor high susceptibility to this drug. Though a few age groups appeared to lack or have lowered resistance to nitrofurantoin and TMP-SMX, the small sample sizes in these groups prevents us from concluding that these drugs may be effective in these age categories. Both may still be useful when the antibiotic profile of an infectious agent is known, but they are inadequate to use as empiric broad-spectrum antibiotics. Cipro is undoubtedly the most potent agent, and it is clear why the IDSA had required the switch from TMP-SMX to Cipro as a first-line UTI therapeutic agent. However, Cipro is no longer infallible; even though it is consistently the most powerful treatment option, resistance to it is rising.

Further research needs to be conducted to draw firm conclusions tying extenuating factors to antibiotic resistance. First, a more in-depth version of the Collegedale clinic study is needed, investigating patient history and relating previous antibiotic treatment, previous UTI, chronic illness and sexual activity more conclusively to incidence and resistance. Factors contributing to resistance in children might also be worthy of investigation. Whatever the mode or medium, it is clear that more research must be done, not only to gauge the continued potency of the common empiric agents,

but to better prevent the spread of resistance and to prepare for the eventual necessity of newer and more powerful drugs.

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Table 1. Comparison of Incidence of Specific Uropathogens in 2001 Studies by Mathai, et al., and Bukharie and Saeed.

	Mathai n=1550	**Bukharie n=461**
E. coli	46.9	58
Enterococcus spp	12.8	13
Klebsiella spp	11.0	21
Pseudomonas aeruginosa	7.5	
Proteus mirabilis	5.0	3
Coagulase-negative Streptococci	3.4	
Group B Streptococci		3

Table 2. Percentage Composition of Samples Obtained From Chattanooga Area (Memorial Labs) and Collegedale Medical Center, February and March 2002

	Chattanooga n=108	**CMC n=17**
E. coli	54.6	52.9
K pneumoniae	13.9	17.6
Ps. aeruginosa	5.6	5.9
Prot. mirabilis	3.7	11.8
Other*	16.8	11.8

*includes various *Citrobacter* spp, *Enterobacter* spp, *Klebsiella oxytoca*, *Providencia rettgerii*, *and Morganella morganii.*

Table 3. Percentage of Isolates Resistant to Selected Antimicrobial Agents in Chattanooga Area (Memorial Labs), February-March, 2002.

	E. coli n=59	***K. pneumoniae n=15***	***Ps. aeruginosa n=6***	***Prot. mirabilis n=4***
Ampicillin	28.8	100	100	0
Cefazolin	1.7	0	100	0
Ciprofloxacin	1.7	0	50	25
Nitrofurantoin	0	46.7	100	100
Trimeth/Sulfa	10.3	13.3	100	25

Table 4. Percentage of Isolates Resistant to Selected Antimicrobial Agents in 2000, S. Sharp. Memorial Hospital, Chattanooga, TN.

	E. coli n=2900	*K. pneumoniae* n=805	*Ps. aeruginosa* n=768	*Prot. mirabilis* n=420
Ampicillin	33	99	99	9
Cefazolin	4	2	100	3
Ciprofloxacin	2	2	33	11
Nitrofurantoin	1	44	100	98
Trimeth/Sulfa	12	7	97	9

Table 5. Percent Resistance to Selected Microbial Agents, Irrespective to Etiologic Agent, Memorial Labs, 2002.

Ampicillin n=54	Cefazolin n=20	Ciprofloxacin n=9	Nitrofurantoin n=22	Trimeth/Sulfa n=18
50	19	8	29	18

Table 6. Resistance Rates by Age Group of Female Population (n=80), Irrespective to Etiologic Agent, from Memorial Labs, 2002.

Age	Ampicillin	Cefazolin	Ciprofloxacin	Nitrofurantoin	Trimeth/Sulfa
0-9	25	0	0	13	13
10--19	40	20	0	20	20
20-29	89	22	11	22	11
30-39	40	0	0	0	20
40-49	33	33	17	17	17
50-59	57	0	0	14	0
60-69	75	25	13	25	25
70-79	27	13	0	27	13
80-89	31	25	13	6	13
90-99*	100	0	0	0	0

*Only one sample was obtained within this age group, therefore the resistance to ampicillin is misrepresented as more extreme than is probable.

Table 7. Resistance Rates by Age Group of Male Population (n=28), Irrespective to Etiologic Agent, from Memorial Labs, 2002.

Age	Ampicillin	Cefazolin	Ciprofloxacin	Nitrofurantoin	Trimeth/Sulfa
20-29*	0	0	0	0	0
30-39	0	0	0	0	0
40-49	50	0	0	0	0
50-59	60	0	0	0	20
60-69	100	25	25	50	25
70-79	43	29	14	43	29
80-89	88	50	25	50	38

*No male samples were obtained from patients younger than 20, or older than 89.

Table 8. Percentage of Isolates Resistant to Selected Antimicrobial Agents from Collegedale Medical Center, February-March, 2002.

	E. coli *n=9*	*K. pneumoniae* *n=3*	*Ps. Aeruginosa* *n=1*	*Prot. Mirabilis* *n=2*
Ampicillin	33	100	100	0
Cefazolin	0	0	100	0
Ciprofloxacin	0	0	0	0
Nitrofurantoin	0	67	100	100
Trimeth/Sulfa	0	0	100	0

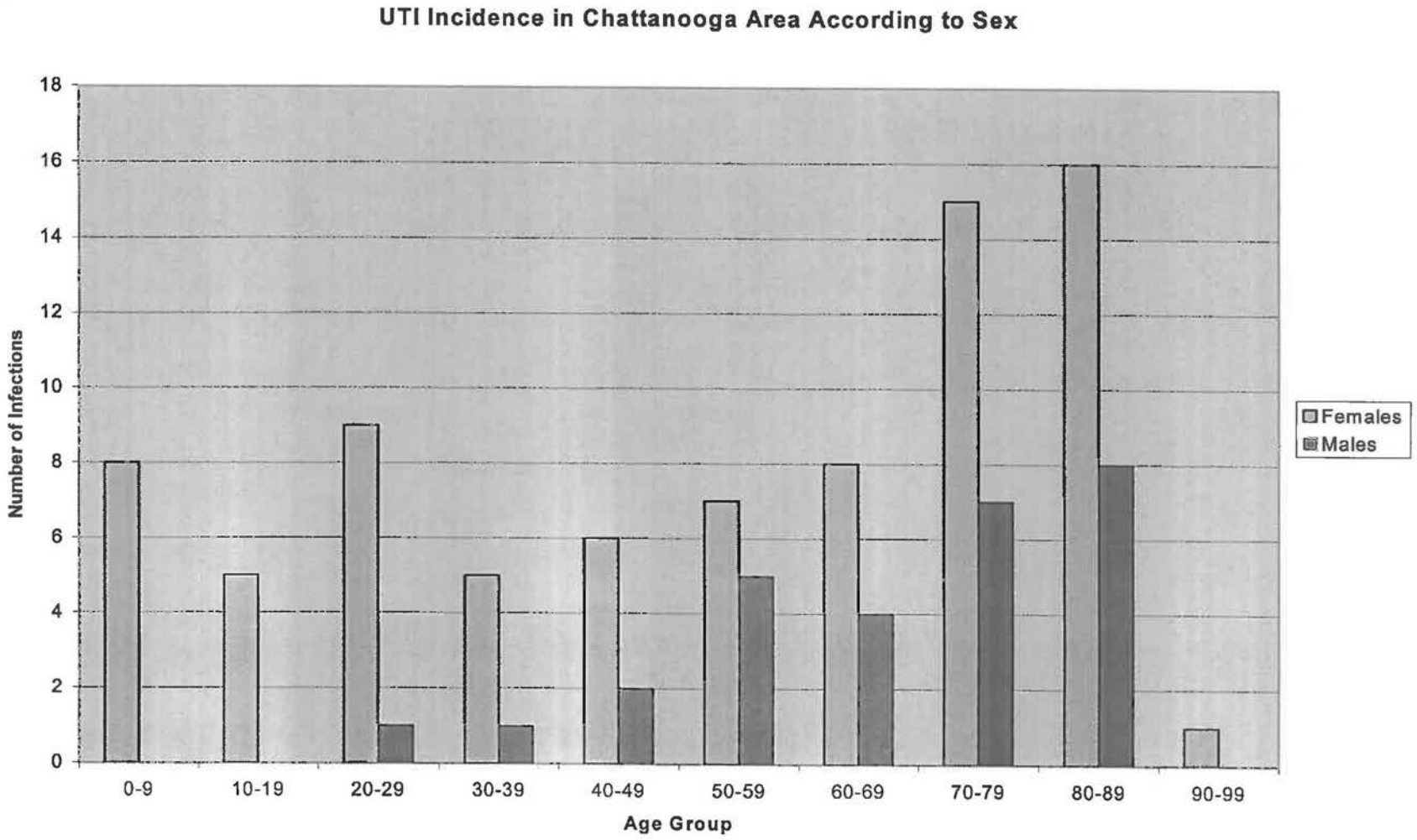

Figure 1. Number of UTI infections in females (n=80) and males (n=28) from the Chattanooga area, according to age groups.

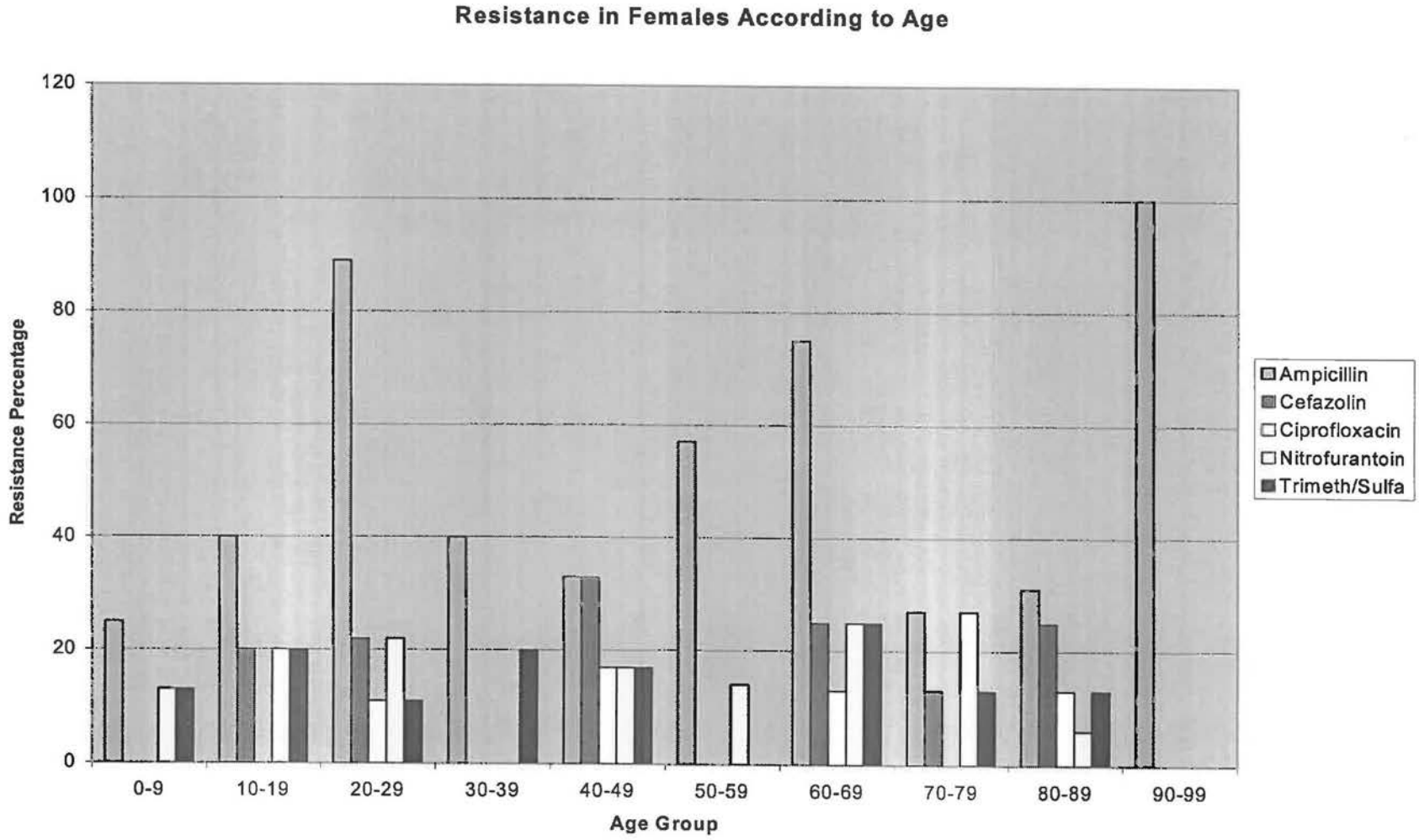

Figure 2. Percent resistance according to age groups, in isolates obtained from UTI-infected females in the Chattanooga area.

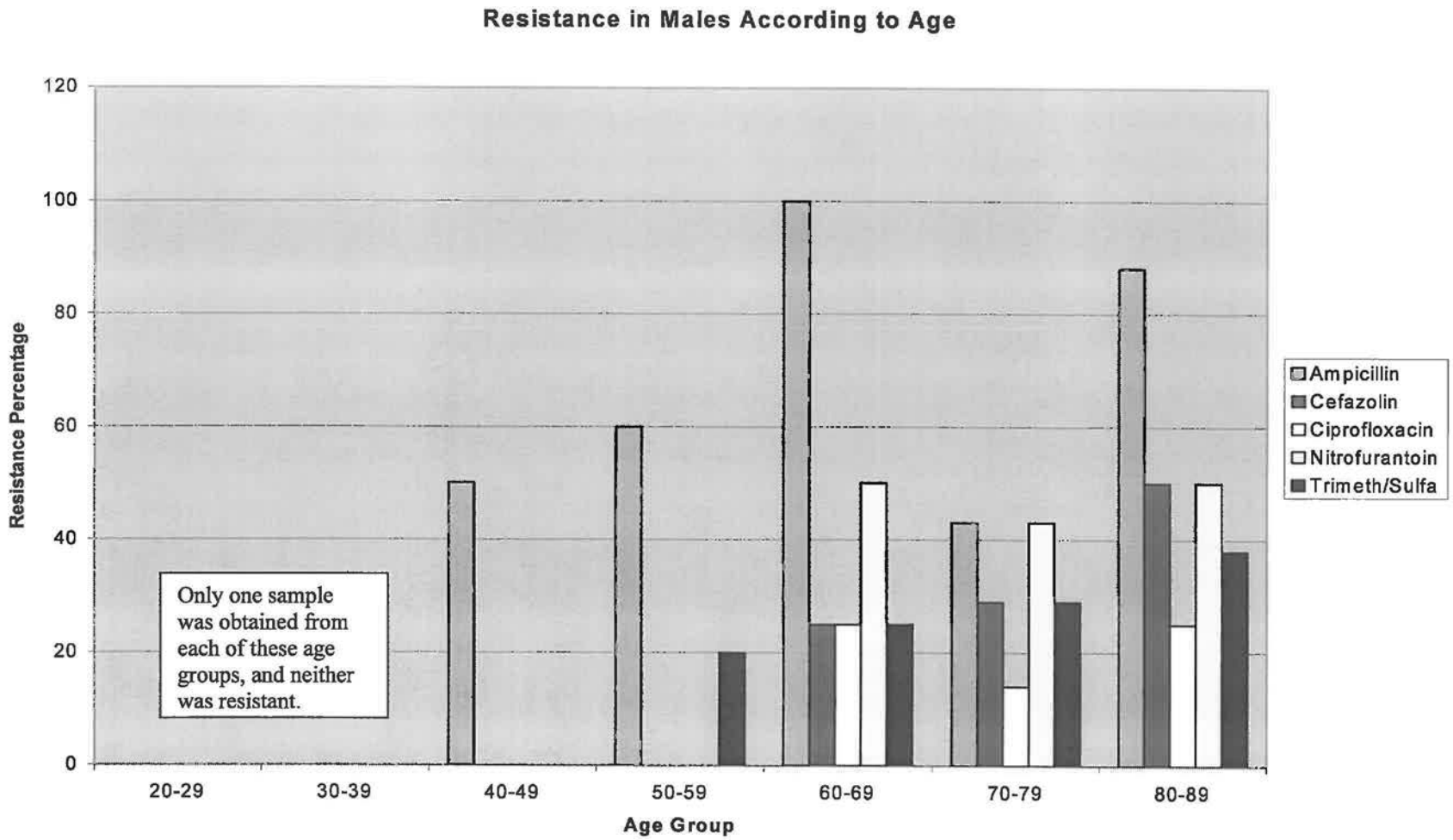

Figure 3. Percent resistance according to age groups, in isolates obtained from UTI-infected males in the Chattanooga area.

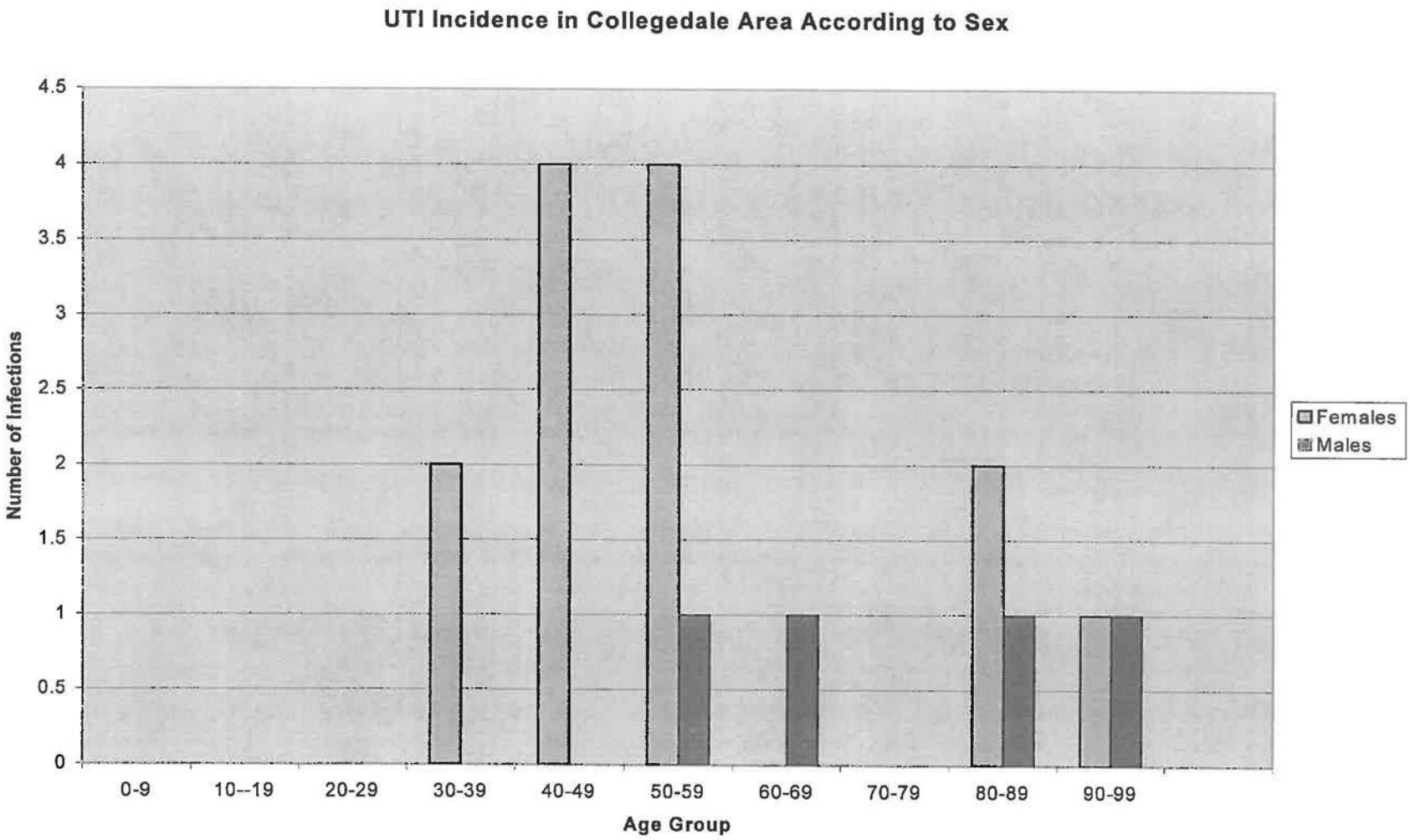

Figure 4. Number of UTI infections in females (n=13) and males (n=4) from the Collegedale area, according to age groups.

Southern Scholars Senior Project

Name: Kristin Stagg Date: 1/16/02 Major: Biology (Biomed)

Senior Project

A significant scholarly project, involving research, writing, or special performance, appropriate to the major in question, is ordinarily completed the senior year. The project is expected to be of sufficiently high quality to warrant a grade of A and to justify public presentation.

Under the guidance of a faculty advisor, the Senior Project should be an original work, should use primary sources when applicable, should have a table of contents and works cited page, should give convincing evidence to support a strong thesis, and should use the methods and writing style appropriate to the discipline.

The completed project, to be turned in in duplicate, must be approved by the Honors Committee in consultation with the student's supervising professor three weeks prior to graduation. Please include the advisor's name on the title page. The 2-3 hours of credit for this project is done as directed study or in a research class.

Keeping in mind the above senior project description, please describe in as much detail as you can the project you will undertake. You may attach a separate sheet if you wish:

Cipro has recently been elevated as the gold standard in UTI antibiotic treatment. But much controversy surrounds whether this very expensive drug is actually necessary in most cases of UTI. I will be working w/ Drs. Winters and Jarrell in Collegedale, to determine what organisms (there are several) are causing UTI's in this area, and also examine the antibiotic resistance of these microbes. My hypothesis is that the long-worthy and less expensive antibiotics, bactrim and macrodantin, are still adequate and very effective.

Signature of faculty advisor Stephen A. Nyirady Expected date of completion April 15

Approval to be signed by faculty advisor when completed:

This project has been completed as planned: ✓

This in an "A" project: Yes

This project is worth 2~~,3~~ hours of credit: ✓

Advisor's Final Signature Stephen A. Nyirady

Chair, Honors Committee _____ Date Approved: _____

Dear Advisor, please write your final evaluation on the project on the reverse side of this page. Comment on the characteristics that make this "A" quality work.

SOUTHERN SCHOLARS SENIOR PROJECT

Name: Kristin Stagg '02 Date: 9/7/01 Major: Biology Biomed

SENIOR PROJECT

A significant scholarly project, involving research, writing, or special performance, appropriate to the major in question, is ordinarily completed the senior year. The project is expected to be of sufficiently high quality to warrant a grade of A and to justify public presentation.

Under the guidance of a faculty advisor, the Senior Project should be an original work, should use primary sources when applicable, should have a table of contents and works cited page, should give convincing evidence to support a strong thesis, and should use the methods and writing style appropriate to the discipline.

The completed project, to be turned in in duplicate, must be approved by the Honors Committee in consultation with the student's supervising professor three weeks prior to graduation. Please include the advisor's name on the title page. The 2-3 hours of credit for this project is done as directed study or in a research class.

Keeping in mind the above senior project description, please describe in as much detail as you can the project you will undertake. You may attach a separate sheet if you wish:

We want to look @ S. aureus incidence and MRSA resistance profiles in an Antibiotic-experienced population and compare results to those of an Antibiotic-naive population. Samples will be studied here in Collegedale, hopefully w/ Dr. Winters' help – possibly using mother-child pairs – and in Nicaragua on the Nursing department's Mission trip during Spring break. Most research and procedure preparation will be done before the trip in March.

Signature of faculty advisor Stephen A. Nyirady Expected date of completion 5/02

Approval to be signed by faculty advisor when completed:

This project has been completed as planned: Yes

This in an "A" project: Yes

This project is worth 2-3 hours of credit: Yes

Advisor's Final Signature Stephen A. Nyirady

Chair, Honors Committee _____ Date Approved: _____

Dear Advisor, please write your final evaluation on the project on the reverse side of this page. Comment on the characteristics that make this "A" quality work.

Ideally - we will culture @ least 50-100 mother/child pairs from Dr. Winter's office. This is because we'd also like to look @ the incidence of S. aureus carriage in children of ~~carri~~ mother-carriers. The greater portion of patients in the Nicaragua clinics are mothers and their children, so in order to make a more solid study our sample here in collegedale should be that as well— and it would allow this extra element of study.

If we cannot obtain these samples w/ Dr. Winters' collaboration... we will instead use this and next semester's microbiology students (about 80) for only the S. aureus incidence and Antibiotic resistance comparison.

Procedure involves simple nasal swabs — non-invasive, no pain, no side effects — with permission of patients, of course.

Swabs will be cultured ASAP from Dr. Winter's office, and in Nicaragua, on Mannitol-Salt Agar plants specially prepared for the trip.

Culture and Antibiotic testing will be done @ SAU in the micro lab, by myself and Dr. Myirady.