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Community-acquired Urinary Tract Infections: Treatment, Outcomes, and Antimicrobial Resistance

by

Sharon Phillips Smith

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Epidemiology

in the

Graduate Division

of the

University of California, Berkeley

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Community-acquired Urinary Tract Infections: Treatment, Outcomes, and Antimicrobial Resistance

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By Sharon Phillips Smith

Abstract

Community-acquired Urinary Tract Infections: Treatment, Outcomes, and Antimicrobial Resistance

by

Sharon Phillips Smith

Doctor of Philosophy in Epidemiology

University of California, Berkeley

Professor Arthur L. Reingold, Chair

Community-acquired urinary tract infections (CA-UTI) are one of the most common infections in young women. Reports of increasing resistance to the antimicrobial drugs commonly prescribed to treat CA-UTI, evidence of wide-spread dissemination of strains of multi-drug resistant *Escherichia coli* that can cause community outbreaks of CA-UTI, and expanding appreciation of the importance of the rational use of antibiotics are challenging the traditional management of this disease.

This dissertation is comprised of two population-based studies that were performed in California women to investigate the epidemiological features of CA-UTI with an emphasis on the antimicrobial resistance of causative bacteria. An eight-year retrospective cohort study, utilizing administrative, laboratory, and pharmacy data, was conducted in a large health maintenance organization to describe and identify changes in uropathogen etiology and antimicrobial resistance, and in empirical antimicrobial treatment practices and outcomes. In addition, a four period cross-sectional study was performed in a university population to investigate the relationship between changes in the prevalence of genotype-based clonal groups of uropathogen *E. coli* and the prevalence of antimicrobial resistance.

These studies found that during the study period of 1998 through 2005 less than 20% of the *Escherichia coli* causing uncomplicated CA-UTI (UCA-UTI) were resistant to the first line empirical treatment antimicrobial, trimethoprim/sulfamethoxazole (TMP/SMX). No trends were detected in the proportions of *Escherichia coli* that were resistant to TMP/SMX (range 14% – 17%) or to nitrofurantoin (range 1.1% - 2.1%). In contrast, a small but steady increase in the proportion of *Escherichia coli* that were resistant to ciprofloxacin (range 0.4% - 2.8%) was observed. Over the same period of time, the use of ciprofloxacin as empirical treatment for UCA-UTI steadily increased (range 13% - 30%) while the use of TMP/SMX decreased (range 47% - 61%). However, no sustained decreases in treatment failure (range 17.2% - 18.3%) or in microbiologically incompatible treatment (range 8.4% – 10.6%) were detected. These findings suggest that TMP/SMX remains a viable empirical treatment for women with UCA- UTI in these populations.

Molecular typing of *Escherichia coli* causing CA-UTI revealed that the prevalence of antimicrobial resistance was influenced by a small number of *Escherichia coli* clonal groups. This finding suggests that the prevalence of antimicrobial resistant UTI in a community is not only the result of community prescribing practices and individual antimicrobial use but can be significantly impacted by the introduction and circulation of strains of uropathogens that are already drug resistant. Thus, strategies developed to maintain the usefulness of empirical treatment options for CA-UTI must include interventions that target the sources of antimicrobial resistant uropathogens.

Dedication

This dissertation is lovingly dedicated my family, Harry, Kerelyn, and Sierra Smith.

Their love, encouragement, and support were indispensible to the process and their music

sustained me throughout the dance.

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Chapter 1: Dissertation Overview

Urinary tract infections (UTI) are one of the most common infections seen in the outpatient setting. Over 7 million UTI cases occur each year in the U.S., resulting in over 8 million physician visits [1]. One third of all women will have a UTI by the age of 24 and over half of all women will have at least one UTI in their lifetime [2]. The economic impact associated with outpatient management of UTI is substantial, with costs estimated at $1.6 - $ 2.5 billion annually [3, 4]. Treatment of UTI is usually empirical, involving a short course of an antimicrobial agent [5].

Clinical management of community-acquired UTI (CA-UTI) has become complicated due to several factors: the perception that antimicrobial resistance to commonly prescribed antimicrobial agents is steadily increasing among uropathogens; documentation of outbreaks of community-acquired UTI caused by unique strains of multi-drug resistant *Escherichia coli* (*E. coli*); and the greater appreciation of the ecological damage often associated with the increased use of broad spectrum antimicrobials in the community (i.e. the disruption of normal flora, the selection of drug resistant organisms and the resultant colonization or infection with multi-drug-resistant organisms) [6, 7]

Resistance, among uropathogens, to trimethoprim/sulphamethoxazole (TMP/SMX), the first line empirical agent for treatment of CA-UTI, rose dramatically during the 1990s [8] and varies significantly by geographic region [9, 10], with the prevalence of TMP/SMX resistant *E. coli* reaching 22% in California and Washington state [11, 12]. On the other hand, resistance to nitrofurantoin and to fluoroquinolones, a class of broad spectrum antimicrobials commonly used to treat UTI, remains low among uropathogens in the U.S., Canada, and most of Europe; over 97% of *E. coli* from patients with UTI remain susceptible to these drugs. However, disturbingly high prevalences of strains with resistance to fluoroquinolones are being reported from other areas of the world, such as Spain (15%) [13], Bangladesh (26%) [14] Turkey (18%) [15], and Latin America (>18%) [16]. Furthermore, studies in the U.S. suggest that resistance to fluoroquinolones, among uropathogenic *E. coli,* is steadily increasing and that fluoroquinolone resistance in those *E. coli* resistant to TMP/SMX is as high as 9.5% [10].

There is a growing awareness that the use of broad spectrum antimicrobials to treat infections that could be successfully treated with narrow spectrum agents may contribute to a decrease in the effectiveness of these drugs in treating the more serious infections in which they may be the last remaining treatment option. Of concern are studies that suggest that physicians may be reacting to reports of increasing community levels of TMP/SMX resistance by replacing the use of TMP/SMX as first line therapy for CA-UTI with the use of a broad spectrum fluoroquinolone [5, 17].

These findings, combined with the paucity of new treatment options, underscore the possible utility of investigating the effectiveness of TMP/SMX and older treatment options, such as cephalexin and nitrofurantoin, for empirical treatment of uncomplicated community-acquired UTI (UCA-UTI).

Determining the prevalence of resistance to cephalexin, the first generation oral cephalosporin recommended for UTI treatment during pregnancy and in young children, is difficult because cephalexin is not included in the standard automated antimicrobial testing systems used by most U.S. clinical laboratories and, as a result, specific antibiogram data are not readily available. The Clinical Laboratory Standards Institute (CLSI) currently recommends that the results of the in vitro susceptibility testing against cephalothin be used to represent the susceptibility of an organism to cephalexin. However, a recent Canadian study [18] found that, among *E. coli* strains recovered from patients with UTI, automated cephalothin susceptibility testing results significantly over-stated the nonsusceptibility of cephalexin when compared with direct testing against cephalexin. In addition, national surveys of antimicrobial resistance among uropathogen in the United States do not generally report cephalothin susceptibility data. However, an early study performed in Washington state [19] reported that, by 1996, the proportion of uropathogens that were resistant to cephalothin was close to 30%.

The Infectious Diseases Society of America (IDSA) recommends that ongoing surveillance be conducted among patients with UCA-UTI to provide physicians with information on local uropathogen antimicrobial resistance and to monitor changes in the susceptibility of uropathogens to empirically prescribed antimicrobial agents. Aggregate laboratory data alone are insufficient to accurately characterize antimicrobial resistance in UCA-UTI. Short term empirical treatment of CA-UTI is often complete before urine culture and susceptibility testing results are returned to practitioners and pretreatment urine cultures are not considered cost effective for management of uncomplicated UTI disease. Therefore, physicians are more likely to order cultures only on "problem" patients, i.e. those with risk factors for a complicated UTI or those for whom empirical treatment has failed. Consequently, urine samples submitted for testing tend to under-represent uncomplicated UTI, *E. coli* uropathogens, and antibiotic susceptible organisms.

Wide variations in the reported resistance of uropathogens in different geographic regions of the US and in different patient populations, as well as the limitations inherent in relying on aggregate routine laboratory data, highlight the necessity of well designed, population-based epidemiologic studies to characterize uropathogen antimicrobial resistance, as well as management strategies and treatment outcomes among women with UCA-UTI.

The research reported in this dissertation was designed to investigate the epidemiological features of CA-UTI in women, with a focus on the antimicrobial resistance of the causative uropathogens. This dissertation consists of two population-based epidemiological studies performed among women, ages 15 – 60 years, in Northern California. An eight-year retrospective cohort study, utilizing administrative, laboratory and pharmacy data from a large health maintenance organization, was conducted to describe and identify changes in the etiology of CA-UTI, and antimicrobial resistance patterns among uropathogens, and in empirical antimicrobial treatment practices and outcomes. In addition, a four period cross-sectional study that collected and analyzed urine specimens from all women presenting to a university clinic with symptoms suggestive of UTI was performed to describe the genotype-based clonal composition of community-acquired uropathogenic *E. coli* and to investigate the impact of transient *E. coli* clonal groups on antimicrobial resistance estimates. In addition, both studies

tested the hypothesis that the resistance of uropathogenic *E. coli* to empirically prescribed antimicrobials was increasing over time.

Chapter 2 of this dissertation provides the background for the studies performed and summarizes current knowledge pertaining to the management of CA-UTI infections in women and to antimicrobial resistance among the bacteria causing these infections.

Chapter 3 details the objectives, study design, methods, setting, and populations in the retrospective cohort study performed in the large health maintenance organization.

Chapter 4 reports the distributions and antimicrobial susceptibilities of uropathogens from the microbiologically investigated CA-UTI identified during the cohort study and examines whether the resistance of uropathogens to empirically prescribed antimicrobial agents is increasing in this population.

Chapter 5 explores empirical antimicrobial treatment drug choice and urine culture ordering practices of practitioners treating CA-UTI in the cohort population. The suitability of empirically prescribed antimicrobial agents is investigated among culture-confirmed CA-UTI. In addition, short-term (i.e. 30-day) clinical outcomes and treatment effectiveness are examined among women with acute UCA-UTI.

Chapter 6 describes the population of women with UCA-UTI who received cephalexin empirical treatment and examines the usefulness of cephalothin and cefazolin (the other routinely tested first generation cephalosporin) susceptibility testing results in predicting treatment outcomes at 30 days.

Chapter 7 details the study design, objectives, methods and results from the cross-sectional study performed in the university community. The antimicrobial resistance of uropathogenic *E. coli* from women with CA-UTI is examined over the four study periods and the hypothesis that the resistance of uropathogenic *E. coli* to empirically prescribed antimicrobial agents is increasing is tested in this population. ERIC2-PCR genotyping is performed to elucidate the clonal composition of the population of uropathogenic *E. coli* and to examine the association of identified ERIC2 clonal groups with changes in antimicrobial resistance.

Chapter 8 summarizes the principal results from Chapters 4 through 7 and discusses the strengths and limitations of the studies and the implications for further research.

References, figures and tables are located at the end of the dissertation.

Chapter 2: Background: Community-acquired Urinary Tract Infections in Women

Introduction

Urinary tract infections (UTI) are one of the most common community-acquired infections in the U.S. While mortality is rare, the disease burden and the social and economic costs associated with these infections are substantial. Treatment for UTI, one of the most common reasons for prescribing antimicrobials in North America, is usually empiric, involving a short course of an antimicrobial agent. Reports of increasing resistance to the antimicrobials commonly prescribed to treat community-acquired UTI as well as the documentation of community outbreaks of multi-drug resistant UTI caused by unique strains of uropathogen *E. coli* and the expanding appreciation of the importance of the rational use of antibiotics are challenging the traditional management of this disease.

Epidemiology of UTI

The annual global incidence of UTI is estimated to be greater than 250 million UTI per year [20]. UTI is primarily a disease of young, healthy women. One third of all U.S. women will have a UTI by the age of 24 and 60% will have at least one UTI in their lifetime [2]. Over seven million cases of UTI occur each year in U.S. women, resulting in approximately 8.9 million cystitis-related physician visits, 1.3 million emergency room visits, and 200,000 hospital admissions [1]. It has been estimated that, among US women, non-prescription UTI healthcare expenditures exceed $2.4 billion annually [1]and additional antimicrobial prescription costs exceed $200 million [3]. Griebling [4] has estimated that the 1999 out-of-pocket healthcare costs of women with a UTI diagnosis were 40% higher than those of women without UTI.

UTI incidence peaks in young, sexually active women, ages 20 –34 years. Foxman's [21] research on college women suggests that a case of community-acquired UTI (CA-UTI) is associated with over six days of symptoms leading to the lost of two to three days of class or work attendance. Recurrence of UTI symptoms within three to four months of the initial episode is not uncommon, occurring in about 30% - 40% of UTI cases [22, 23]. Serious complications such as sepsis or death occur but are rare.

Risk Factors for UTI

Both genetic and behavioral factors play a role in the development of UTI. Women with a family history of recurrent UTI are more likely to experience recurrent UTI themselves [24]. Expression of HLA-A3 and the nonsecretor status of the P1 and Lewis (Le(a-b-) and Le(a+b-)) blood group antigens have been shown to increase the likelihood of recurrent UTI due to the presence of uropathogen binding glycolipids on vaginal and uroepithelial cells [4, 25] Recent sexual activity and the use of diaphragms and certain types of spermicides are strongly associated with an increased risk of UTI in premenopausal women [26, 27]. Disruption of commensal lactobacilli in the vaginal tract following antimicrobial use increases the risk of vaginal colonization with UTI-causing pathogens. This colonization is thought to be a precursor

to UTI. Contrary to traditional beliefs, epidemiological studies have not shown that hygiene and voiding habits are associated with the risk of UTI [21, 24].

UTI Disease Spectrum

The term "urinary tract infections" is used to refer to a number of distinct clinical syndromes, each with its own unique epidemiological, pathogenic, diagnostic and treatment considerations. Successful clinical management of a patient with UTI symptoms requires an accurate syndromic diagnosis. The human urinary tract is normally sterile and all the UTI syndromes are marked by the presence and multiplication of microorganisms in the normally sterile sites and most involve the invasion of uroepithelial cells and a resultant inflammatory response. UTI syndromes differ in the extent of the inflammatory response, the location of the infection within the urinary tract and the underlying host characteristics of the patient.

Acute cystitis (bladder or lower UTI infection), the most common UTI syndrome, is characterized by a bacterial infection of the lower urinary tract, the bladder and/or the urethra, and is diagnosed primarily on the presence of voiding symptoms and urine signs. Symptoms include urination urgency and frequency with pain or burning, and may include hematuria and suprapubic or low back pain [28]. These diagnostic symptoms are often accompanied by signs of cloudy or malodorous urine. Symptoms of common sexually transmitted diseases (STDs), especially *Chlamydia* infections, overlap those of acute cystitis and may confuse an accurate diagnosis but, unlike cystitis, STDs are usually accompanied by signs of vaginal discharge or irritation. Two UTI syndromes overlap cystitis: the frequency-dysuria syndrome includes acute cystitis as well as urethritis caused by sexually transmitted pathogens, trauma or chemical irritation; and the acute urethral syndrome includes patients with symptoms of cystitis but with negative or low count urine cultures. Pyelonephritis, a more invasive infection, involves inflammation of the kidney and renal pelvis with concomitant fever and flank pain or tenderness, and may be accompanied by nausea and/or vomiting. Other UTI syndromes include asymptomatic bacteriuria or funguria, and prostatitis, as well as intrarenal or perinephric abscess, and urosepsis. [29-31]

This dissertation is limited to the study of community onset acute cystitis in adult women.

A number of anatomical, medical, and functional conditions predispose a patient to be at a greater risk for UTI infection or recurrence, to be more likely to fail therapy, or to be infected with a more diverse or resistant spectrum of causative organisms. Acute cystitis in these patients is classified as complicated UTI and management strategies are more aggressive than those for patients with uncomplicated UTI. Conditions suggestive of a complicated UTI include the following: anatomical or functional abnormalities that interfere with the normal defense mechanisms of the urinary tract, such as a single or diseased kidney, obstruction of the urinary flow, or surgical reconstruction or instrumentation of the urinary tract; physiological conditions, such as chronic renal failure, diabetes, pregnancy, immune suppression, or transplant; host functional limitations, such as incontinence, spinal cord injury, or those associated with the extremes of age; and recent antimicrobial exposure. [28, 31-33]. Patients with complicated UTI are often recommended to receive pretreatment urine cultures, treatment with a broad spectrum antibiotic, and a longer duration of therapy [31, 34].

Microbiology

Traditionally, CA-UTI have been considered opportunistic infections caused by endogenous gut flora. The classic model of infection assumes that commensal intestinal flora descend and colonize the rectum and perineum of women and then, through mechanical activity such as sexual intercourse ascend the urethra, and infect the bladder. Enteric gram negative rods have been shown to cause 70% – 95% of acute bacterial cystitis in women. *Escherichia coli* (*E. coli*) remains the most frequently isolated organism in all settings, accounting for >80% of CA-UTI, with *Proteus mirabilis*, *Klebsiella* species, *Staphylococcus saprophyticus* and *Enterococcus* species commonly causing between 2-10% of the remaining cases. *Enterobacter, Serratia,* and *Citrobacter* species*, Pseudomonas aeruginosa,* and *Group B streptococcus* as well as *Candida* species, *ureaplasma* and *mycoplasma hominis* are recognized to cause a smaller number of UTI cases and are more common in complicated infections [28, 35]. Isolation of *Staphylococcus aureus* and *Mycobacterium tuberculosis* from urine usually occurs due to bloodstream seeding from other sites of infection.

The advent of molecular typing and virulence gene identification has refined the classic model. It is now recognized that the majority of uropathogenic *E. coli* that cause CA-UTI are descended from a limited number of phylogenic groups, and possess a diverse collection of virulence factors that promote the colonization and infection of the urinary tract, stimulate an inflammatory reaction, and aid persistence in the bladder epithelial cells [36-38].

Origin of Infection

While a host's gut floral is recognized as the immediate source of the causative agent of their UTI, the reservoirs and routes of transmission of bacterial strains and antimicrobial resistant strains capable of causing UTI are inadequately understood. Genotyping of *E. coli* uropathogens has shown that sexual transmission may occur [39, 40] and that unique strains may be shared among household members and their pets. Whether household sharing is a result of person/animal to person/animal transmission or of parallel acquisition from an external source such as contaminated food or water is still unclear [41-43].

Antimicrobial resistance in pathogens causing UTI, traditionally held to result from individual antimicrobial use or local prescribing practices, is coming under closer scrutiny. Antimicrobial use in agriculture and food animal production is increasingly implicated in the creation, maintenance, and dissemination of drug-resistant strains of uropathogenic *E. coli* [44-50] Johnson et al have found that a substantial proportion of U.S. retail meats, especially poultry products, are contaminated with antimicrobial resistant strains of *E. coli* that possess virulence factors associated with human disease [47, 50].

Community-wide outbreaks of multi-drug resistant CA-UTI have been documented [12, 51, 52] and extensive geographic distribution of multi-drug resistant clones has been shown to occur [53]. Community outbreaks of UTI may occur more often than previously thought and these outbreaks may result from the introduction of a virulent or antimicrobial resistant bacterial strain from a common source such as food or water. The introduction of such a strain, if

resistant, may dramatically alter the resistance prevalences in that community for the period of time that the strain is present.

Management of Uncomplicated UTI

In 1975, Kunin developed guidelines for the diagnosis of UTI which recommended a diagnostic urinalysis as well as pre-treatment and post treatment quantitative urine cultures [54]. A clean catch morning specimen yielding $\geq 10^5$ colony forming units (CFU) per mL of urine of a single UTI-associated pathogen was found to be highly correlated with the presence of a urinary tract infection. Later research refined the laboratory criteria; voided urine specimens from women with clinical signs and symptoms of acute cystitis that yielded lower counts (10^2 to 10^4 CFU) of a single uropathogen were found to be indicative of UTI [55]. The diagnostic criteria of $\geq 10^3$ CFU/mL of urine of a single uropathogen has been estimated to be 80% sensitive and 90% specific for identifying a UTI in symptomatic women [56.].

Diagnostic management of acute cystitis has continued to evolve and the use of urine cultures for diagnosis of uncomplicated CA-UTI (UCA-UTI) in symptomatic women has decreased significantly. A 1997 cost analysis reported that empirical treatment, without laboratory studies, was the most cost effective treatment strategy for women with acute uncomplicated cystitis [57] and surveys performed in the 1990s found that only 30% - 50% of UTI patients received a pretreatment urine culture [58, 59]. Recent studies suggest that certain combinations of voiding symptoms and an absence of vaginal symptoms have a predictive value of 90% for acute cystitis. [60, 61] and the safety and effectiveness of telephone management of UCA-UTI has been shown in a number populations [34, 62-64]. Practitioners generally begin empirical treatment of UTI based on signs and symptoms alone or with the addition of a urinalysis dip stick test for nitrites and leukocyte esterase. Thus, urine cultures, when performed on women with UCA-UTI, are primarily used to guide follow-up therapy if initial empirical treatment fails.

Treatment

About 50% of UTI will spontaneously resolve after 2 - 4 weeks in the absence of treatment. However, antimicrobial treatment quickly alleviates symptoms and substantially shortens their duration [65-68]. Empirical antimicrobial treatment has been found to be successful when an infection is related to a narrow and predictable range of causative organisms and when the prevalence of resistance to commonly prescribed antimicrobials is low (e.g. <20%). UCA-UTI in women have been found to meet these requirements [56, 61]. Treatment for CA-UTI in women generally includes the empirical prescription of a short course of an antimicrobial agent. Antimicrobials commonly prescribed for treatment of UCA-UTI in the U.S. include trimethoprim/sulfamethoxazole (TMP/SMX), fluoroquinolones (usually ciprofloxacin), nitrofurantoin, and cephalexin. Clinical cure rates are estimated to be 90 – 95% with the use of TMP/SMX or fluoroquinolones, 85% with the use of nitrofurantoin, and 50 – 85% with β-lactam drugs, such as cephalexin [69] [56, 70, 71].

In 1999, the Infectious Diseases Society of America (IDSA) developed evidence-based guidelines for the treatment of acute uncomplicated UTI in non-pregnant women. A three-day

course of TMP/SMX was recommended as first line treatment in geographic areas where the prevalence of resistance to TMP/SMX, among *E. coli* strains causing UCA-UTI, remained below 20%. The use of nitrofurantoin or fluoroquinolones was suggested in areas where the prevalence of resistance to TMP/SMX was known to be high [56].

TMP/SMX is an economical combination drug that has been used for over 25 years to safely and effectively treat UTI. Trimethoprim and sulfamethoxazole work in synergy to disrupt successive steps in the bacterial folate synthesis pathway, thus inhibiting bacterial DNA replication and transcription. TMP/SMX achieves high urine, serum, and tissues level as well as concentrating in vaginal fluids and has a minimal effect on normal fecal flora. However, this drug is not active against *Enterococcus* or *Pseudomonas* species [72] and has been associated with skin rash, gastrointestinal upset and bone marrow toxicity and is contraindicated for use in pregnant women and neonates [73]. Antimicrobial resistance to TMP/SMX in uropathogenic *E. coli*, as discussed below, has become an important issue.

Nitrofurantoin has been used to safely and effectively treat bladder infections for over 50 years and can be used during pregnancy and in pediatric populations [74]. Nitrofurantoin is excreted primary through the kidneys, thus high urine concentrations are achieved [11]. This drug is active against gram positive uropathogens and the development of resistance among *E. coli* has been rare. However, certain fairly common uropathogens, such as *Morganella, Proteus* and *Providencia* species, are intrinsically resistant to this drug   Nitrofurantoin is generally prescribed with a five to seven day dosing regimen and can be used as prophylaxis to prevent recurrent infections. Nitrofurantoin has the advantage of attacking multiple bacterial sites and metabolic pathways [75]; it disrupts bacterial carbohydrate metabolism and inhibits the synthesis of DNA, RNA, proteins, and the bacterial cell wall [76]. The treatment of CA-UTI with nitrofurantoin has a number of advantages. Nitrofurantoin has minimal impact on normal intestinal and vaginal flora and does not increase problems with antibiotic-associated infections such as *Clostridium difficile*. It is not closely related to other antimicrobials so it has a low capacity for co-selection of resistance with drugs used to treat more serious infections. Furthermore, nitrofurantoin is only used to treat CA-UTI and is not used in hospitals or other institutions, and is not used in animal husbandry for growth promotion; therefore there is little over all selective pressure for nitrofurantoin resistance [77]. Unfortunately, nitrofurantoin has extremely poor tissue penetration and low achievable blood levels, rendering it ineffective for treatment of pyelonephritis and contraindicated in patients with renal failure [78]. In addition, nitrofurantoin does not concentrate in the vaginal secretions so it does not eradicate uropathogens from the vagina [28]. The use of nitrofurantoin has been associated with gastrointestinal effects and, at high doses, with hepatic and pulmonary toxicity [28].

Aminopenicillins and oral cephalosporins (i.e. the *B*-lactam drugs, ampicillin and cephalexin) attain high concentrations in the urine and are active against gram positive as well as gram negative uropathogens. Ampicillin was the common drug of choice in the early 1970s, but was soon replaced with newer drugs, such as TMP/SMX, which had shorter dosing regimens, better clinical performance, and fewer adverse effects. Currently *B*-lactam drugs are prescribed with a seven day dosing regimen. These drugs act by binding antagonistically to bacterial penicillin binding proteins and blocking the transpeptidation reaction which cross links peptidoglycan during bacterial cell wall biosynthesis. Antimicrobial resistance, as discussed

below, limits their current use. Although no longer recommended as first line empirical treatment for CA-UTI. [11, 56], these drugs are often used to treat CA-UTI in young children, pregnant women and patients known to be infected with a gram positive uropathogen.

Ciprofloxacin and other fluoroquinolones are broad spectrum antimicrobials which are extensively used for empirical treatment of many different types of infections. These drugs are active against most uropathogens and have excellent bioavailability, achieving high tissue and urine concentrations [11]. Ciprofloxacin is usually prescribed in 1 to 3 day dosing regimes. Fluoroquinolones target bacterial DNA gyrase and DNA topoisomerase IV and cause double-stranded breaks in the bacterial chromosome [79]. The use of fluoroquinolones, which have minimal activity against anaerobes, has a limited impact on normal fecal and vaginal flora [73]. However, although antimicrobial resistance to ciprofloxacin remains low among most uropathogens in the U.S., ciprofloxacin use has been found to select for ciprofloxacin resistant organisms [80-82]. In addition, because fluoroquinolones are often the last remaining drug choice for severe infections, there is a growing recognition of the importance of reducing community level selective pressure for resistance to this class of drug. Therefore, reducing the use of fluoroquinolones for the treatment of less serious infections, such as CA-UTI, that could be successfully treated with other antimicrobials has become an important component of antimicrobial stewardship programs.

Antimicrobial Resistance

Clinical management of CA-UTI is complicated by reports that the prevalences of resistance to the commonly prescribed antimicrobials, TMP/SMX, ampicillin, and cephalothin, are steadily increasing [10, 83, 84]. In addition, antimicrobial resistance among uropathogens is recognized to vary by geographic location [85] and to be impacted by the transient geographical dissemination of resistant clonal groups of *E. coli*, i.e. CgA, [12, 86] as well as by horizontal gene transfer among multiple strains [87]. A study of UTI isolates from women with acute UCA-UTI performed in Washington state revealed that, among *E. coli* uropathogens, resistance to TMP/SMX doubled from 9% in 1992 to 18% in 1996, resistance to cephalothin increased from 20% to 28% and resistance to ampicillin increased from 26% to 34%, while resistance to nitrofurantoin and to ciprofloxacin remained below 2% [19]. Although nitrofurantoin resistance remains low among *E. coli* uropathogens, <1% in many studies [10, 11, 88], intrinsic resistance to nitrofurantoin exists among a number of secondary uropathogens such as *Morganella, Proteus* and *Providencia* species. While resistance to fluoroquinolones remains low; with over 97% of *E. coli* isolated from CA-UTI in the U.S. susceptible to ciprofloxacin, resistance to fluoroquinolones has displayed a consistent stepwise increase from 0.7% in 1995 to 2.5% in 2001. Importantly, fluoroquinolone resistance in those *E. coli* isolates already resistant to TMP/SMX is much greater (9.5%) [10]. Also of concern are the disturbingly high prevalences of resistance to fluoroquinolones that have been reported among uropathogens from other areas of the world; 37% from regions of Europe, 69% from India, and >18% from Latin America [16, 89, 90].

Because UTI treatment drugs had the ability to concentrate to high levels in the urine, they were traditionally believed to eradicate both susceptible and resistant uropathogens. However, recent studies suggest that women with TMP/SMX resistant infections experience

increased clinical failure if they are treated with TMP/SMX [85, 91-93]. Because urine culture and susceptibility results, when performed, are often not available until after the completion of treatment, it is important for practitioners to be able to identify women who are likely to be infected with a TMP/SMX resistant uropathogen. Results of studies investigating predictors of TMP/SMX resistance among women with CA-UTI are conflicting [31]. Risk factors found to be associated with TMP/SMX resistance in various studies include antibiotic use in the past three months, especially TMP/SMX use, Hispanic or Asian ethnicity, out of state or out of country travel, diabetes, recent hospitalization, and infection with CgA *E. coli* [94-98].

In 2003, a panel of UTI experts was assembled by the Alliance for the Prudent Use of Antibiotics to review the 1999 IDSA empirical treatment guidelines for acute UCA-UTI. Prompted by numerous reports that fluoroquinolones were rapidly replacing TMP/SMX as the treatment drug of choice for UCA-UTI [17, 99, 100], as well as by evidence that fluoroquinolone treatment of UTI could select for fluoroquinolone resistant fecal *E. coli* [80, 81], an updated approach to empirical therapy for acute UCA-UTI was developed. This proposal reiterated that TMP/SMX should remain the first line therapy for treatment of UCA-UTI in communities where the prevalence of *E. coli* resistance to TMP/SMX is < 20% in women with UCA-UTI. It stressed the importance of using non-fluoroquinolone antimicrobials, such as nitrofurantoin, to treat the mild to moderate UCA-UTI cases in which TMP/SMX was not an option. The use of fluoroquinolones was recommended to be reserved for women with severe disease who have an allergy to TMP/SMX, who have received non-fluoroquinolone antibiotic therapy in the last 3 months, or who live in communities where the prevalence of *E. coli* resistance to TMP/SMX is ≥ 20% [101].

Importantly, the panel of UTI experts also called into question the advisability of using surveillance system or traditional hospital antibiogram estimates to represent the prevalence of uropathogen resistance to treatment antimicrobials among women with UCA-UTI. The panel delineated the two common biases, culture selection bias and sampling bias, which often skew surveillance and traditional laboratory antibiogram estimates of antimicrobial resistance. Culture selection bias occurs when practitioners limit the use of urine cultures in UTI patients with UCA-UTI, a practice that is increasingly encouraged as a healthcare cost saving measuring. Sample selection bias occurs in surveillance samples which draw from hospital laboratories and in hospital laboratory antibiograms because these samples over-represent hospitalized patients, sicker patients and patients with complicated UTI. Both these bias lead to samples that are likely to over-estimate the antimicrobial resistance of organisms infecting patients with UCA-UTI. In addition, traditional hospital antibiograms often include isolates from patients with other types of infections such as respiratory, blood or wound infections. Recognizing that the current susceptibility data needed to make informed empirical treatment choices is generally not available to the practitioner, this panel emphasized the importance of developing new methods to make less biased regional estimates of antimicrobial resistance among the uropathogens infecting women with UCA-UTI, such as using community outpatient UTI data from offices or clinics or university populations to estimate local resistance prevalences. They also stressed that additional research was needed to determine the effectiveness of nitrofurantoin treatment in populations. The panel recommended that the IDSA reevaluate and clarify their recommendations for the use

of second line UTI treatment options to reflect the increasing understanding of the damage that can result from the unnecessary use of broad spectrum antimicrobials in the community [101].

Successful management of CA-urinary tract infections is a process that requires on-going surveillance and research to detect outbreaks of resistant UTI, to monitor changes in the antimicrobial resistance of common uropathogens, to evaluate the current effectiveness of available antimicrobial treatment options, and to tailor treatment guidelines to reflect regional conditions. Further research is needed to identify the conditions and mechanisms that lead to the development and dissemination of antimicrobial resistant and virulent uropathogens. In addition, studies are needed to refine the current understanding of individual risk factors for antimicrobial resistant UTI infections to allow practitioners to successfully treat women with UCA-UTI while limiting the use of broad spectrum antimicrobials.

Chapter 3: Definitions and Populations; Retrospective Cohort Study

Study Design and Objectives

An eight year, population-based, retrospective cohort study was performed using secondary administrative, laboratory, and pharmacy data to evaluate the epidemiologic features of community-acquired urinary tract infections in women receiving healthcare from the Kaiser Permanente Northern California Health Plan (KPNC). This study sought to describe and identify changes in uropathogen etiology, antimicrobial resistance, empirical antimicrobial treatment practices and outcomes, and microbiological investigation by urine culture to provide the population-specific knowledge necessary to evaluate regional prevalences of antimicrobial resistance among uropathogens and to tailor existing national empirical treatment guidelines to the KPNC population. In addition, this study evaluated how well in-vitro susceptibility testing predicts the clinical outcome of antimicrobial treatment among women with uncomplicated community-acquired urinary tract infections.

Study Setting

The Kaiser Permanente Northern California Health Plan (KPNC) is a nonprofit healthcare organization which provides integrated health care services to approximately 3.1 million members. Services are provided at 17 medical centers and over 54 clinics in more than 15 counties in Northern California. KPNC members comprise about a quarter of the population in the counties served, and while generally reflecting the race, ethnicity, and socioeconomic status of their communities, may under represent those at the extremes of the socioeconomic spectrum [62, 102].

Study Subjects

Data from six KPNC administrative databases were used to identify all women seeking outpatient treatment for community-acquired acute cystitis from January 1, 1998 through December 31, 2005 (Table1). Potential subjects included all KPNC members with an identified urinary tract infection (UTI) event, defined as an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) code for acute cystitis (595.0, 595.2, 595.9, 599.0), pyelonephritis (590), or UTI during pregnancy (64663.003, 64663.004) [4], or a positive urine culture result with antimicrobial susceptibility data for one or two uropathogens. Male members and females below the age of 15 or over the age of 60 were excluded. Additional information, covering one year before their first identified UTI event through January 31, 2006, was obtained on each potential subject. Age, preferred KPNC service site, treatment drug and other antimicrobial usage, membership, and pertinent ICD-9 data were collected from the six electronic data sources detailed in Table 1.

Study protocols were approved by the Kaiser Permanente Northern California Institutional Review Board and by the Committee for Protection of Human Subjects at the University of California at Berkeley.

Definitions

UTI Case Definitions

All identified UTI events were classified as either a primary UTI event, defined as the first identified UTI event (as defined above) in a calendar year with no other UTI events in the preceding 365 days, or as a secondary UTI event. Secondary UTI events were further classified as a duplicate UTI event, a recheck UTI event, or a recurrent UTI event, based on the date of the UTI-related ICD-9 code or positive urine culture relative to treatment date and to other UTI events (Table 2). Treatment date was defined as the first antimicrobial prescription date occurring on or within two days after the UTI event date. Continuous membership, used as an indicator of complete UTI and medical history, was defined as a record of KPNC membership covering the time period of 365 days before through 30 days after a primary UTI event. Each primary UTI event with complete membership was classified by onset type (Table 3).

Community-acquired primary UTI events (CA-UTI) were further classified as a complicated or uncomplicated UTI. CA-UTI in pregnant women, in women with recent antimicrobial treatment or treatment of healthcare complications, and in women with pyelonephritis, genitourinary abnormalities, diabetes, immune deficiency, or concurrent bacterial infection were classified as a complicated (CCA-UTI) (Table 4). Recent antimicrobial treatment was defined as a Pharmacy Information Management System (PIMS) (Table 1) database record for an antibiotic prescription or as an antibiotic poisoning ICD-9 code (960.0-961.9) 2 – 30 days before the UTI date (Table 4).

CA-UTI which did not fit the definition of a CCA-UTI were classified as uncomplicated CA-UTI (UCA-UTI).

Empirical Treatment Definition

A CA-UTI was considered treated if an antimicrobial prescription code in the PIMS database occurred on or within two days following the UTI date. Treatment date was defined as the date of the first antimicrobial prescription within the time period. More than one antimicrobial code captured on the treatment date was considered to be part of the same treatment and treatment was classified as combination therapy. CA-UTI with a single antimicrobial code on the treatment date were considered to have received mono-therapy.

Treatment Failure Definition

Treatment failure, defined as an additional use of the KPNC healthcare system for the primary CA-UTI, was assessed over a 30 day risk period from the beginning of UTI treatment. Empirical treatment was considered to have failed if a recheck UTI ICD-9 code, a new urine culture, or an additional antibiotic treatment PIMS code occurred within the risk period. An additional antibiotic treatment PIMS code for patients with a primary UTI complicated by a bacterial infection or other condition requiring antimicrobial treatment during the risk period was not sufficient to define treatment failure. One of the other criteria needed to be met as well.

Culture-confirmed UTI Definition

The Laboratory Utilization Reporting System (LURS) was used to identify all routine urine cultures performed at the central KPNC laboratory on study women during the study period. All diagnostic pretreatment urine cultures, those performed before the treatment date if available, and within two days of an identified CA-UTI event were evaluated. A CA-UTI was culture confirmed by a positive urine culture if one or two uropathogens were identified to the species level and susceptibility testing was performed. A CA-UTI was classified as an antimicrobial resistant UTI if any of the infecting uropathogens were reported with intermediate or resistant susceptibility to the specified antimicrobial. During the study period all urine cultures and susceptibility testing were performed at one central laboratory using the broth microdilution method and interpreted by Clinical and Laboratory Standards Institute (CLSI) guidelines. Non-susceptible isolates, those interpreted by CLSI guidelines as intermediate or resistant, were classified as resistant. Pan-susceptibility (PanS) was defined as tested and reported as susceptible to trimethoprim/ sulfamethoxazole (TMP/SMX), nitrofurantoin, ciprofloxacin, and cefazolin. Multi-drug resistance (MDR) was defined as tested and reported as non-susceptible to two or more of the preceding antimicrobial agents. Gram positive organisms tested and reported as resistant to oxacillin were reported as resistant to cephalothin and cefazolin. Reported antimicrobial resistance proportions were based on the actual number of isolates tested for each antimicrobial agent.

Microbiologically Appropriate Treatment Definition

A treated culture-confirmed CA-UTI was classified as having received a microbiologically appropriate treatment if the CA-UTI was treated with a drug to which the infecting uropathogens were reported as susceptible based on the CLSI Guidelines for the clinical interpretation of antimicrobial susceptibility testing results. A cephalexin treatment was considered to be microbiologically compatible if cefazolin antimicrobial susceptibility testing was performed and reported as susceptible.

Populations

Women

Between January 1, 1998 and December 31, 2005, a population of 318,499 KPNC women between the ages of 15 and 60 (median age at UTI 35.6 years) who had 397,174 primary UTI events (Figure 1) was identified. Thirty-eight percent (121,308) of these women were excluded due to incomplete information; all the UTI events in 73,653 women had membership data spanning less than one year before through 30 days after the beginning of their UTI treatment and an additional 47,655 women were missing a recorded treatment for all their UTI events. Women excluded for incomplete information were younger (median age at UTI, 33 years) than those remaining in our study (median age at UTI 38 years). An additional 20,800 (11%) women, those with no identified community-onset UTI, were excluded. The study population, therefore, consisted of 176,391 women (median age at study entry 37 years) with at least one primary treated CA-UTI; altogether these women had 205,677 CA-UTI (median age at UTI 38 years) (range of 1 – 5 UTI per woman) (Table 2).

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Complete Primary UTI

Of the 234,685 primary UTI with complete information that occurred from January 1, 1998 to December 31, 2005 (Figure 2), 54% (126,226) had a pretreatment urine culture performed and 34% (79,875) were microbiologically confirmed by a positive culture.

Two percent (4,799 UTI) of the primary UTI were hospital-acquired, 10% (23,316) were healthcare-associated and less than <1% (893) were of unknown onset (See Table 3 for onset definitions). UTI that were not identified as community-acquired were excluded from further analysis.

Community-acquired UTI

Eighty – eight percent (205,677 UTI) of the identified primary UTI (in 176, 391 women) were classified as community-acquired (Table 9). Antimicrobial treatment drug and urine culture submission practices were investigated in this population of women with a CA-UTI.

Sixty-five percent (134,240) of the CA-UTI in 121,743 women were classified as uncomplicated. Treatment outcome was evaluated in this population of previously healthy women.

Urine Cultures

From January 1, 1998 through December 31, 2005, 243,440 women, ages 15 – 60 years, submitted 507,125 urine specimens to the KP regional laboratory for culture and susceptibility testing. Forty-four percent (224,898) of these cultures, from 195,808 women, were diagnostic pretreatment urine cultures, those performed before treatment, if recorded, and within two days of an identified primary UTI event. Sixty – eight percent (152,314) of the diagnostic urine cultures were positive for one or two antimicrobial susceptibility tested uropathogens (Figure3).

Two percent (4,653) of the 224,898 diagnostic urine cultures were from women with no evidence of KPNC membership and 23% (50,965) had incomplete membership data. Without a record of continuous membership in the KPNC system for one year before the urine culture was obtained, insufficient information was available to determine whether the culture was from a UTI that was community-acquired or was associated with a hospital stay or a healthcare procedure exposure (Table3). Incomplete membership information also precluded an accurate determination of whether the patient had indications for a complicated UTI (Table 4). Cultures with incomplete KPNC membership were excluded from further analysis.

Eighty-six percent (144,854) of the 169,280 primary UTI cultures from the 147,835 women with complete membership information (those who were KP members for at least one year before and 30 days after their UTI event) were classified as community-acquired (Figure3). Sixty-eight percent (98,266) of the urine cultures from primary CA-UTI were reported as positive for one or two susceptibility-tested uropathogens.

From 1998 to 2005, we identified 98,266 positive diagnostic urine cultures from 89,397 women with a primary CA-UTI event (median age at UTI event, 37 years, and range of 1 to 5 cultures per woman). Treatment information was available for 71% (69,494) of these urine

cultures. The 98,266 positive diagnostic urine cultures were further classified by the UTI disease of the patient at the time of the UTI. Thirty-nine percent (38,560) were found to be from a CA-UTI that was complicated by recent antimicrobial treatment, pyelonephritis, pregnancy, diabetes, immune deficiency, or concurrent bacterial infection (CCA-UTI) (Table 4). The remaining sixty–one percent (59,706) of the cultures were associated with an UCA-UTI event.

Microbial etiology and uropathogen antimicrobial susceptibility was investigated in this population.

Community-acquired Uropathogens

Sixty-two different uropathogens (99,241 isolates) were identified and tested for antimicrobial susceptibility from the 98,266 CA-UTI-associated diagnostic urine cultures. Uropathogens isolated from UCA-UTI accounted for 61% of the laboratory sample of isolates while 39% were from CCA-UTI.

In 2001, the KPNC regional laboratory discontinued routine susceptibility testing and standardized reporting of *Staphylococcus saprophyticus*, a uropathogen estimated to account for 5% – 15% of UCA-UTI in young women [35, 103, 104] This procedural change resulted in a significant under-reporting of this organism from 2001 to 2005. Because the inclusion of those *Staphylococcus saprophyticus* isolates that received susceptibility testing would bias our etiology and antimicrobial susceptibility proportion estimates and temporal trends, the 1,222 *Staphylococcus saprophyticus* isolates were analyzed separately. Based on the 1,077 *Staphylococcus saprophyticus* that were isolated during 1998 – 2000 when routine reporting and testing occurred, *Staphylococcus saprophyticus* was estimated to accounted for 3.7% (95% CI 3.4 – 3.9%) of KPNC community-acquired uropathogens.

Among the 98,019 non-*Staphylococcus saprophyticus* community-acquired uropathogens, 85.6% (83,929 isolates) were identified as *Escherichia coli* (*E. coli*), 11.4% (11,478) were other gram negative rods and 2.7% (2,612) were gram positive uropathogens (Table 5). This population of organisms was used to estimate community-acquired uropathogen antimicrobial susceptibility proportions and trends.

Culture-confirmed Treated Community-acquired UTI

Thirty-four percent (69,494 CA-UTI) of the 205,677 CA-UTI with complete treatment and membership information were confirmed by a positive diagnostic urine culture (Figure 5). Of the 69,494 culture-confirmed CA-UTI in 64,896 women (median age at UTI 37.4 years, range 1 – 5 UTI per woman), 62% (43,055 CA-UTI in 41,318 women) were classified as UCA-UTI (Table 10).

Culture-confirmed CA-UTI for which treatment data were available represented 71% of all identified culture-confirmed primary CA-UTI. Those excluded due to lack of treatment information tended to be in younger women (median age at UTI 36.1 years), and were more likely to be complicated and to be caused by uropathogens other than *E. coli* than were the CA-UTI remaining in the study. CA-UTI caused by *E. coli* accounted for 88% of treated CA-UTI but only 80% of excluded CA-UTI. This difference in etiology resulted in a corresponding

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difference in the proportion of antimicrobial resistance between the two populations. Among uropathogens from the excluded CA-UTI, the proportion of pan-susceptible isolates was higher (risk difference [RD] 1.4%, 95% CI 0.7% to 2.0%) and the proportion with TMP/SMX resistance was lower (RD -4.4%, 95% CI -3.9% to -4.9%) than among uropathogens from CA-UTI with treatment information. At the same time, the proportions of isolates with ciprofloxacin resistance (RD 0.6%, 95% CI 0.4% to 0.8%), nitrofurantoin resistance (RD 2.3%, 95% CI, 1.9% to 2.7%) or cefazolin resistance (RD 0.4%, 95% CI 0.04% to 0.8%) were higher among uropathogens from excluded CA-UTI than from CA-UTI with treatment information.

One percent (693) of culture-confirmed CA-UTI received combination therapy and 3.4% (2,355) were treated with a drug other TMP/SMX, nitrofurantoin, cephalexin or ciprofloxacin. Treatment appropriateness was evaluated in the population of 66,446 culture-confirmed CA-UTI in 62,253 women (median age 37.5 years, range 1 – 5 CA-UTI per woman) who received mono-therapy with one of the four common treatment antimicrobials.

Among the 43,055 culture-confirmed UCA-UTI with treatment information, 302 were treated with combination therapy and 316 UCA-UTI were caused by more than one uropathogen: these 618 UCA-UTI were excluded from further analysis (Table 10). Treatment outcomes were investigated in the remaining 42,437 UCA-UTI in 40,754 women (median age at UTI 34.8 years), which were treated with a single antimicrobial agent and caused by a single uropathogen (range 1 - 4 UCA-UTI per woman). This study population represents 70% of all identified culture-confirmed UCA-UTI and over- represents *E. coli* infected UCA-UTI. Similar to the differences seen in the larger population of all CA-UTI, excluded UCA-UTI occurred in slightly younger women (< 1 year difference in median age at UCA-UTI) and were less likely to be caused by *E. coli* (RD -6.7%, 95% CI -6.1% to -6.7%). Among uropathogens from excluded UCA-UTI, the proportions with pan-susceptibility (RD -1.0%, 95% CI -0.2% to -1.8%) and with TMP/SMX resistance (RD -2.4%, 95% CI -1.8% to -3.0%) were lower, while the proportions with ciprofloxacin resistance (RD 0.6%, 95% CI 0.4% to 0.8%), with nitrofurantoin resistance (RD 2.7%, 95% CI 2.2% to 3.2%), and with cefazolin resistance (RD 0.9%, 95% CI 0.4% to 1.3%) were higher than in uropathogens from the UCA-UTI remaining in the study population.

Cephalexin mono-therapy was used to treat 15% (6,309 UCA-UTI) of the remaining 42,437 UCA-UTI. Among these cephalexin-treated UCA-UTI, 88% (5,569) were infected with *E. coli*. Seventy-three percent (4,076) of the *E. coli* isolates from these UCA-UTI were tested for susceptibility to both cephalothin and cefazolin. The effectiveness of cephalothin and cefazolin susceptibility testing to predict treatment outcomes was investigated in this population (Table13).

Chapter 4: Microbial Etiology and Antimicrobial Susceptibility of Community-acquired Uropathogens

Introduction

Empirical treatment of uncomplicated community-acquired urinary tract infections (UCA-UTI) in women is complicated by reports of increasing resistance to commonly prescribed antimicrobial agents. It is well known that the proportion of TMP/SMX resistance among *Escherichia coli* (*E. coli*), the leading pathogen causing urinary tract infections (UTI) in women, varies with geographic location within the USA as well as over time. The Infectious Diseases Society of America's (IDSA) evidence-based guidelines for empirical treatment of UCA-UTI in women recommend the replacement of their first line antimicrobial, TMP/SMX, with nitrofurantoin or ciprofloxacin in populations where the local prevalence of resistance to TMP/SMX among *E. coli* strains causing UCA-UTI exceeds 20%. An additional IDSA recommendation calls for the establishment of efficient systems to monitor resistance among uropathogens, especially *E. coli*, in local populations.

The most recent estimate of antimicrobial resistance among uropathogens from national US surveillance systems [9] [85] has suggested that in northern California the proportion of uropathogenic *E. coli* that are resistant to TMP/SMX had risen to over 20%. However, it is recognized that results from multi-site surveillance systems, as well as those from traditional cumulative antibiograms produced by hospital or regional laboratories, may be biased by over-representation of hospital-acquired and healthcare-associated isolates, as well as by isolates from patients with more severe disease or with complicated infections [101, 105]. In addition, while antibiograms produced by hospitals or regional laboratories may be stratified by ordering service or ward, they are rarely stratified by host demographic factors such as age or sex, or by severity of disease or site of infection. They will, therefore, include strains from men, children, and the elderly, as well as strains from infections other than UTI.

Large healthcare delivery systems with integrated administrative, laboratory, and pharmacy computer systems, such as the Kaiser Permanente Northern California Health Plan (KPNC), can cost-effectively provide the data necessary for less-biased estimates of current antimicrobial resistance prevalences in selected populations, such as women with UCA-UTI.

Here we report the distribution and antimicrobial susceptibility of bacterial uropathogens isolated from microbiologically investigated community-acquired UTI (CA-UTI) in female KPNC patients, ages 15 – 60 years. In addition, we test the hypothesis that the resistance of uropathogens to empirically prescribed antimicrobial agents is increasing over time.

Methods

Data from six KPNC administrative databases were used to identify women, ages 15 to 60 years old, who sought outpatient treatment within the KPNC system for community-acquired acute cystitis from January 1, 1998 through December 31, 2005. Protocols for subject identification and urinary tract infection classification are described in Chapter 3, Methods and

Populations. In brief, ICD-9 codes and positive urine culture results were used to identify urinary tract infection (UTI) events. Primary UTI events (defined as the first UTI in a calendar year with no other UTI events in the preceding 365 days) were identified and classified as community-acquired or as hospital/healthcare associated infections. The latter were subsequently excluded from additional analysis. Those UTI found to be community-acquired were further classified as uncomplicated or complicated based on host characteristics (Table 4).

The KPNC Laboratory Utilization Reporting System (LURS) was used to identify all routine urine cultures performed on KPNC women during the study period. Here we analyze laboratory results from diagnostic urine cultures, those performed before treatment, if recorded, and within two days of an identified primary CA-UTI event. A CA-UTI was classified as culture-confirmed by a positive urine culture if one or two uropathogens were identified to the species level and susceptibility testing was performed. During the study period all urine cultures and susceptibility testing were performed at the KPNC Regional Clinical Microbiology Laboratory using the broth microdilution method and interpreted by Clinical and Laboratory Standards Institute (CLSI) guidelines. Gram positive organisms testing resistant to oxacillin were classified as resistant to cephalothin and cefazolin. Non-susceptible isolates, those interpreted by CLIA guidelines as having intermediate or resistant susceptibility, were classified as resistant.

Statistical Analysis

Due to the changes in the KPNC protocol for the testing and reporting of *Staphylococcus saprophyticus* that were implemented in 2001, *Staphylococcus saprophyticus* results were analyzed separately. Antimicrobial resistance proportions were based on the actual number of isolates tested for each antimicrobial agent. The relationships between age and other factors of interest were examined by grouping women's age at onset of UTI into five age categories, 15 – 20 years, 21 – 30 years, 31- 40 years, 41 – 50 years and 51- 60 years. Although the large sample size for most comparisons significantly reduces random error, all comparisons of proportions were tested by the Chi-square 2-tailed test. Cuzick's test for trend, supplemented with visual inspection, was used to detect trends in etiology and antimicrobial resistance. To account for the fact that individual women could have had up to eight diagnostic primary UTI cultures (one per year) during the study period, all analyses were adjusted for clustering within the individual. Estimate ranges given in the text represent the robust cluster-adjusted 95% confidence interval around the population estimate. Relative risk estimates were calculated using a log-binomial or a modified Poisson regression model (GEE [106, 107])with robust errors adjusted for UTI disease (where appropriate), age-group, year of UTI onset, and clustering within the individual. All statistical analyses were performed using Stata, version 10.0 (StataCorp).

Results

Urine Cultures

From 1998 to 2005, we identified 98,266 positive diagnostic urine cultures from 89,397 women with CA-UTI (median age at UTI event, 37 years; range of 1 to 5 cultures per woman). Thirty-nine percent (38,560) of these cultures were from CA-UTI complicated by anatomical or surgical genitor-urinary abnormalities, pyelonephritis, pregnancy, diabetes, immune deficiency,

recent antimicrobial treatment, or a concurrent bacterial infection (CCA-UTI) (Table 4). The remaining sixty –one percent (59,706) of the cultures were associated with an UCA-UTI (Figure 3). The proportion of uropathogens isolated from UCA-UTI ranged from a low of 58% in 2005 to a high of 63% in 2003.

Etiology

Sixty-two different uropathogens (99,241 isolates) were isolated and tested for antimicrobial susceptibility from the 98,266 CA-UTI-associated diagnostic urine cultures identified (Figure 4).

Antimicrobial susceptibility testing and reporting of *Staphylococcus saprophyticus* at the KPNC regional laboratory underwent a dramatic change beginning in 2001, resulting in a significant under-reporting of this organism from 2001 to 2005. Based on the data from1998 - 2000, 3.7% (95% CI 3.4 % – 3.9%) of community-acquired uropathogens were identified as *Staphylococcus saprophyticus* (Figure 6). This uropathogen was 21% more likely to be isolated from UCA-UTI than from CCA-UTI, (RR 1.21 95% CI 1.06 – 1.37), and was more prevalent in younger women (Tables 5 & 6). From 1998 – 2000, 78.1% (95% CI 75.6 – 80.6%) of the 1,045 *Staphylococcus saprophyticus* isolates were susceptible to TMP/SMX, nitrofurantoin, ciprofloxacin and cefazolin. While antimicrobial resistance to nitrofurantoin or to ciprofloxacin was rare (less than 1%), 3.2% (95% CI 2.1 – 4.2%) of *Staphylococcus saprophyticus* were resistant to TMP/SMX and resistance to cephalexin could not be accurately estimated. A total of 1,222 *Staphylococcus saprophyticus* isolates were identified over the eight years of the study; these isolates were excluded from further analysis.

Among the 98,019 non-*Staphylococcus saprophyticus* uropathogens, enteric gram negative rods (97%) were the most common pathogens isolated from women with CA-UTI. *Escherichia coli* (*E. coli*) accounted for 86% (83,929 isolates) of the community-acquired isolates; 4.3% (4,241) were *Klebsiella pneumoniae* and 4.0% (3,939) were *Proteus mirabilis* (Table 5). Three percent of isolates were gram positive uropathogens: two percent (1,890) were *Enterococcus species* while fewer than 1% (712) were *Staphylococcus aureus* (4% of the *S. aureus,* 23 isolates, were MRSA).

As expected, the distribution of uropathogens varied with the UTI disease (Table 5 & Figure 6). *E. coli* was 4% more likely to be isolated from UCA-UTI (adjusted RR 1.04, 95% CI 1.03 – 1.05) than from CCA-UTI, while other enteric organisms, such as *Klebsiella* species*, Proteus* species and *Enterococcus,* were more often isolated from complicated disease. After adjusting for year and age at UTI, *Klebsiella* species were 43% (RR 1.43, 95% CI 1.35 – 1.51), *Proteus* species were 9% (RR 1.10, 95% CI 1.03 – 1.16), and *Enterococcus* species were 42% (RR 1.42 95% CI 1.30 – 1.56) more likely to be isolated from CCA-UTI than from UCA-UTI.

The risk of infection with a *Klebsiella species* (95% *Klebsiella pneumoniae*) steadily increased with age among women with both complicated and uncomplicated disease (p<0.001): women over 50 years were over twice as likely to be infected with a *Klebsiella species* than were

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women under 21 years (RR 2.29, 95% CI 2.06 – 2.55). No consistent age trends were detected for *E. coli*, *Proteus* species or *Enterococcus species*.

Antimicrobial Susceptibility

From 1998 – 2005, 95,597 uropathogens (98% of all uropathogens, 99.9% of *E. coli*, 97% of "Other" gram negative rods but only 22% of gram positive uropathogens) were tested for susceptibility to all four of the common treatment drugs: TMP/SMX, ciprofloxacin, nitrofurantoin and cefazolin (cefazolin susceptibility testing was used to estimate cephalexin susceptibility). The proportion of resistance to these antimicrobial agents varied by uropathogen (Tables 7 & 8, Figures 7&11), year (Figures 7, 8, &9) and UTI disease (Table 7, Figures 9&10) as well as by the age of the woman at the time of UTI onset (Figures 10& 11).

Seventy-one percent of all tested uropathogens (94% of gram positive uropathogens, 76% of *E. coli* but only 29% of "Other" gram negative rods) were found to be susceptible to all four common treatment drugs (pan-susceptible, PanS). Although the proportion of PanS isolates varied by year (range 69% - 73%), no consistent temporal trend was detected. While 80% of the *E. coli* isolated from UCA-UTI were PanS, only 70% of those from CCA-UTI were PanS. On the other hand, the proportion of non-*E. coli* uropathogens that were pan-susceptible did not vary significantly by UTI disease.

As expected, the proportion of uropathogens testing PanS varied by age with a range of 70% in women over 50 years to 75% in women under 21 years. Interestingly, while isolates from the youngest women in our study, those under 21 years old, were significantly more likely to be susceptible to all four treatment drugs, the proportion of PanS isolates did not vary significantly by age group among isolates from women ages 21 years and older. After adjusting for UTI disease and year, uropathogens from women, 21 years and older, were 10% (RR 1.10 95% CI 1.07 – 1.13) more likely to be resistant to at least one treatment drug than were isolates from women under 21.

Multi-drug resistance (MDR) (defined as resistance to two or more of the common treatment drugs: TMP/SMX, ciprofloxacin, nitrofurantoin and cephalexin (cefazolin susceptibility testing was used to estimate cephalexin susceptibility) remained infrequent in this population (5.4%, 95% CI 5.2 – 5.5) and was much more common among "Other" gram negative rods (OGNR) (15.6%) than it was among *E. coli*, (4.1%), or among gram positive uropathogens (GPC) (1.0%). Five percent of all uropathogens (4% of *E. coli*, 14% of OGNR, <1% of GPC)) were resistant to two drugs, 0.38% (377 isolates) were resistant to three drugs (all gram negative rods) and 0.02% (24 isolates, 20 *E. coli* isolates, 4 OGNR) were resistant to all four common treatment drugs.

The proportion of isolates resistant to treatment antimicrobials varied significantly by uropathogen. In general, resistance to common treatment antimicrobials remained low among gram positive cocci (Table 7, Figure 8). The major exception was resistance to ciprofloxacin; 10.6% of the 1,890 *Enterococcus* isolates tested resistant to ciprofloxacin.

Among the gram negative uropathogens, *E. coli* (88% of gram negative isolates) were significantly more likely to be resistant to TMP/SMX (RR 3.2, 95% CI 3.0 – 3.5), ciprofloxacin (RR 2.2, 95% CI 1.8 – 2.8) and to cephalothin (RR 1.7, 95% CI 1.6 – 1.8) than were other gram negative rods. Conversely, OGNR (22% of gram negative isolates) were more likely to be resistant to nitrofurantoin (RR 37.1%, 95% CI 35.2 – 39.2), and cefazolin (RR 3.1, 95% CI 3.0 – 3.3) than were *E. coli* isolates (Tables 7 & 8, Figure 7). Due to the high proportion of OGNR with nitrofurantoin resistance, these uropathogens were much more likely to be MDR than were *E. coli* isolates (adjusted RR 3.7, 95% 3.5 – 4.0).

TMP/SMX Resistance

From 1998 – 2005, 17.6% of the 95,811 tested isolates were resistant to TMP/SMX (19.2% of *E. coli*, 6.1% of OGNR, and <1% of GPC) (Table 7). Although TMP/SMX resistance among all CA-UTI isolates decreased significantly from the highest proportions seen during the first two years of the study, we detected no sustained temporal trend in TMP/SMX resistance over the eight years of the study (Figures 7, 8 & 9). Among *E. coli* isolates, TMP/SMX resistance decreased from a high of 21.0% (95% CI 20.2 – 21.9) in 1998 to a low of 18.1% (95% CI 17.4 – 18.8) in 2003, returning to 19.7% (95% CI 19.0 – 20.4) by 2005.

Resistance to TMP/SMX varied with host age group (Figures 10 & 11); uropathogens from women 21 years and older were 16% more likely to be resistant to TMP/SMX than were those from women under 21 years of age (RR1.16, 95% CI 1.12 – 1.21).

Clinically significant differences in the proportion of resistance to TMP/SMX were found by UTI disease and by infecting organisms (Tables 7 & 9 and Figures 7, 8 & 9). From 1998 – 2005, 14.3% of uropathogens (15.5% of *E. coli* isolates, 4.6% of non- *E. coli* isolates,) from UCA-UTI were resistant to TMP/SMX, while among CCA-UTI the proportion with resistance to TMP/SMX was 22.7% (25.2% in *E. coli* isolates, 7.4% in non- *E. coli* isolates). Uropathogens from CCA-UTI were 58% (RR 1.58, 95% CI 1.53 – 1.62) more likely to be resistant to TMP/SMX than were uropathogens from UCA-UTI, and *E. coli* isolates were over three times more likely to be resistant to TMP/SMX than were non-*E. coli* isolates (RR 3.39, 95% CI 3.1 – 3.6).

Co-resistance to ciprofloxacin, nitrofurantoin or cefazolin occurred in 22% (3,680) of the 16,839 TMP/SMX resistant isolates (20% among *E. coli* and 67% among OGNR) and was more common ($p ≤ 0.001$) in isolates from CCA-UTI (23%) than in isolates from UCA-UTI (21%). Fourteen percent (2,251) of TMP/SMX resistant *E. coli* were co-resistant to cefazolin, 5% (770) were co-resistant to ciprofloxacin and 3% (493) were co-resistant to nitrofurantoin. Twenty-one percent (136) of TMP/SMX resistant OGNR were co-resistant to cefazolin, 4% (30) were co-resistant to ciprofloxacin and 63% (402) were co-resistant to nitrofurantoin.

Ciprofloxacin Resistance

Although resistance to ciprofloxacin, 1.5% (1.4% of *E. coli*, 1.9% of non-*E. coli* isolates), remained low in the 97,616 isolates tested (Table 7), a steady increase in ciprofloxacin resistance over time was detected. Ciprofloxacin resistance ranged from a low of 0.75% (95% CI, 0.59 - 0.92%) in 1998 to a high of 2.58% (95% CI, 2.32 – 2.85%) in 2005. Interestingly, this sustained

temporal trend of increasing resistance (p <0.001) was seen only among *E. coli* isolates (Figure 7). Resistance to ciprofloxacin was high among *Enterococcus* isolates 10.6% (95% CI 9.0 – 12.2%) and an unexpected temporal trend of decreasing ciprofloxacin resistance (p <0.001) was detected. The proportion of *Enterococcus* that were resistance to ciprofloxacin fell from a high of 17.9% in 1998 to 5.6% in 2005.

Ciprofloxacin resistance among *E. coli* uropathogens increased steadily with the age group of the woman. *E. coli* isolates from CA-UTI in women 21 years and older were 16% more likely to be resistant to ciprofloxacin than were those from CA-UTI in women under 21 years of age (RR1.16, 95% CI 1.12 – 1.21) and *E. coli* from CA-UTI in women over 50 years of age were over twice as likely to be ciprofloxacin resistant as were those from women under 21 years old (adjusted RR 2.34, 95% CI 1.88 – 2.93). This steady trend of increasing resistance with age was observed only among *E. coli* isolates (Figure11).

A majority (63%) of ciprofloxacin resistant uropathogens (71% of 1,201 *E. coli*, 24% of 250 Non- *E. coli* isolates) were resistant to at least one other common treatment antimicrobial. Sixty-two percent (801) of the 1,289 ciprofloxacin resistant (CiproR) uropathogens tested for susceptibility to TMP/SMX were found to be resistant to TMP/SMX (TSR) as well. Uropathogens that were resistant to TMP/SMX were over 8 times more likely to be resistant to ciprofloxacin than were those isolates that were susceptible to TMP/SMX (adjusted RR 8.6, 95% CI 7.6 – 9.8). Fifty-seven percent (459) of the TSR-CiproR uropathogens were isolated from CCA-UTI and 96% (770) were *E. coli*. Thirteen percent (100) of the TSR-CiproR isolates were found to be resistant to nitrofurantoin (NitroR). Sixty-five percent of these TSR-CiproR-NitroR pathogens were isolated from CCA-UTI, 75% were *E. coli* and 24% were also resistant to cefazolin.

Nitrofurantoin Resistance

Nitrofurantoin resistance was observed in 8.8% (95% CI 8.6 – 8.9%) of the 97,694 uropathogens tested over the eight years of the study, rising from a low of 7.6% (95% CI 7.1 – 8.1%) in 1998 to a high of 11.0% (95% CI: 10.48 – 11.53%) in 2004 (Table 7 & 9, Figures 7, 8 & 9).

As expected, resistance to nitrofurantoin varied dramatically by uropathogen species (Tables 7 & 9, Figures 7, 8 & 9). Importantly nitrofurantoin resistance remained uncommon among gram positive uropathogens (0.4%) and among *E. coli* isolates (1.7%). "Other" gram negative rods (63% were nitrofurantoin resistant) were much more likely to be resistant to nitrofurantoin (RR 37.9, 95% CI 35.9 – 39.9). Although no temporal trends in nitrofurantoin resistance were observed among isolates of *E. coli, Staphylococcus or Enterococcus*, "Other" gram negative rods (11.7% of isolates) displayed a dramatic temporal trend of increasing nitrofurantoin resistance (p ≤0.001), going from 53.2% (95% CI 50.3% - 56.1%) in 1998 to 76.8% (95% CI 74.8-78.8%) by 2005 (Figure 7). While this trend can be partially explained by an increased frequency of isolating those organisms intrinsically resistant to nitrofurantoin (*Morganella*, *Proteus* and *Providencia* species) (3.7% of isolates in 1998, 4.2% in 2005), increasing resistance to nitrofurantoin among *Klebsiella pneumonia* (the second most commonly isolated uropathogen) was driving this trend. While the proportion of all CA-UTI caused by

Klebsiella pneumonia remained fairly stable over the study period, 4.3% (range 3.8% in 2000 to 4.8% in 2005), the proportion of *Klebsiella pneumonia* isolates that were resistance to nitrofurantoin increased from 21% in 1998 to 34% by 2003 and then rose sharply to over 70% in 2004 and 2005. The sharp increase observed during 2004 and 2005 was seen across all KPNC regions and age groups of women. Nitrofurantoin resistance among *Klebsiella pneumoniae* isolates did not vary by age group.

A consistent sustained trend in increasing nitrofurantoin resistance with age was observed among *E. coli* isolates ($p \leq 0.001$). *E. coli* from women ages 51 – 60 years were 33% more likely to be resistant to nitrofurantoin as were *E. coli* from women 15 – 21 years old (RR 1.33, 95% CI 1.11 – 1.60. No age trend in nitrofurantoin resistance was observed among gram positive uropathogens.

Co-resistance was high, 28%, among the 8,546 nitrofurantoin resistant uropathogens; 47% (675) of nitrofurantoin resistant *E. coli* and 24% (1,690) of nitrofurantoin resistant OGNR were also resistant to TMP/SMX, ciprofloxacin and/or cefazolin. Thirty-four percent (493) of nitrofurantoin resistant *E. coli* were co-resistant to TMP/SMX, 18% (262) to cefazolin and 8% (121) to ciprofloxacin, while of 19% (1,352) of nitrofurantoin resistant OGNR were co-resistant to cefazolin, 6% (493) to TMP/SMX, and <1% (46) to ciprofloxacin. Co-resistance was more common ($p =0.001$) in isolates from CCA-UTI (30%) than it was in those from UCA-UTI (26%).

Cephalexin Susceptibility

Cephalexin susceptibility is rarely tested outside of research settings because the CLSI has not set clinical interpretative guidelines for this antimicrobial agent. CLSI currently recommends the use of in vitro cephalothin testing to predict in vivo susceptibility to cephalexin. Most clinical laboratories in the U.S. have adopted automated testing systems that include susceptibility testing of cephalothin and cefazolin or, more recently, cefazolin alone. Studies from Canada and Taiwan [18, 108] suggest that in vitro testing of cephalothin by automated methods may significantly over state the nonsusceptibility of cephalexin, while cefazolin testing was found to understate the nonsusceptibility of cephalexin. The KPNC Central Laboratory discontinued routine testing of uropathogens for cephalothin susceptibility in 2004 and currently relies on the results of cefazolin testing to infer susceptibility to cephalexin.

Cephalothin Resistance

From 1998 – 2003 the proportion of community-acquired uropathogens that tested resistant to cephalothin among was high, 33.5% (95% CI 33.2 – 33.8%) (35.5% among *E. coli* isolates, 20.8% among "Other" gram negative rods, and 4.2% among gram positive uropathogens). A consistent temporal trend of decreasing resistance to cephalothin ($p \leq 0.001$) was found among uropathogenic gram negative rods: cephalothin resistance among *E. coli* isolates ranged from 42.4 % in 1998 to 29.1% in 2003, while cephalothin resistance among OGNR ranged from 23.8% in 1998 to 18.8% in 2003. Uropathogens isolated from women with CCA-UTI were 13% (RR 1.13, 95% CI 1.11 – 1.16) more likely to be resistant to cephalothin than were those isolated from women with UCA-UTI. No age trends were detected in the proportion of isolates that were resistant to cephalothin.

Cefazolin Resistance

The proportion of uropathogens testing resistant to cefazolin, 7.0% (95% CI 6.8 – 7.2%) (5.6% among *E. coli* isolates, 17.6% among "Other" gram negative rods and 4.1% among gram positive cocci), was significantly lower than the proportion testing resistant to cephalothin and displayed a steady decline over the eight years of our study, from 9.2% in 1998 to 5.8% in 2005. A significant sustained trend toward decreasing cefazolin resistance was observed only among *E. coli* isolates ($p \leq 0.001$), ranging from a high of 8.0% (95% CI 7.4 – 8.5) in 1998 to a low of 3.7% (95% CI 3.3 – 4.0) in 2004. Although the proportion of "Other" gram negative rods that were resistance to cefazolin decreased over the study period, from a high of 19.4% in 1999 to a low of 16.8% in 2005, no consistent significant temporal trend was detected.

Unlike resistance to cephalothin, "Other" gram negative rods were over three times as likely to be resistant to cefazolin as were *E. coli* isolates (RR 3.11, 95% CI 3.0 – 3.26).

Isolates from CA-UTI in women 31 – 40 years old were the most likely to be resistant to cefazolin. No sustained trend of increasing resistance with age was observed.

A majority of the 6,707 cefazolin resistant uropathogens (58%) were co-resistance to TMP/SMX, nitrofurantoin or ciprofloxacin. Forty-eight percent (2,251) of cefazolin resistant *E. coli* were co-resistant to TMP/SMX, 6% were co-resistant to nitrofurantoin and 4% were co-resistant to ciprofloxacin. In contrast, among the 1,966 cefazolin resistant "Other" gram negative rods, co-resistance to nitrofurantoin was most common, 69%, and only 7% were co-resistant to TMP/SMX and less than 1% were co-resistance to ciprofloxacin.

Uropathogens isolated from women with CCA-UTI were 30% (RR1.30, 95% CI 1.24 – 1.37) more likely to be resistant to cefazolin than were those isolated from women with UCA-UTI.

UTI Disease

Although microbial etiology varied by UTI disease (see Etiology), we did not find a significant difference in the diversity of etiological agents; 50 species of uropathogens were isolated from UCA-UTI while 52 species were isolated from CCA-UTI and *E. coli* accounted for over 80% of uropathogens in both populations.

Uropathogens causing complicated UTI were significantly more resistant to common treatment antimicrobials (adjusted RR 1.37, 95% CI 1.34-1.40) than were those causing uncomplicated UTI. They were 58% more likely to be resistant to TMP/SMX (RR 1.58, 95% CI 1.53– 1.62), 54% more likely to be resistant to ciprofloxacin (RR 1.54, 95% CI 1.39 - 1.71), 18% more likely to be resistant to nitrofurantoin (RR 1.18, 95% CI 1.13 – 1.23), 30% more likely to be resistant to cefazolin (RR1.30, 95% CI 1.24 – 1.37) and 53% more likely to be multi-drug resistant (RR1.53, 95% CI 1.45 – 1.62) when come to uropathogens from UCA-UTI.

The IDSA empirical treatment guidelines for UCA-UTI recommend that routine mechanisms be developed to assess the antimicrobial susceptibility of uropathogens from uncomplicated disease in local communities in order to modify their guidelines if the prevalence

of resistance to TMP/SMX among *E. coli* isolates from women with UCA-UTI exceeds 20%. In Table 8, we provide the 1995 antimicrobial susceptibility data for uropathogens from woman with CA-UTI stratified by UTI disease. Resistance to TMP/SMX among *E. coli* from women with UCA-UTI remains below the critical value of 20%.

Discussion

This study demonstrates that electronic data can be used to provide current information on trends in the microbial etiology and the antimicrobial susceptibility of uropathogens causing community-acquired urinary tract infections in a large well defined, geographically localized population. In addition, we have shown that existing electronic data can be used to characterize urine culture isolates from a laboratory database by demographic and clinical status, thus providing a less biased estimate of the antimicrobial resistance of uropathogens from patients with UCA-UTI and other specific populations of interest.

Our study confirms that, as expected, the distribution of organisms infecting woman with culture-confirmed CA-UTI in the KPNC population remained stable over the eight years of our study (Figure 6) and was broadly consistent with earlier reports from the U.S. and Canada [9, 11] and Europe [89, 104].

Importantly, our data found that the steep increases in the proportions of uropathogens resistant to TMP/SMX or to first generation cephalosporins that were observed during the 1990s have not continued into the new millennium. In the KPNC population, resistance to these antimicrobials peaked in 1998 and 1999. On the other hand, we did observed a small but steady and significant increase in the proportion of gram negative uropathogens that were resistance to ciprofloxacin throughout the eight years of our study.

Similar to the findings of a recent population-based study of pyelonephritis performed in the state of Washington [109], we found that the proportion of uropathogens resistant to TMP/SMX decreased during the study period among both complicated and uncomplicated UTI and among both *E. coli* isolates and other uropathogens. However, no consistent temporal trend of decreasing resistance was detected. Overall resistance to TMP/SMX among all uropathogens continued below the 20% critical value over the eight years of our study, while among *E. coli* uropathogens TMP/SMX resistance had dropped below the 20% critical value by 2001. Importantly, our disease classification algorithm (Table 4) provided a method to identify a population of CA-UTI, those classified as uncomplicated, in which TMP/SMX resistance among all uropathogens remained at or below 15% throughout the study, and ranged from 14% to17% among *E. coli* uropathogens.

Surprisingly, a steady trend of decreasing resistance to the first generation cephalosporins, cephalothin and cefazolin was observed among all uropathogens. We found that among uropathogenic *E. coli,* cephalothin resistance decreased from 42.4 % in 1998 to 29.1% in 2003, and cefazolin resistance decreased from 8% in 1998 to less than 4% by 2005. This unexpected finding was mirrored by a similar trend of decreasing resistance to ampicillin (p <0.001) among these uropathogens. Ampicillin resistance decreased from 47% in 1998 to 40% by 2005. This finding is in keeping with the results from our smaller, population-based cross-

sectional study performed in the same geographic area, which found that cephalothin resistance among *E. coli* isolated from women with UCA-UTI decreased from 34% in 2003 to 28% in 2005 [44]. On the other hand, our results are in contrast to those of Czaja et al who found that cephalothin resistance increased among *E. coli* isolated from patients with pyelonephritis from 34% in 1997 to 49% in 2001 [109].

Although nitrofurantoin resistance remains uncommon (<3%) in *E. coli* and gram positive uropathogens, it is very common (63%) in the 11% of uropathogens identified as non-*E. coli* gram negative rods. Thirty-five percent of these isolates were uropathogens that are considered to be intrinsically resistant to nitrofurantoin and most of the others, such as *Serratia, Enterobacter* and *Klebsiella* species, have become highly resistant.

Although ciprofloxacin resistance remained low in our population of uropathogens (1.5%), we have documented a steady increase in resistance among *E. coli* uropathogens. By 2005, ciprofloxacin resistance among *E. coli* isolates had reached 2.8%, 2% among UCA-UTI and 3.4% among CCA-UTI. Importantly, we found that ciprofloxacin resistance is mainly observed in uropathogens that are resistant to at least one other antimicrobial.

We found that in northern California in 2005, 16% of the *E. coli* and 4% of the "Other" gram negative rods that were causing uncomplicated community acquired UTI were resistant to TMP/SMX, 2% of *E. coli* and 62% of OGNR were resistant to nitrofurantoin, 4% of *E. coli* and 15% of OGNR were resistant to cefazolin, and 2% of *E. coli* and <1% of OGNR were resistant to ciprofloxacin.

The effectiveness of empirical TMP/SMX treatment of women with UCA-UTI in populations where the estimated prevalence of resistance among *E. coli* uropathogens falls in the 10 – 20% range is unknown. Therefore these data will be used in conjunction with treatment antimicrobial use, treatment appropriateness, and treatment outcome data from Chapter 5 to investigate this question and to inform the development of up-to-date treatment guidelines for UCA-UTI in women in the KPNC health maintenance system.

This study has notable advantages over large national surveillance systems and traditional facility-specific antibiograms for estimating the proportions of UCA-UTI –causing uropathogens that are resistant to commonly prescribed antimicrobials. KPNC provided a large well-defined population representative of women in northern California. All uropathogen identification and susceptibility testing were performed at a single facility. Electronic linking of existing administrative databases enabled the cost-effective characterization and subsequent analysis of urine cultures diagnostic of CA-UTI. The large number of well-characterized uropathogen isolates available for analysis allowed us to provide more precise estimates of the antimicrobial resistance proportions and trends needed to tailor nationwide guidelines to our local population.

Limitations of the laboratory data result from the retrospective and longitudinal nature of the study. These limitations include the possibility of undisclosed changes in laboratory protocols which could distort temporal trends in the data. In this analysis we did not limit our population to the smaller population of CA-UTI for which we had treatment data. It is possible, therefore, that some of our isolates were collected after the start of antimicrobial treatment.

In conclusion, our data demonstrate that the etiology of CA-UTI among women, ages 15 – 60 years, remains stable and that over 70% of all uropathogens (76% of *E. coli*) remain susceptible to all of the common treatment antimicrobials, TMP/SMX, nitrofurantoin, cephalexin and ciprofloxacin. We have also shown that susceptibility to TMP/SMX and β-lactam drugs increased, while susceptibility to ciprofloxacin among *E. coli* uropathogens and susceptibility to nitrofurantoin among non-*E. coli* gram negative uropathogens decreased during the eight years of our study.

Chapter 5: Treatment and Treatment Outcomes in Community-acquired Urinary Tract Infections

Introduction

Practitioners can not wait the current 2 – 4 day turn-around time required to receive the results of a urine culture before prescribing antimicrobials to treat women with symptomatic community-acquired urinary tract infections (CA-UTI). They are, therefore, dependent on evidence-based medicine to guide their empirical treatment choices. Although the current Infectious Diseases Society of America (IDSA) treatment guidelines maintain that a short course of trimethoprim-sulfamethoxazole (TMP/SMX) remains the first line treatment for acute uncomplicated bacterial cystitis, treatment with nitrofurantoin or ciprofloxacin is suggested in geographic regions in which a high proportion of *Escherichia coli (E. coli)* uropathogens from uncomplicated CA-UTI (UCA-UTI) are resistant to TMP/SMX [56]. What constitutes a clinically significant high proportion of resistance varies among experts. The IDSA guidelines recommended a range of 10 – 20% as the appropriate threshold for changing empirical treatment to nitrofurantoin or ciprofloxacin [56] but this suggested threshold was not based on evidence [101]. In many populations, resistance to TMP/SMX lies within this range of 10% – 20%, leaving practitioners without clear guidance. Furthermore, choosing a replacement drug is not straightforward. The use of nitrofurantoin is complicated by lower cure rates, extremely poor tissue penetration and low blood levels, longer treatment regimens, intrinsic resistance among non-*E. coli* gram negative uropathogens, and the frequency of associated gastrointestinal upset and other side effects, especially acute and chronic pulmonary syndromes [56, 101, 110]. The prevalence of resistance to beta-lactam drugs, such as cephalexin, and their reduced efficacy when compared with TMP/SMX, nitrofurantoin or ciprofloxacin, is thought to preclude their usefulness as empirical treatment. In addition, there is a growing awareness of the "collateral damage", which that is associated with the use of cephalosporins and quinolone drugs, such as the disturbance of normal flora and the selection of and colonization or infection with antibiotic resistant organisms or *Clostridium difficile* [6, 7]. The use of ciprofloxacin has been associated with the development of fluoroquinolone resistance in the community, the emergence of plasmid – mediated resistance mechanisms and resultant loss of effectiveness for treatment of more serious disease [79-82, 111, 112].

Unfortunately, the laboratory data needed to determine what proportion of *E. coli* uropathogens from UCA-UTI are resistance to TMP/SMX in specific populations are usually not available. Practitioners, therefore, must rely on reports from national surveillance systems or traditional local antibiograms, which tend to over-represent complicated-UTI, resulting in inflated estimates of resistance. Although the results from the latest large surveillance studies suggest that the proportion of uropathogens in the San Francisco Bay region that are resistant to TMP/SMX is continuing to rise and has exceeded the threshold for change [10, 11], the laboratory results from the KPNC cohort reported in Chapter 4 as well as the results of our smaller cross-sectional study reported in Chapter 7, suggest that, by 2005, the prevalence of resistance to TMP/SMX among *E. coli* isolates from UCA-UTI had stabilized at approximately 16%.

International and U.S. nationwide studies [5, 17, 113, 114] have suggested that despite IDSA guidelines that recommend restricting the use of fluoroquinolone drugs to the treatment of severe UTI, the use of ciprofloxacin for treatment of UCA-UTI is continuing to rise. Studies are needed to examine how physicians in areas with higher reported prevalences of TMP/SMX resistance are changing their treatment prescribing practices and what effect these changes are having on treatment outcomes and treatment appropriateness in their patients and on the antimicrobial resistance within their communities. In addition, further study is needed to evaluate the effectiveness of TMP/SMX treatment in populations where 10% - 20% of the *E. coli* that cause UCA-UTI are resistant to TMP/SMX.

To investigate how practitioners are responding to IDSA guidelines and reports of high TMP/SMX resistance prevalences and to help clarify the selection bias inherent in the use of routine laboratory data to formulate local antibiograms, we report treatment and microbiological investigation practices for CA-UTI in female members of the Kaiser Permanente Northern California Health Plan (KPNC). In addition, we examine the microbiological compatibility of antimicrobial treatment among culture-confirmed CA-UTI that were treated with one of the four common treatment drugs To begin to understand how changing treatment practices and antimicrobial resistance are affecting treatment outcomes, we also report the short-term (30 day) clinical outcome among women with acute UCA-UTI.

Methods

Secondary electronic data were used to identify all community-acquired primary UTI events in Kaiser Permanente Northern California Health Plan women, ages 15 to 60 years old, for which treatment and membership data were available. Protocols and definitions used for subject identification, urinary tract infection classification, empirical treatment identification, and treatment outcomes are described in Chapter 3. In brief, ICD-9 codes and positive urine culture results were used to identify primary urinary tract infection events in study women. Primary UTI events without a complete record of membership in KPNC as well as those without a record of treatment on or within two days following the UTI date were excluded from these analyses. Primary CA-UTI that received treatment were further classified as complicated or uncomplicated based on host characteristics (Table 4). Appropriate treatment was defined as the prescription of an antimicrobial drug to which the infecting uropathogens were susceptible. As noted in Chapter 4, cefazolin susceptibility testing is not performed by the KPNC central laboratory; therefore the results of cefazolin susceptibility testing were used as proxy for susceptibility to cephalexin. Treatment failure was defined as an additional use of the KPNC healthcare system for the primary CA-UTI within 30 days of the UTI treatment record.

Statistical Analysis

Treated CA-UTI with complete membership information were examined for trends in treatment, appropriateness of treatment, and microbiological investigation practices over the eight years of the study. Thirty-day treatment outcome was assessed among treated UCA-UTI only. Complicated CA-UTI were excluded from these analyses because significant heterogeneity in treatment outcomes was observed among women with various complicating conditions (data not shown). In addition, a reasonable likelihood exists that our treatment failure algorithm may overestimate treatment failure in some women with complicated CA-UTI (e.g.

those with pyelonephritis or pregnancy) who may be seen for additional follow-up during the risk period, thereby, generating an additional UTI-related ICD-9 code, whether or not their treatment was successful.

The relationship between age and other factors of interest were examined by grouping women's age at UTI into five age categories, 15 – 20 years, 21 – 30 years, 31- 40 years, 41 – 50 years and 51- 60 years. Regional effects were estimated by grouping the 51 KPNC treatment sites into 14 regions. Antimicrobial treatment was classified into six categories: mono-therapy with trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, nitrofurantoin, cephalexin, or "other" antimicrobial, and combination therapy with multiple antimicrobials.

Although the large sample size for most comparisons significantly reduces random error, all comparisons of proportions were tested by the Chi-square 2-tailed test. Visual inspection and Cuzick's test for trend were used to detect trends in antimicrobial therapy and treatment failure. To account for the fact that individual women could have had up to eight primary UTI (one per year) during the study period, all analyses were adjusted for clustering within the individual. Robust confidence intervals adjusted for clustering were reported as a measure of the precision of our estimates.

Relative risks were estimated using multivariable log-binomial or Poisson regression (GEE [106, 107]) with robust errors, adjusting for year of UTI diagnosis, region (where appropriate), age group, and clustering within the individual. Statistical interactions between age categories and treatment antimicrobials were investigated within the treatment failure regression model. None were detected (data not shown). All statistical analyses were performed using Stata, version 10.0 (StataCorp).

Results

Community-acquired UTI

Between January 1, 1998 and December 31, 2005, we identified 205,677 CA-UTI with complete membership and treatment information in 176,391 women (range 1 – 5 CA-UTI per woman, median age at UTI 37.9 years) (Figure2). Fourteen percent of the CA-UTI were in women ages 15 – 20, 21% in women ages 21 – 30, 23% in women ages 31 – 40, 24% in women ages 41 – 50 and 19% (38,558) in women ages 51 – 60 years (Table 9).

Thirty-five percent (71,437) of the CA-UTI were classified as complicated CA-UTI (CCA-UTI). The proportion of CA-UTI classified as complicated varied over the study period from a low of 31% in 1998 to a high of 38% in 2005. As expected, women with CCA-UTI were older (median age at UTI 41 years) than those with UCA-UTI (median age at UTI 36 years) (Table 9).

Treatment of Community-acquired UTI

Practitioners prescribed 37 different antimicrobial agents (1 - 3 different drugs per CA-UTI) to patients within two days of their CA-UTI event. Ninety-six percent (97% of UCA-UTI,

94% of CCA-UTI) events were treated with one of four common treatment drugs: TMP/SMX (48%), ciprofloxacin (27%), nitrofurantoin (10%), and cephalexin (12%) (Table 9).

Choice of treatment drug varied significantly by year (Figures 12 & 15), by age group (Figure 13), by Kaiser region (data not shown), and, mostly strikingly, by UTI disease (Figures 14 &15).

The proportion of CA-UTI treated with TMP/SMX steadily decreased over the eight years of the study, from 56% during 1998 (61% of UCA-UTI, 43% of CCA-UTI) to 41% (47% of UCA-UTI, 30% of CCA-UTI) in 2005, while the proportion treated with ciprofloxacin rose continuously from 16% in 1998 (13% of UCA-UTI, 24% of CCA-UTI) to 35% (30% of UCA-UTI, 44% of CCA-UTI) in 2005 (Figures 12 &15).

Unlike treatment with TMP/SMX and ciprofloxacin, the proportion of CA-UTI treated with cephalexin and nitrofurantoin showed no sustained temporal trends and varied only minimally by UTI disease. CA-UTI treatment with cephalexin was most common during the first two years of the study. Approximately 14% of CA-UTI during 1998 and 1999 and 11-12% of CA-UTI from 2000 through 2005 were treated with cephalexin, while the proportion of CA-UTI treated with nitrofurantoin varied between 9 and 11% over the study period.

Practitioners were more likely to prescribe TMP/SMX or cephalexin to younger women and ciprofloxacin to older women. The likelihood of mono-therapy with ciprofloxacin increased steadily with the increasing age of the woman (Figure 13). The proportion of CA-UTI treated with ciprofloxacin increased from 13% of CA-UTI (10% of UCA-UTI, 23% of CCA-UTI) in women younger than 21 years (baseline) to 35% (29% of UCA-UTI, 41% of CCA-UTI) in women over 50 years (RR 2.28, 95% CI 2.21 – 2.37). Conversely, TMP/SMX and cephalexin mono-therapy steadily decreased with the age of the woman. Fifty-six percent of CA-UTI (60% of UCA-UTI, 42% of CCA-UTI) in women younger than 21years (baseline) were treated with TMP/SMX and 20% (21% of UCA-UTI, 18% of CCA-UTI) were treated with cephalexin, while only 43% of CA-UTI (49% of UCA-UTI, 35% of CCA-UTI) in women over 50 years were treated with TMP/SMX (RR 0.83, 95% CI 0.82-0.84) and just 10% (10% of UCA-UTI, 9% of CCA-UTI) were treated with cephalexin(RR 0.54, 95% CI 0.52-0.56).

While UCA-UTI (across all age groups) were most commonly treated with TMP/SMX (54% with TMP/SMX, 22% with ciprofloxacin), CCA-UTI were treated slightly more often with ciprofloxacin (35.9%) than with TMP/SMX (35.7%). TMP/SMX remained the most common mono-therapy for CCA-UTI in women ages 15-40 years (TMP/SMX 36%, ciprofloxacin 31%), while CCA-UTI in women ages 41-60 years were more often treated with ciprofloxacin (ciprofloxacin 40%, TMP/SMX 36%,). After adjusting for age, region and year, the likelihood of a CCA-UTI receiving mono-therapy with ciprofloxacin was 54% greater than if the CA-UTI was uncomplicated (RR 1.54, 95% CI 1.51-1.56).

Microbiological Investigation

To understand how KPNC clinicians' urine culture ordering practices may have biased the sample of culture-confirmed CA-UTI available for further analysis, we investigated which CA-UTI received a routine urine culture with susceptibility testing.

Fifty-three percent of CA-UTI (58% of CCA-UTI, 50% of UCA-UTI) were microbiologically investigated with a pretreatment urine culture and 34 % (37% of CCA-UTI, 32% of UCA-UTI) were microbiologically confirmed by a positive urine culture (Table 10). The probability that a CA-UTI would be microbiologically investigated varied significantly by year, region (data not shown), patient age group, treatment, and UTI disease. Microbiological investigation of CA-UTI increased over time, rising from 47.3% in 1998 to 56.6% in 2005. After adjustment for age group, UTI disease, treatment, and region, CA-UTI were 15% (RR 1.15, 95% CI 1.13 – 1.17) more likely to be cultured in 2005 than they were in 1998. While a steady rise in the proportion of UCA-UTI receiving urine cultures (range 43% in 1998 to 54% in 2005) was detected, no such temporal trend was detected among CCA-UTI (range 56% in 2001 to 60% in 2005). Interestingly, CA-UTI in women under 21 years of age ,the age group most likely to have a pretreatment urine culture performed, were 32% more likely to be cultured than were those in women 21 years and older (RR 1.32, 95% CI 1.31 – 1.34). CA-UTI treated with a drug other than TMP/SMX were 17% more likely to have been cultured than those treated with TMP/SMX (RR 1.17, 95% CI 1.16 – 1.18) and CCA-UTI were 14% more likely to have been cultured than UCA-UTI (RR 1.14, 95% CI 1.13– 1.15). Treatment failure was more common (22.6%) among culture-confirmed UCA-UTI than it was among those UCA-UTI not confirmed by a positive urine culture (15.5%).

Only 63% of the 109,484 microbiologically investigated CA-UTI were culture-confirmed by positive a pre-treatment culture. This proportion did not vary significantly by UTI disease (63.6% of UCA-UTI vs. 63.3% of CCA-UTI, $p = 0.4$). Therefore, our laboratory sample of uropathogens from treated CA-UTI over represents uropathogens from CA-UTI in women 15 – 20 years old, women with CCA-UTI and women who were not treated with TMP/SMX. In addition, the laboratory sample of uropathogens from UCA-UTI over represents UCA-UTI that subsequently failed treatment.

Treatment Appropriateness

Among the 66,446 culture-confirmed CA-UTI from 62,253 women (median age 37.5 year, range 1 – 5 CA-UTI) who received mono-therapy with one of the four most common treatment antimicrobials, fewer than 1% (358) were infected with a uropathogen that was not tested for susceptibility to the treatment drug received; 9% (6,078) received inappropriate treatment with a drug to which the infecting organism was resistant and 90% (60,010) received a microbiologically appropriate treatment drug. The proportion of cases receiving inappropriate treatment did not vary significantly by UTI disease ($p = 0.51$) and was highest during the first three years of the study. By 2001, inappropriate treatment had dropped from 1998 -2000 levels of 10.5% (range 9.7 – 11.0%) to 8.7% where it remained for the last five years of the study (range 8.2 – 8.9%) (Figures 16)

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Uncomplicated Community-acquired UTI

Treatment Outcomes in Uncomplicated Community-acquired UTI

To investigate outcomes in empirically treated CA-UTI, we limited our analysis to the 134,240 UCA-UTI in previously healthy women. Treatment failure, defined as an additional use of the KPNC healthcare system for the primary UTI within 30 days of treatment, occurred in 17.8% of the UCA-UTI (Table 11). Despite the steadily increasing use of ciprofloxacin as empirical treatment, the incidence of UCA-UTI failing treatment remained relatively stable over the eight years of the study, varying by only 1% and ranging from a high of 18.3% in 1999, when 13% of UCA-UTI were treated with ciprofloxacin, to a low of 17.2% in 2002, when 23% were treated with ciprofloxacin. By 2005 almost 30% of UCA-UTI received ciprofloxacin mono-therapy and 17.6% of UCA-UTI failed treatment. No sustained temporal trend in treatment failure was detected.

The likelihood of treatment failure varied significantly by age (range 16.4% to 19.5%) and treatment antimicrobial (range 15.8% - 26.1%) (Table 11 & Table 12). UCA-UTI in older women were more likely to fail treatment; UCA-UTI in women 51 – 60 years old were 22% more likely to fail treatment than were those in 21-30 year olds, the least likely age-group to fail treatment (RR 1.22, 95% CI 1.16 – 1.30).

The lowest incidence of treatment failure occurred among UCA-UTI receiving ciprofloxacin mono-therapy (15.8%, RR 1.00) followed by UCA-UTI receiving nitrofurantoin mono-therapy (17.2%, RR 1.05 – 1.16), TMP/SMX mono-therapy (17.9%, RR 1.12 – 1.19), and cephalexin mono-therapy (19.2%, RR 1.13 - 24) (Table 11& Table 12). To understand treatment appropriateness and effectiveness in the KPNC population it is necessary to evaluate the impact of an individual's uropathogen antimicrobial resistance on her treatment outcome.

Culture-confirmed UCA-UTI

To examine the influence of antimicrobial resistant uropathogens on treatment failure and treatment effectiveness, we further investigated microbial etiology and antimicrobial susceptibility, treatment drug choice, and treatment outcomes among the 42,437 mono-therapy treated, single uropathogen infected UCA-UTI from 40,754 women (median age 34.8 years)(Table 10). This population was less likely to be treated with TMP/SMX (50%) than were all treated UCA-UTI (54%) and more likely to be treated with cephalexin (15% compared to 12% in the larger population) and with nitrofurantoin (11% compared to 9%).

Etiology and Antimicrobial Resistance

Similar to the results from Table 6 in Chapter 4, 88% (37,549) of this smaller population of UCA-UTI were infected with *E. coli*, 9% (3,794) with a non-*E. coli* enteric gram negative rod and 3% (1,094) with a gram positive uropathogen. Antimicrobial resistance varied slightly from that of the larger population reported in Table 7. From 1998 – 2005, 75.5% of uropathogens from UCA-UTI were susceptible all four treatment drugs, while14.8% were resistant to TMP/SMX, 7.2% were resistant to nitrofurantoin, 0.98% to ciprofloxacin, and 6.1% to cefazolin (Table 10). Four percent of UCA-UTI were caused by an organism that was multi-drug resistant (MDR). For this study, a multi-drug resistant uropathogen was defined as a uropathogen that

was tested and reported resistant to two or more of the four treatment drugs. Multi-drug resistance was high among UCA-UTI with ciprofloxacin resistant pathogens (65%); 60% were additionally resistant to TMP/SMX; 9% were also resistant to nitrofurantoin, and 12% were also resistant to cefazolin.

Temporal trends in the antimicrobial resistance of uropathogens infecting this smaller population of UCA-UTI paralleled those observed in the larger population of uropathogens from all CA-UTI reported in Chapter 4. A significant temporal trend of increasing resistance to ciprofloxacin was detected; Ciprofloxacin resistance increased from 0.39% in 1998 to 1.88% in 2005 (p< 0.001). Conversely, significant trends of decreasing resistance to cefazolin and to cephalothin were detected (p < 0.001). UCA-UTI with cefazolin resistant pathogens declined from 7.4% in 1998 to 4.8% in 2005, while those with cephalothin resistant organisms decreased from 36.3% in 1998 to 26.5% in 2003. Routine cephalothin susceptibility testing was discontinued in 2004. No sustained temporal trends in TMP/SMX or nitrofurantoin resistance were detected. Resistance to TMP/SMX ranged from a high of 15.8 % in 1999 to a low of 13.5% in 2001 and had increased to15.4% by 2005. Nitrofurantoin resistance was 8.4% in 2005 and ranged from a low of 6.0% in 2002 to a high of 9.3% in 2004.

Treatment Failure and Treatment Effectiveness

Treatment failure, defined as a subsequent use of the KPNC healthcare system for the primary UTI event within the 30 day risk period, occurred in 22.6% (9,576) of mono-therapy treated, single uropathogen infected UCA-UTI. Treatment failure was more prevalent in this population than it was in the larger population of all treated UCA-UTI, where treatment failure occurred in 17.8% of UCA-UTI. UCA-UTI in this smaller study population were 47% more likely to fail treatment than were the 68% of treated UCA-UTI that were excluded from this study (RR 1.47, 95% CI 1.44 – 1.51).

Treatment failure was more common (24%) during the first three years of the study, after which it stabilized around 22% for the remaining five years. As expected, treatment failure varied significantly with the antimicrobial resistance of the infecting uropathogen: 17.3% of UCA-UTI with a uropathogen that was susceptible to TMP/SMX, nitrofurantoin, cefazolin and ciprofloxacin (PANS-UTI) failed treatment; 27% of UCA-UTI with a nitrofurantoin resistant uropathogen failed treatment; 32% of UCA-UTI with a cefazolin resistant uropathogen failed treatment; 48% of UCA-UTI with a TMP/SMX resistant uropathogen failed treatment, 51% of UCA-UTI with a ciprofloxacin resistant uropathogen failed treatment (Table 13) and 66% of the 228 UCA-UTI with a uropathogen resistant to both TMP/SMX and ciprofloxacin failed treatment.

After adjustment for age group, KPNC region, year, and clustering within the individual, mono-therapy with TMP/SMX was the most effective treatment for the 75% of UCA-caused by a PANS uropathogen, while nitrofurantoin and ciprofloxacin mono-therapy were slightly less effective in preventing treatment failure (Table 13). PANS-UTI that were treated with an antibiotic other than TMP/SMX were 29% more likely to fail treatment (RR 1.29, 95% CI 1.23 - 1.36): those treated nitrofurantoin were 8% (RR 1.08, 95% CI 1.00 – 1.19) more likely to fail treatment; those treated with ciprofloxacin were 15% (RR1.15, 95% CI 1.07 – 1.23) more likely

to fail treatment; and those treated with cephalexin were 37% (RR1.37, 95% CI 1.28 – 1.48) more likely to fail treatment than were those treated with TMP/SMX (Table12).

Nitrofurantoin and ciprofloxacin were almost equally effective ($p= 0.975$) in successfully treating the 15% of UCA-UTI with TMP/SMX resistant uropathogens and TMP/SMX was nearly as effective ($p= 0.361$) as ciprofloxacin for treating the 7% of UCA-UTI with uropathogens that were resistant to nitrofurantoin. Ciprofloxacin was the most effective drug for treating the 6% of UCA-UTI with cefazolin resistant uropathogens, while nitrofurantoin and cephalexin ($p= 0.891$) were the most effective treatments for the 1% of UCA-UTI with ciprofloxacin resistant uropathogens (Table 13). Co-resistance to TMP/SMX among ciprofloxacin resistant uropathogens (60% of ciprofloxacin resistant uropathogens were also resistant to TMP/SMX) and among cephalexin resistant pathogens (32% of cefazolin resistant organisms were also resistant to TMP/SMX) contributed to the reduced effectiveness of TMP/SMX to treat these infections. Co-resistance to TMP/SMX remained low, 8.6%, among nitrofurantoin resistant uropathogens.

Inappropriate treatment occurred in 8.5% of this population. Fourteen percent of TMP/SMX treatments, 7% of nitrofurantoin treatments, 6% of cephalexin treatments and 1% of ciprofloxacin treatments were microbiologically inappropriate (used to treat a UCA-UTI caused by a uropathogen that tested resistant to the treatment drug). Inappropriate TMP/SMX treatment ranged from a high of 15.4% in 1999, when 53% of UCA-UTI were treated with TMP/SMX, to a low of 12% in 2001, when 52% of UCA-UTI received TMP/SMX treatment. On the other hand, inappropriate treatment with ciprofloxacin ranged from a low of 0.3% in 1998, when 15% of UCA-UTI were treated with ciprofloxacin, to a high of 2.3% in 2005, when 29% of UCA-UTI received ciprofloxacin treatment.

Over the eight years of our study, 50% of PANS-UTI were treated with TMP/SMX, 21% with ciprofloxacin, 15% with cephalexin and 11% with nitrofurantoin. The use of TMP/SMX to treat pan-susceptible UTI decreased steadily over the study period, from 57% in 1998 to 44% in 2005 ($p < 0.001$), while the use of ciprofloxacin to treat PANS-UTI increased steadily from13.6% of treatment in 1998 to 28.4% in 2005. The proportion of PANS-UTI that were treated with nitrofurantoin ranged from 10% in 2002 to 12% in 2003 and the proportion treated with cephalexin ranged from highs of 17% in 1999 and 2002 to a low of 13% in 2003.

Discussion

From 1998 through 2005, TMP/SMX remained the drug of choice for empirical treatment of UCA-UTI among women, ages 15 through 60 years, in the Kaiser Permanente Northern California Health Plan. However, during this time period practitioners were increasingly replacing TMP/SMX with ciprofloxacin for treatment of both CCA-UTI and UCA-UTI, and by 2003 ciprofloxacin had replaced TMP/SMX as the treatment of choice for CCA-UTI. It is likely that the observed changes in treatment practices were in response to practitioners' perceptions that the local prevalence of resistance to TMP/SMX among uropathogens was continuing to increase and that the empirical use of ciprofloxacin would decrease the likelihood of a prescribing a drug to which the causative agent of their patient's UTI was resistant (microbiologically inappropriate treatment). Our study did not support these perceptions.

From 1998 through 2000, the increase of 7% in the proportion of women with CA-UTI receiving ciprofloxacin treatment was accompanied by only a 1% decrease in the risk of inappropriate treatment (Risk Difference -1.0%, 95% CI -0.06% to -2.0%). More importantly, over the next five years, despite an additional increase of 9.5% in the proportion of CA-UTI receiving ciprofloxacin treatment, there was no additional decrease in the risk of microbiologically inappropriate treatment. Furthermore, it is important to note that over this time period, the proportion of CA-UTI that were caused by a ciprofloxacin resistant pathogen steadily increased from 0.6% in 1998 to 2.4% in 2005, and that the proportion of CA-UTI that were caused by a TMP/SMX resistant uropathogen varied from a high of 20.4% in 1998 to lows of 17.8% in 2001 and 2004 (Figure 16).

Among the 65% of CA-UTI that occurred in women with uncomplicated UTI disease, ciprofloxacin treatment more than doubled from 13% of treatments in 1998 to 30% in 2005 and TMP/SMX treatment of UCA-UTI steadily decreased from 62% in 1998 to 47% in 2005. In this population, where 14.9% of UTI were caused by a TMP/SMX resistant pathogen (range, 15.7% in 1998 to 13.7% in 200, returning to 15.4% in 2005), microbiologically inappropriate treatment decreased only 1.7% from 1998 through 2001 (RD -1.7%, 95% CI -0.6% to 2.9%) and then remained stable at 8.6% (95% CI 8.3 – 9.0%) over the next four years. In addition, despite substantial changes in treatment drug choice, the incidence of treatment failure among UCA-UTI, 17.8%, remained stable in our population, decreasing less than 1% over the eight years of the study while the proportion of UCA-UTI caused by a ciprofloxacin resistant uropathogen increased steadily from 0.4% in 1998 to 1.9% in 2005 (Figure 17).

Our study detected a higher prevalence of treatment failure in our northern California population than has been detected in similar studies performed in Europe [115] [116], in which approximately 14% of UCA-UTI failed treatment. These studies were performed in an earlier time period, 1991 – 2000, and in countries where different antimicrobials are commonly prescribed. To our knowledge our study is the only study of its kind to be performed in the US.

Although the incidence of treatment failure was lowest in those UCA-UTI that were treated with ciprofloxacin, our investigation of treatment effectiveness in the smaller population of culture-confirmed UCA-UTI suggests that ciprofloxacin is not significantly more effective than TMP/SMX or nitrofurantoin for the treatment of microbiologically compatible infections. Among the 76% of UCA-UTI that were caused by uropathogens that were susceptible to all four treatment options studied, TMP/SMX treatment was the most effective treatment: TMP/SMX treatment was associated with a 7% – 23% lower risk of treatment failure when compared to ciprofloxacin treatment (Table13). The observed increased risk of treatment failure with ciprofloxacin was surprising. One possibility is that our data may be biased by uncontrolled confounding by indication; a practitioner may prescribed the perceived most effective treatment more often to those patients who are more likely to fail treatment due to reasons other than microbiological incompatibility. While we used our disease classification to exclude women with medically complicating factors (described in Chapter 3) that would predispose a patient to microbiological resistance and treatment failure, we can't rule out the possibility of confounding by indication by factors that are not accessible through existing electronic data. Another possibility is that our results were biased by misclassification of ciprofloxacin resistance. Fluoroquinolone resistance in *E. coli* can result from *qnrA*, *qnrB, qnrC* and *qnrS* genes, which

are located on plasmids. Plasmid based resistance may be weakly expressed during standard in-vitro susceptibility testing and thus may be reported as CLS susceptible when they are in fact resistant in-vivo [79] It is also possible that a true difference in biological or clinical cure rate exists between TMP/SMX and ciprofloxacin. However, a clinical trial investigating the effectiveness of a 3 day ciprofloxacin regime, with 7 day regimes of TMP/SMX and nitrofurantoin that was performed by Iravani et al. in 1999 [117] demonstrated treatment equivalency among all three agents. Be that as it may, our study has found no evidence that ciprofloxacin treatment is superior to TMP/SMX or nitrofurantoin for treatment of UCA-UTI with pan-susceptible uropathogens.

Based on susceptibility testing, over 64% of ciprofloxacin treatments for CA-UTI in the KPNC population were used to treat infections that, barring patient intolerance, could have been successfully treated with other treatment options; 72% of ciprofloxacin treated UCA-UTI and 58% of ciprofloxacin treated CCA-UTI were infected with uropathogens that were susceptible to all four treatment drugs.

The use of cephalexin treatment for uncomplicated UTI remains problematic. Our data support the IDSA conclusion that B-lactam drugs are less effective for treatment of UTI, even when resistance is not apparent from susceptibility testing. Cephalexin treatment was associated with significantly increased treatment failure among all populations except among UCA-UTI caused by ciprofloxacin resistant uropathogens. Cephalexin treated UCA-UTI that were caused by a pan-susceptible uropathogen were 38% more likely to fail treatment than were those that were treated with TMP/SMX. In addition, cephalexin susceptibility is rarely tested outside of research settings because the Clinical Laboratory Standards Institute has been not set clinical interpretative guidelines for this antimicrobial agent. Cephalothin or in the KPNC population, cefazolin, susceptibility testing is used as a proxy to assess resistance to cephalexin resistance among uropathogens. In Chapter 6 we will explore cephalexin treatment of UCA-UTI in the KPNC population and determine the utility of cephalothin and cefazolin susceptibility testing to predict treatment failure. In addition, we will determine the ability of TMP/SMX, ciprofloxacin and nitrofurantoin susceptibility testing to predict treatment failure within the populations treated with these agents.

Surprisingly, despite practice guidelines [31, 118] that suggest that routine microbiological investigation is not warranted for CA-UTI in previously healthy women, KPNC practitioners are increasingly including pretreatment urine cultures and susceptibility testing in their clinical care of woman with UCA-UTI. Microbial investigation of UCA-UTI increased 11% over the eight years of our study, while it increased only 3% among CCA-UTI. This suggests that laboratory samples in our population maybe becoming more rather than less representative of uncomplicated infections over time. Despite the changes in urine culture ordering practices, we found that the 2005 laboratory sample of uropathogens from treated CA-UTI continued to over –represent isolates from CA-UTI in women 15 to 20 years old, isolates from CCA-UTI, and isolates from UCA-UTI in women who subsequently failed treatment.

In conclusion, our investigation of uropathogen antimicrobial susceptibility and treatment appropriateness among all CA-UTI, as well as our exploration of treatment failure and treatment effectiveness among UCA-UTI, suggest that the first line UTI treatment drugs, TMP/SMX and

nitrofurantoin, remain viable treatment options for a large proportion of CA-UTI in the KPNC population. In addition, we have found that the increasing replacement of TMP/SMX treatment with empirical ciprofloxacin treatment has had a minimal effect on the proportion of CA-UTI that received appropriate treatment and has had no effect on the frequency of treatment failure among UCA-UTI. Importantly our study suggests that the use of ciprofloxacin in patients who could be successfully treated with a narrow spectrum antimicrobial may be fueling the sustained increase in ciprofloxacin resistance observed among uropathogens over the eight years of the study.

Chapter 6: Cephalexin Treatment of Uncomplicated Community-acquired Urinary Tract Infections: Outcomes and Antimicrobial Susceptibility Testing

Introduction

Antimicrobial drug choice for empirical treatment of uncomplicated community-acquired urinary tract infections (UCA-UTI) has become complicated by relatively high levels of resistance to trimethoprim/sulphamethoxazole (TMP/SMX), the recommended first line treatment antimicrobial, as well as by an increasing appreciation of the negative consequences often associated with the unnecessary use of broad spectrum antimicrobials such as fluoroquinolones, (i.e. the disruption of normal flora, the selection of drug resistant organisms, and the resultant colonization or infection with multi-drug resistant organisms). Limited treatment options underscore the need to investigate the effectiveness of older urinary tract infection (UTI) treatment options, such as cephalexin. Antimicrobial resistance prevalence estimates are used to guide the selection of antimicrobial agents for empirical treatment of community-acquired UTI (CA-UTI). Unfortunately, determining the prevalence of resistance to cephalexin among uropathogens is difficult. The Clinical Laboratory Standards Institute (CLSI) has not established specific guidelines for interpreting cephalexin susceptibility testing results and most clinical laboratories in the U.S. have adopted automated testing systems that do not include direct susceptibility testing for this drug. CLSI currently recommends that the results of the in vitro susceptibility testing with cephalothin be used to represent the susceptibility of an organism to cephalexin. Practitioners, therefore, use cephalothin resistance prevalence estimates to gauge the usefulness of cephalexin as an empirical treatment option. Unfortunately, national surveys of antimicrobial resistance among uropathogens in the U.S. generally do not report cephalothin susceptibility data.

While current UTI treatment guidelines [38, 56, 101] no longer recommend the use of cephalexin, except in special populations (i.e. pregnant women or young children), we have found (Chapter 5) that practitioners in the Kaiser Permanente Northern California Health Plan (KPNC) system continue to prescribe cephalexin to about 12% of women with CA-UTI. From 1998 through 2003, the KPNC regional laboratory tested gram negative uropathogens for susceptibility to both cephalothin and cefazolin but not to cephalexin. In 2004, the microbiology laboratory of KPNC adopted a method of antimicrobial susceptibility testing of uropathogens that does not test for either cephalothin or cephalexin susceptibility. Because no first generation oral cephalosporin is currently being tested, KPNC practitioners must now rely on the results of cefazolin testing to infer the susceptibility of a gram negative uropathogen to cephalexin.

In general, cefazolin appears to be much more active than cephalothin against gram negative uropathogens, leading to significantly lower reported prevalences of resistance to cefazolin than to cephalothin. In Chapter 4 we reported that, among *Escherichia coli* (*E. coli*) isolated from patients with CA-UTI, 35% were resistant to cephalothin while only 6% were resistant to cefazolin. However, among other gram negative uropathogens, the difference was not as dramatic; 21% of non-*E. coli* gram negative uropathogens were resistant to cephalothin and 18% were resistant to cefazolin. A finding that 35% of uropathogenic *E. coli* are resistant to

cephalothin suggests that empirical treatment of UTU with cephalexin may no longer be effective while a finding that only 6% of uropathogenic *E. coli* are resistant to cefazolin resistance suggests that cephalexin remains a useful as empirical treatment for UTI. In addition, the results of a recent Canadian study [18], as well as unpublished data from our study reported in Chapter 7, suggest that neither cephalothin nor cefazolin susceptibility testing results accurately reflect cephalexin susceptibility. In these studies, in vitro testing of cephalothin by automated methods significantly over-stated the nonsusceptibility of cephalexin found through direct testing while cefazolin testing was found to under-estimate the nonsusceptibility of cephalexin. Practitioners are left in a quandary; organisms testing susceptible to cephazolin often test resistant to cephalothin. A study which investigates the ability of cephalothin and cefazolin in vitro susceptibility testing results to predict the outcome of cephalexin treatment among KPNC UTI patients is overdue.

Here we investigate the population of female KPNC, ages 15 – 60 years, with UCA-UTI who received cephalexin mono-therapy as their empirical antimicrobial treatment during the period of January 1, 1998 through December 31, 2005. Further, we explore how well cephalothin and cefazolin susceptibility testing results predict 30-day treatment outcomes in those cephalexin-treated UCA-UTI that were caused by an *E. coli* strain tested for susceptibility to both cephalothin and cefazolin. In addition, among the *E. coli* causing the UCA-UTI described in Chapter 5, we compare the sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratios of cephalothin, cefazolin, TMP/SMX, nitrofurantoin and ciprofloxacin susceptibility testing to predict clinical outcome.

Methods

This study used existing administrative healthcare claims data as well as pharmacy and laboratory data, to identify all of the women who received mono-therapy with cephalexin to treat their UCA-UTI during the study period of 1998 – 2005. Procedures for subject identification, urinary tract infection and urine culture classification, as well as empirical treatment and treatment outcome definitions are detailed in Chapter 3. We determined 30-day treatment outcomes in this population and defined treatment failure as the additional use of the KPNC system for the UCA-UTI event within 30 days of commencing cephalexin treatment. In addition, we investigated how well the population of cephalexin-treated women who received a urine culture as part of their diagnostic work-up reflected all cephalexin-treated women in our study.

To evaluate the usefulness of susceptibility testing to predict 30-day treatment outcomes, we limited the study population to those cases that were identified as being caused by a single *E. coli* uropathogen that was tested for susceptibility to both cephalothin and cefazolin.

Statistical Analysis

Because individual women could have had up to eight primary UTI (one per year) during the study period, all analyses were adjusted for clustering within the individual. Robust confidence intervals, adjusted for clustering, were reported as a measure of the precision of population estimates. Relative risks were estimated using multivariable modified Poisson regression with cluster adjusted robust errors, adjusting for year, region, and age-group. The

ability of cephalothin and of cefazolin susceptibility testing to predict 30-day treatment outcome was investigated using age-group adjusted log-binomial regression with cluster adjusted robust errors, as well with diagnostic testing parameter analysis. Diagnostic odds ratios were adjusted for age-group and clustering and their confidence intervals were calculated using cluster adjusted bootstrapped errors. All statistical analyses were performed using Stata, version 10.0 (StataCorp).

Results

Cephalexin-treated UCA-UTI

From the larger study population of 134,240 UCA-UTI described in Chapter 5, we identified 16,005 (12%) UCA-UTI in 15,595 women (median age at UTI 31.7 years) (range, 1 – 5 cephalexin-treated UCA-UTI per woman), that were treated with cephalexin mono-therapy (cUCA-UTI) (Table13). Fifty-five percent (8,814) of cUCA-UTI were from a single KPNC Region, Region A. UCA-UTI from Region A were 5.67 times (RR 5.67, 95% CI 5.5 – 5.8%) as likely to receive cephalexin mono- therapy as were UCA-UTI from other KPNC regions.

The likelihood of cephalexin treatment of UCA-UTI decreased steadily with the increasing age-group of the woman: UCA-UTI in 15 – 20 year old women were 85% (RR 1.85, 95% CI 1.77 – 1.94) more likely to be treated with cephalexin than were those in 51 - 60 year old women.

The proportion of UCA-UTI treated with cephalexin mono-therapy was highest during the first two years of the study (14%) and then varied between 10% and 12% over the remaining six years. UCA-UTI occurring in 1998 were 26% more likely to be treated with cephalexin than were those UCA-UTI occurring in 2005 (RR 1.26, 95% CI 1.19 – 1.32).

Microbiological Investigation

In 61% (9,728) of the 16,005 cUCA-UTI, a pretreatment urine specimen was sent to the regional laboratory for microbiological investigation by culture and susceptibility testing. The proportion of cUCA-UTI with specimens sent for urine culture substantially increased from 45.6% in 1998 to 65.5% by 2000 and then ranged from a low of 64.0% in 2005 to a high of 66.7% in 2003. Practitioners were more likely to order urine cultures in younger women and for those that would subsequently fail treatment. Women under the of age 21 years were 42% (RR 1.42, 95% CI 1.38 – 1.45) more likely to submit a urine specimen for culture than were women ages 21 to 60 years, while women that would subsequently fail treatment were 10% (RR 1.10, 95% CI 1.06 – 1.13) more likely to have had a urine sample sent for culture than were those that were successfully treated.

Sixty-five percent (6,309) of the microbiologically investigated cUCA-UTI (39% of all cUCA-UTI) were reported positive for a single susceptibility-tested uropathogen and less than one percent (45) were reported as positive for two uropathogens. Eighty-eight percent (5,609) of the 6,399 uropathogens isolated from cUCA-UTI were identified as *E. coli*. The remaining 12% (790) of isolates were identified as 23 different uropathogens: 74% (583) were non-*E. coli*

members of the Enterobacteriaceae family, 19% (150) were *Staphylococcus species*, 6% (51) were *Enterococcus species* and less than 1% (6) were other gram negative rods.

Antimicrobial resistance among the 6,399 uropathogens isolated from cUCA-UTI was similar to that observed among all mono-therapy treated UCA reported in Chapter 5: 76% (95% CI 75.1% – 77.2%) of uropathogens from cUCA-UTI were pan-susceptible, defined as tested and susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin; 32% (95% CI 31.1% – 33.8%) were resistant to cephalothin; 14% (95% CI 12.9% – 14.6%) were resistant to TMP/SMX; 7% (95% CI 6.8% – 8.1%) were resistant to nitrofurantoin; 6% (95% CI 5.3% – 6.5%) were resistant to cefazolin; and 0.8% (95% CI 0.59% – 1.03%) were resistant to ciprofloxacin. Not surprisingly, antimicrobial resistance ranged widely among different uropathogens (Table 15).

Treatment Outcomes

Treatment failure, as a measure of 30-day treatment outcomes, was defined as a subsequent use of the KPNC healthcare system for the primary UTI within 30-days of treatment onset. The incidence of treatment failure was 19.2% (95% CI 18.6% – 19.8%) in the 16,005 UCA-UTI that were treated with cephalexin. Although treatment failure varied by year, from a high of 22% (95% CI 20.2 – 24.0) in 2001 to a low of 17% (95% CI 15.7 – 19.0) in 2004, no consistent temporal trend was detected over the eight years of the study. Similar to the age trends among all UCA-UTI reported in Chapter 5, treatment failure was more likely in cUCA-UTI in older women; women over 40 with a cUCA-UTI were 16% (RR 1.16 95% CI 1.09- 1.25) more likely to fail treatment than were women ages 15 to 40.

Treatment failure also varied by whether or not the UTI was culture-confirmed and by the causative uropathogen. Treatment failure occurred in 23.4% (95% CI 22.3% – 24.4%) of the 6, 354 culture-confirmed cUCA-UTI (adjusted RR 1.43, 95% CI 1.34 – 1.52) but in only 16.5% (95% CI 15.8% – 17.2%) of the 9,651 cUCA-UTI that were not culture-confirmed. Twenty-three percent (95% CI 21.9% – 24.1%) of the 5,607 cUCA-UTI that were caused by *E. coli*, 28% (95% CI 24.7% – 32.0%) of the 589 cUCA-UTI that were caused by a non-*E. coli* gram negative rod, and 20.0% (95% CI 14.3% – 25.5%) of the 201 cUCA-UTI that were caused by a gram positive uropathogen failed treatment..

Antimicrobial Susceptibility Testing

Because treatment failure varied significantly by uropathogen, the examination of the utility of cephalothin and cefazolin susceptibility testing as a proxy for cephalexin susceptibility was limited to those cUCA-UTI caused by a single *E. coli* strain. Seventy-three percent (4,076) of the 5,569 *E. coli* isolates from cUCA-UTI were tested for cephalothin susceptibility, while 100% were tested for cefazolin susceptibility; 73% (4,076) of the *E. coli* isolates were tested for both. The final study population for investigating the utility of cephalothin and cefazolin susceptibility testing results as a predictor of treatment outcome, therefore, consisted of those 4,076 *E. coli* UCA-UTI (25% of cUCA-UTI) from 4,036 women, ages 15 to 60 years (1 to 3 UTI per woman) (Table 14). The incidence of treatment failure in the final study population of 4,076 cUCA-UTI caused by *E. coli* tested for susceptibility to cephalothin and cefazolin was 24.4% (95% CI 23.1% – 25.7%). The final study population over-represents cUCA-UTI occurring

during 2000 through 2003; cUCA-UTI in younger women; and cUCA-UTI that failed treatment. cUCA-UTI from women under 21 years of age were 44% more likely to be included in the final study population than were those from women 21 years and older (adjusted RR1.44, 95% CI 1.36 – 1.51). cUCA-UTI in the final study population were 41% (adjusted RR 1.41, 95% CI 1.31– 1.51) more likely to have failed treatment than were the 11,929 cUCA-UTI that were excluded from the final analyses.

Among the 4,076 *E. coli* isolates from the final study population, 1,377 (33.8%) were resistant to cephalothin, while only 187 (4.6%) were resistant to cefazolin. A total of 2,696 *E. coli* strains (66.1%) were susceptible to both drugs, 184 (4.5%) were resistant to both drugs, 1,193 (29.3%) were resistant to cephalothin but susceptible to cefazolin, and three (<1%) were susceptible to cephalothin but resistant to cefazolin. The sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratios of cephalothin and cefazolin susceptibility testing to predict treatment failure are presented in Table 16. In the study population, where the prevalence of treatment failure was 24.4%, cefazolin susceptibility testing was found to be a more specific but less sensitive predictor of an *E. coli* UCA-UTI that would fail cephalexin treatment than was cephalothin susceptibility testing. Treatment failure occurred in 31.4% (positive predictive value of cephalothin resistance) of the cephalothin resistant *E. coli* UTI and in 54.5% of the cefazolin resistant *E. coli* UTI. After adjusting for age-group, cUCA-UTI caused by cephalothin resistant *E. coli* were 50% (RR1.50, 95% CI 1.35 – 1.67) more likely to fail treatment than were cUCA-UTI caused by cephalothin susceptible *E. coli* while cUCA-UTI caused by cefazolin resistant *E. coli* were over twice as likely to fail treatment (RR 2.38, 95% CI 2.06 – 2.74) as were cUCA-UTI caused by cefazolin susceptible *E. coli*.

Overall, cefazolin susceptibility testing results were marginally better at predicting cephalexin treatment outcomes than were cephalothin susceptibility testing results (Table 16). Cefazolin susceptibility testing had a positive likelihood ratio of 3.72 (95% CI 2.18 – 4.91), a negative likelihood ratio of 0.923 (95% CI 0.90 – 0.94), and an age-adjusted diagnostic odds ratio (the positive likelihood ratio divided by the negative likelihood ratio) of 4.04 (95% CI 2.80 – 5.28) for predicting treatment failure. The corresponding values for cephalothin susceptibility testing results to predict treatment failure among women with a cephalexin treated UCA-UTI were as follows: positive likelihood ratio, 1.42 (95% CI 1.30 – 1.55); negative likelihood ratio 0.816 (95% CI 0.77 – 0.87); and age-adjusted diagnostic odds ratio, 1.74 (95% 1.49 – 1.98).

We used Fagan's diagnostic nomogram for pre and post test probabilities [119], Hayden and Brown's [120] guide to the use of likelihood ratios and McGee's mnemonic [121, 122] for simplifying the use of likelihood ratios for interpreting clinical findings to determine how much practical information a practitioner receives from the results of susceptibility testing of cephalothin and cefazolin to predict a patient's probability of treatment failure if they receive cephalexin as treatment for their UCA-UTI. Based on these guidelines, a diagnostic test with a likelihood ratio (LR) of 1 to 2 will add less than 15% to the pretest probability of disease and a LR of 0.5 to 1 will subtract will less than 15%, resulting in no practical change in the post-test probability of disease. A small change in the post test probability of disease results from tests with an LR of 2 to 5 or 0.2 to 0.5 which adds or subtracts 15% – 30% from the pre-test probability of disease; a moderate addition or subtraction of 30% - 45% results from tests with an LR of 5 - 10 (or 0.1 – 0.2); and a large addition or subtraction of over 45% results from tests with

a LR of over 10 (or less than 0.1). In this study population of cephalexin treated women with a 23% - 26% pretest probability of treatment failure, a cefazolin susceptibility test report of "nonsusceptible"(LR 3.72) will increase the post-test probability of treatment failure by a only small percentage of approximately 15% -30%, while a cefazolin susceptibility test report of "susceptible" (LR 0.82) and a cephalothin susceptibility test report of either "nonsusceptible" (LR 1.42) or "susceptible" (LR 0.92) adds no significant information, changing the probability of treatment failure by less than 15% (Table 16).

To determine whether our results indicate a failure specific to cephalothin and cefazolin susceptibility testing or whether there is a systematic inability of antimicrobial susceptibility testing to predict treatment failure (as defined in our study) among women with UCA-UTI caused by *E. coli*, we examined the diagnostic performances of TMP/SMX, nitrofurantoin and ciprofloxacin susceptibility testing results to predict treatment outcomes in patients treated with these drugs (See Chapter 5 for population details). The results are presented in Table 17. Susceptibility testing results for TMP/SMX, nitrofurantoin and ciprofloxacin were insensitive (less than 50%) but specific (over 95%) for predicting treatment failure among patients treated with these antimicrobials. Based on the likelihood ratios of the individual susceptibility tests, we found that, unlike cephalothin and cefazolin susceptibility testing results, a TMP/SMX, a nitrofurantoin or a ciprofloxacin susceptibility testing report of "resistant" added strong evidence (positive LRs of over ≥10) that an *E. coli* UCA-UTI will fail treatment if an antimicrobial agent to which the pathogen has tested resistant is used for treatment.

The diagnostic odds ratio is the ratio of the likelihood ratio of a positive result to the likelihood ratio of a negative result, which provides a single statistic to summarize the performances of a diagnostic test and to allow a comparisons across tests and populations. Because diagnostic odds ratios are derived from logistic models they can be adjusted for confounding variables such as age. Based on a comparison of the age adjusted diagnostic odds ratios of the treatment antimicrobial susceptibility test for each treatment population (e.g. TMP/SMX susceptibility test results in TMP/SMX treated patients, nitrofurantoin susceptibility test results in nitrofurantoin treated patients, etc.), TMP/SMX susceptibility test results in TMP/SMX treated patients performed best at predicting treatment failure with an age group adjusted diagnostic odds ratio of 20.16 (95% CI 18.14 – 22.18) while cephalothin susceptibility testing results in cephalexin treated patients performed worst with an age group adjusted diagnostic odds ratio of 1.74 (95% CI 1.49 – 1.99) (Table 17).

Discussion

Our results demonstrate that neither cephalothin nor cefazolin antimicrobial susceptibility testing results add significant information for predicting the clinical outcome of cephalexin treatment of CA-UTI. Unlike testing for resistance to TMP/SMX, ciprofloxacin and nitrofurantoin, which adds strong evidence that treatment with a drug to which the infecting uropathogen tests nonsusceptible increases the likelihood of treatment failure, cephalothin susceptibility test results add no evidence and cefazolin testing adds minimal evidence. The lack of an informative test for susceptibility to cephalexin is a major concern for physicians in the KPNC population where over 10% (up to 38% of UCA-UTI in one large KPNC region) of UCA-UTI are treated with cephalexin mono-therapy and where cephalexin remains an important

antimicrobial for the treatment of UTI in pregnant women and young children. Practitioners are unable to track the changing prevalence of resistance to cephalexin among uropathogens and in individual cases are unable to determine whether a treatment failure in a cephalexin-treated patient is due to antimicrobial resistance or to another cause. In addition, in cases where initial empirical treatment with a drug other than cephalexin fails due to antimicrobial resistance, practitioners are unable to determine whether cephalexin treatment is a viable non-empirical second treatment option.

Although we reported in Chapter 5 that cephalexin treatment was the least effective of the four common treatment antimicrobials in all populations examined (Table 12), 81% of KPNC women receiving cephalexin treatment for their UCA-UTI required no further care for their UTI in the 30 days following treatment. This suggests that cephalexin remains a viable empirical treatment option. Unfortunately, without an accurate method for ascertaining the susceptibility of uropathogens to cephalexin, practitioners are left without the ability to monitor changes in the suitability of this treatment option and may be reluctant to use cephalexin in cases where TMP/SMX or nitrofurantoin treatment is contra-indicated.

Clinical laboratories in the USA currently rely on the CLSI to set clinical interpretation guidelines for their susceptibility testing, and manufacturers of antimicrobial susceptibility testing systems will not include antimicrobial agents that do not have CLSI-approved interpretation standards. Our data strongly suggest that an accurate evaluation of the appropriateness of cephalexin treatment for UTI requires the direct testing of cephalexin susceptibility rather than the use of uninformative proxy testing. We recommend that the CLSI evaluate and publish clinical guidelines for cephalexin susceptibility testing and that the FDA and manufacturers of automated clinical antimicrobial testing develop and approve clinical systems that allow the routine testing of cephalexin susceptibility for common uropathogens. Practitioners need to make rational empirical treatment choices and reduce the unintended negative effects that can result from the use of inappropriate antimicrobial agents and from the unnecessary use of broad spectrum antimicrobials when narrow spectrum agents would be effective.

Chapter 7: Temporal Changes in the Prevalence of Community-Acquired Antimicrobial-Resistant Urinary Tract Infection Affected by *Escherichia coli* Clonal Group Composition

Introduction

     Escherichia coli (*E. coli*) urinary tract infection (UTI) is one of the most common community-acquired infections in women. Resistance to empirically prescribed antimicrobial agents complicates the management of this disease [10, 83, 84]. In addition, reports of community outbreaks of multi-drug resistant (MDR) UTI caused by unique clonal groups of uropathogenic *E. coli* [12, 51, 52] raise a number of questions: Do undetected outbreaks contribute to temporal fluctuations in the prevalence antimicrobial resistance in a specific community? Are changes in the prevalence of drug-resistant UTI in a community more dependent on the transient introduction or disappearance of genetically similar groups of drug-resistant *E. coli* than on antimicrobial drug use or prescribing practices in that community?

     The conventional approach to understanding antimicrobial resistance, which relies on tracking temporal changes in resistance among pathogens isolated from routinely submitted culture samples, provides a limited assessment of the prevalence of antimicrobial resistance in a community. Because urine samples from women with uncomplicated UTI are not routinely cultured in most settings, samples used to generate antimicrobial susceptibility data may not be representative of uropathogens from patients with uncomplicated community-acquired UTI. The use of such convenience samples may limit the usefulness of the resistance data generated to guide empirical treatment decisions for these patients.

     Systematic sampling of urine specimens from community-acquired UTI (CA-UTI) patients can eliminate this sampling bias. In addition, genotype analysis of UTI *E. coli* isolates can augment susceptibility testing by delineating the temporal contributions of unique and genetically related strains. A more comprehensive picture of the dynamics of community-acquired antimicrobial drug-resistance can inform empirical treatment decisions and may facilitate the development of rational strategies for preserving the effectiveness of available treatment options.

     Here, we report the results of a serial cross-sectional study conducted from 1999 through 2005 in a California university community to test the hypothesis that the resistance of uropathogenic *E. coli* to empirically prescribed antimicrobial agents is increasing and to investigate whether the introduction and circulation of clonal groups of *E. coli* alters the prevalence of antimicrobial resistant UTI.

Methods

Study Design and Sampling Strategy

Between October 1999 and January 2005, we conducted a series of cross-sectional studies at a California university health care service. The study included four 3.5 month sampling periods: period I (October 11, 1999 through January 31, 2000); period II (October 11, 2000 through January 31, 2001); period III (October 11, 2003 through January 31, 2004); and period IV, (October 11, 2004 through January 31, 2005). The collection of period I and II samples was nested within a separate two-year study that examined changes in the prevalence of a major drug resistant clonal group of *E. coli* in this student population [12, 86]. Period III and period IV samples were collected within a second two-year prospective study initiated in October 2003 that examined the dietary habits of students with UTI [48]. Details of the two studies are provided in the respective publications [12, 48, 86].

During each time period, urine specimens were obtained from consecutive patients presenting to the clinic with symptoms suggestive of UTI. An *E. coli* UTI was defined as a UTI from a patient who received a diagnosis of UTI (as stated on the laboratory referral documents) and had a urine culture yielding $\geq 10^2$ colonies per ml of urine of presumptively identified *E. coli*. If multiple urine specimens from the same patient were obtained, only the first specimen yielding an *E. coli* isolate (primary *E. coli* isolate) was included in the analysis. Study protocols were approved by the Committee for Protection of Human Subjects at the University of California at Berkeley.

Urine Collection and Microbiological Methods

All urine specimens collected from clinic patients were picked up daily, preserved in 15% glycerol, and stored at -80^0C until testing. Urine specimens were cultured by standard methods [123]. Colonies of organisms that were isolated at concentrations of $\geq 10^2$ colonies per mL of urine and were presumptively identified as *E. coli* [86, 124] were selected for further testing.

Antimicrobial susceptibility testing for trimethoprim-sulfamethoxazole (TMP/SMX), ciprofloxacin and nitrofurantoin was performed during periods I and II by E-test strip (AB Biodisk, Solna, Sweden). During periods III and IV, as part of a new study design protocol [48], susceptibility testing for 29 antimicrobial agents representing eleven drug classes was performed by the broth microdilution method (Microscan Dade-Behring). All susceptibility testing was interpreted according to Clinical and Laboratory Standards Institute standards. Isolates exhibiting intermediate resistance were interpreted as resistant. An isolate was considered to be multi-drug resistant (MDR) if it was resistant to two or more separate classes of antimicrobial agents.

Genotype Analyses

All TMP/SMX resistant *E. coli* isolates and either a randomly selected subset (period I, 49 [27%]; period II, 104 [62%]; or 100% (periods III and IV, 290 isolates) of TMP/SMX susceptible isolates were genotyped by Enterobacterial Repetitive Intergenic Consensus 2 (ERIC2) PCR, as described elsewhere [12, 125]. Groups of two or more isolates with ERIC2 electrophoretic banding patterns that were indistinguishable by visual inspection were designated

to belong to ERIC2 clonal groups (Cg). Prototype uropathogenic strains clonal group A (CgA [ATCC BA-457]) and CFT073 were included as reference strains for the ERIC PCR tests. Isolates of other representative clonal groups identified during periods I and II were retested for valid comparison with period III and IV isolates.

Statistical Analysis

Comparisons of proportions were tested by Fisher's two-tailed exact test. Cuzick's test for trend was performed to detect trends in resistance prevalence of those antimicrobial agents tested over the four periods of the study.

A test of negative binomial regression versus Poisson regression was used to examine the hypothesis that ERIC2 patterns displayed the same underlying prevalence of TMP/SMX resistance, pan-susceptibility or multi-drug resistance. The basis of this test is that the negative binomial distribution can be thought of as an extension of the Poisson distribution that allows for variation in the underlying proportions of antimicrobial resistance between theERIC2-PCR patterns. A comparison of the relative fit of the Poisson and the negative binomial distributions via the log-likelihoods provides a pseudolikelihood ratio statistic.

Temporal clustering of the major clonal groups (defined as the ERIC2 groups with at least 20 isolates per group) identified over the four sampling periods was investigated with Pearson Chi-square analysis. Poisson and negative binomial regression tests were used to examine the hypothesis that the rate of occurrence of these ERIC2 clonal groups was constant throughout the study period. All statistical analyses were performed, using Stata, version 9.0 (Stata Corp., College Station, TX).

Results

Study Population and *Escherichia coli* Isolates

During the four sampling periods from 1999 to 2005, 1667 patients between the ages of 13 and 68 years of age presented to the university health clinic (University of California, Berkeley) with clinical suspicion of UTI. Of these patients, 780 (47%) had primary *E. coli* isolates recovered at concentrations of $\geq 10^2$ colonies per mL of urine (Table 18). During periods III and IV, *E. coli* accounted for 81% of the uropathogens isolated.

Antimicrobial Resistance

All *E. coli* isolates were tested for susceptibility to TMP/SMX, ciprofloxacin, and nitrofurantoin. Among the 780 *E. coli* isolates, 18% were resistant to TMP/SMX, 2% were resistant to ciprofloxacin and 1% were resistant to nitrofurantoin (Table 18). No trends in the proportion of strains resistant to TMP/SMX, ciprofloxacin, or nitrofurantoin were detected over the four sampling periods (Table 18).

Eleven (8%) of the 141 TMP/SMX resistant isolates were also resistant to ciprofloxacin, while two (1.4%) were also resistant to nitrofurantoin. Isolates that were resistant to nitrofurantoin or ciprofloxacin were uncommon. Thirteen ciprofloxacin resistant *E. coli* were identified; 12 (92%) of these were multi-drug resistant, including 11 (85%) that were resistant to

TMP/SMX, and one that was resistant to both TMP/SMX and to nitrofurantoin. All nine nitrofurantoin-resistant isolates were multi-drug resistant; and those from period III and IV were resistant to between five and eight classes of antimicrobial agents including ampicillin and cephalothin.

During Periods III and IV (when 29 antimicrobial agents were tested), 169 (49%) of the 346 isolates were susceptible to all twenty-nine drugs tested (pansusceptible), while 60 (17%) were resistant to a single agent, and 117 (34%) were resistant to two or more classes of drugs. Fourteen (12%) of the 117 MDR isolates were resistant to six or more of the eleven classes of drugs tested.

Among the 346 *E. coli* isolates from periods III and IV, the proportions resistant to cephalothin and ampicillin were 32% and 31%, respectively. Resistance to ampicillin decreased from 35% of isolates in period III to 24% in period IV (p = 0.049).

ERIC2-PCR Genotyping Results

Among the 584 *E. coli* isolates tested byERIC2-PCR, 35 distinct clonal groups, defined as those comprised of ≥ 2 isolates per group displaying visually indistinguishable electrophoretic banding patterns, were identified. The number of clonal groups identified and the proportion of isolates belonging to such groups increased with the increasing percentage of isolates typed by ERIC2-PCR during each period (Table 19).

During period I, genotyping of all 47 TMP/SMX resistant isolates and 49 (27%) of randomly selected TMP/SMX susceptible isolates identified three clonal groups of isolates displaying indistinguishable banding patterns. Three additional clonal groups were identified during period II, when all 38 TMP/SMX resistant isolates and 104 (62%) of 168 TMP/SMX susceptible isolates were typed [12, 86].

Concurrent genotyping of the 346 *E. coli* isolates during periods III and IV revealed 118 unique ERIC2 patterns. Two hundred sixty four isolates (75%) were identified as belonging to 33 clonal groups. Of the 26 clonal groups first identified among period III isolates, nine (35%) were no longer circulating during period IV. Of the 24 clonal groups infecting patients in period IV, three had not been previously identified.

The four major clonal groups, CgC (49 isolates), CgA (40 isolates), CgH (33 isolates), and Cg3 (20 isolates), accounted for 41% of all the *E. coli* isolates and 54% of the clonally grouped *E .coli* isolates during periods III and IV. CgC (72 isolates) and CgA (61 isolates) were present during all four sampling periods, while CgH (50 isolates) was isolated during each of the last three periods and Cg3 was recovered only during periods III and IV (Table 19).

ERIC2-PCR Clonal Groups and Antimicrobial Resistance

The association of ERIC2 clonal groups with the prevalence of drug resistance was assessed. No statistically significant differences were found in the prevalence of TPM/SMX resistant (*P* = 0.74), multi-drug resistant (*P* = 0.36) or pansusceptible isolates (*P* = 0.54) between clonal and nonclonal group isolates during periods III and IV. However, the antimicrobial drug

susceptibility pattern was significantly associated with specific clonal groups, as assessed by the test of negative binomial vs. Poisson regression (Table 19).

Seventy-eight (55%) of the 141 TMP/SMX resistant *E. coli* isolates belonged to 11 clonal groups. During periods III and IV, these 11 clonal groups accounted for 41 (73%) of 56 TMP/SMX resistant UTI and 159 (46%) of all 346 UTI ($P<0.001$). Four of these clonal groups (10 isolates) were entirely composed of TMP/SMX resistant, MDR isolates and accounted for ten (18%) of 56 TMP/SMX resistant UTI ($P<0.001$) and ten (2.9%) of all 346 UTI, during periods III and IV.

The association of the major clonal groups (CgA, CgC, CgH, and Cg3) with antimicrobial resistance was examined further. These major clonal groups accounted for 203 (35%) of the 584 isolates genotyped in this study. A single clonal group, CgA, was responsible for 40 (12%) of the 346 UTI cases during periods III and IV. However, during these periods, this clonal group accounted for three (60%) of five ciprofloxacin resistant UTI ($P <0.05$), 19 (34%) of 56 TMP/SMX resistant UTI ($P<0.001$), 22 (20%) of 108 ampicillin resistant UTI ($P<0.001$), and 24 (21%) of 117 MDR UTI ($P<0.001$) (Table 19).

None of the 61 CgC isolates identified over the course of our study were resistant to ciprofloxacin or nitrofurantoin and only five (8%; all isolated in Period III) were resistant to TMP/SMX. Although accounting for only 31 (13%) of the 230 UTI during Period III, CgC was responsible for 17 (21%) of 80 ampicillin resistant isolates ($P <0.05$), 17 (20%) of 84 MDR isolates ($P <0.05$), five (14%) of 37 TMP/SMX resistant isolates ($P = 1$) and 11 (10%) of the 108 pansusceptible isolates ($P =0.18$) during period III. However, during period IV, CgC was associated with 18 (16%) of the 116 UTI and 13 (21%) of 61 pansusceptible infections ($P =0.08$) but only one (3.6%) of 28 ampicillin resistant UTI ($P = 0.07$), one (3%) of 33 MDR UTI ($P <0.05$) and none of the 19 TMP/SMX resistant UTI ($P <0.05$).

During periods III and IV, CgH was responsible for 33 (9.5%) of all 346 UTI, three (5.4%) of 56 TMP/SMX resistant UTI ($P =0.32$) and two (50%) of four nitrofurantoin resistant UTI ($P <0.05$). Cg3 accounted for 20 (5.8%) of 346 UTI and 18 (11%) of 169 pansusceptible infections ($P<0.001$) during periods III and IV. Eighteen (90%) of the 20 Cg3 isolates were pansusceptible and two (10%) showed intermediate susceptibility to cephalothin.

Temporal Clustering of ERIC2-PCR Clonal Groups

Temporal clustering, defined as the isolation of the same clonal group strain from two or more women on the same day, was observed during all periods of our study. There were 33 (1.7% of all clinic visits) instances of two or more unrelated patients infected with the same ERIC2 clonal group presenting to the clinic on the same day. Six clonal groups, including CgA and CgC, were responsible for these clusters (Table 20). Although no significant temporal clustering was detected by Chi square or negative binomial regression analysis, notable clusters of pansusceptible Cg3 isolates and TMP/SMX resistant, MDR CgC isolates were observed during period III.

Discussion

Large surveillance networks [84] [10] continue to report trends and marked geographic variation in the prevalences of antimicrobial resistance of uropathogenic *E. coli*; such data are often used to guide empirical treatment choices [126], [56]. However, the increasing use of UTI management strategies that decrease the number of routine urine cultures performed from patients with UCA-UTI may result in antimicrobial susceptibility data that are unrepresentative of women with UCA-UTI. To assess whether such biases exist in the estimation of prevalence of drug resistant CA-UTI, a population-based study was conducted a in a single community over four different periods spanning six years. In each period, the drug susceptibility of all consecutively collected *E. coli* isolates from women with CA-UTI was assessed.

Contrary to expectation, no evidence of increasing or decreasing resistance to commonly prescribed antimicrobial agents was detected in this community over the four years of our study, except for a decrease in ampicillin resistance between periods III and IV. Notably, 75% of this decrease in the prevalence of ampicillin resistance could be attributed to a single *E. coli* clonal group (CgC).

These results are consistent with those from a study performed with a similar sampling strategy at the Stoneybrook University Student Health Service. (Stoneybrook, NY). A comparison of results from a seven-month study period in 2003 with those from a similar period in 1993 [127] found no significant increase in the prevalence of drug resistance. Interestingly, the 14% prevalence of TMP/SMX resistance among *E. coli* isolates recorded by Ansbach et al [127] was observed in a community where TMP/SMX remained the most commonly prescribed empirical therapy for UTI, while in our university community with an 18% prevalence of TMP/SMX resistance, the health service had switched (in early 1999) from prescribing TMP/SMX to treating with nitrofurantoin or ciprofloxacin. The prevalence of nitrofurantoin and ciprofloxacin resistance remained similar in both communities over the different study periods.

Our genotyping results support the growing body of evidence that most CA-UTI are associated with a limited number of strains of *E. coli,* which belong to distinct phylogenic groups [53, 128] and are sometimes associated with community outbreaks [12, 51, 52]. Our study documents that the majority (75%) of all *E. coli* CA-UTI in the university community were associated with ERIC2 clonal group membership. Earlier studies based on the typing of selectively or randomly sampled collections of isolates did not find this level of clonality [86, 96, 129].

Although clonal group *E. coli* isolates were no more likely to be antibiotic resistant than nonclonal group isolates, antibiotic resistance was concentrated within a small number of clonal groups. Furthermore, our six year comparison in the same community provided us with an opportunity to determine if pan-susceptible clonal group strains became resistant over this period. Interestingly, there was little evidence that the acquisition of resistance by initially pansusceptible strains contributed substantially to drug-resistant UTI during any of the sampling periods.

During the first sampling period, Manges et al [12] identified a previously unrecognized multi-drug resistant genetically related group of *E. coli,* CgA. This single group was responsible for 11% of all *E. coli* isolates and 49% of TMP/SMX resistant *E. coli* isolates from patients with CA-UTI at the university health service during period I. Subsequent studies have revealed CgA to be responsible for cystitis, pyelonephritis and septicemia in many geographic locations within the US and Europe [53, 96, 130] [131]. Many CgA isolates exhibit a similar multi-drug resistant antimicrobial susceptibility pattern, PFGE profile, and multilocus sequence type (MLST) membership, and carry a class 1 integron with a single arrangement of class 1 drug-resistance gene cassettes (*dfrA17-aadA5*) [132] [133] The isolation of *E. coli* indistinguishable by ERIC2-PCR that belonged to CgA from animals and retail poultry meat products [45, 49] suggests that contaminated food products could be a source of human drug-resistant CA-UTI. Over the six years of our study, CgA accounted for 12% of all typed isolates and 30% of isolates resistant to TMP/SMX, ciprofloxacin or nitrofurantoin (p<0.001).

This study demonstrates that the proportion of *E. coli* UTI caused by drug resistant strains any one time is greatly affected by the prevalence of a small number of circulating clonal groups of uropathogenic *E. coli.* The probability that different women with no obvious common exposure would be infected with such drug resistant clonal groups by chance alone is low. The resistant clonal *E. coli* groups that were detected are more likely to have already been resistant when introduced into this university community. These observations suggest that the fluctuations in the proportion of UTI in a community that are drug resistant cannot be solely explained by local drug prescribing practices, regardless of what these practices may be. If the antimicrobial drug resistant UTI in this community was a result of human antibiotic prescribing or use practices, the selective pressures of the drugs should have yielded many more genetically distinct drug resistant *E. coli* isolates. Thus, the recommendation to restrict human antibiotic use at the community level may not have the expected impact on diseases such as drug-resistant UTI. Strategies developed to maintain the usefulness of CA-UTI empirical treatment options may need to include interventions that target sources of drug-resistant *E. coli.*

Chapter 8: Summary Results and Conclusions

This dissertation is comprised of two main studies that illuminate the dynamics of antimicrobial resistance among community-acquired uropathogens infecting northern California women and provide current information to inform urinary tract infection (UTI) treatment decisions and to aid the development of evidence-based regional guidelines for empirical treatment of UTI. In addition, the studies provide evidence that the scope of strategies necessary to maintain the usefulness of available empirical treatment options for UTI may need to be broadened to include interventions that target sources of antimicrobial resistant uropathogens, especially *Escherichia coli* (*E. coli*) .

Complementary study designs were used to investigate the changes in antimicrobial resistance among uropathogenic *E. coli* causing community-onset UTI (CA-UTI) in two different populations of northern California women. A retrospective cohort study was performed in a large health maintenance organization that maintains comprehensive electronic data on its patients, the Kaiser Permanente Northern California Health Plan (KPNC). This study illustrated that existing electronic health data can be validly and efficiently used to elucidate the epidemiologic features of uropathogen antimicrobial resistance and to document trends in empirical treatment and in the 30-day outcomes of women with CA-UTI. In addition, a series of cross-sectional studies was performed at a California university healthcare service. This series of studies, which highlighted the important role that molecular typing has in delineating the dynamics of the spread of antimicrobial resistance in CA-UTI, detailed the ERIC2-PCR-defined clonal composition of uropathogenic *E. coli* isolated from CA-UTI and its relationship with antimicrobial resistance; it also corroborated the antimicrobial resistance patterns and trends observed in the larger cohort study.

Strengths and Limitations

Retrospective Cohort Study

The use of electronically-linked administrative, pharmacy, and laboratory data in the cohort study allowed a highly powered, cost-effective, eight-year temporal analysis of antimicrobial resistance trends in a well-characterized convenience sample of isolates from microbiologically-investigated CA-UTI. The additional data that were linked to the laboratory records facilitated the stratification of resistance proportions based on patient characteristics such as age, UTI disease category, and previous antimicrobial use. This study was subject to the limitations inherent in the use of retrospectively examined, secondary data and required a number of assumptions. It was assumed that the exclusions and definitions used to identify the study's subjects and their UTI events allowed us to fully capture all CA-UTI events during the study period and to accurately classify these events as complicated (CCA-UTI) or uncomplicated CA-UTI (UCA-UTI). We assumed that study subjects received all of their medical services within the KPNC system and that these services were fully captured by the computer algorithms. Further, it was assumed that patients who were prescribed antimicrobial drugs within two days of an identified UTI were compliant, taking their medication as prescribed, and that medical services received in the 30-risk period that generated a UTI-related ICD-9 code were due to incomplete resolution of UTI symptoms.

The UTI definitions and disease classifications used in the cohort study required knowledge of a woman's medical services utilization for the 365 days preceding the onset of each UTI event and the definition of treatment failure required knowledge of her utilization of medical services for the 30 days following each primary UTI event. Twenty-five percent (range 23% – 27% annually over the eight years of the study) of the UTI that were initially classified as a primary UTI (no record of an additional UTI in the preceding 365 days) occurred in women whose KPNC membership began less than one year before or ended less than 30 days after their UTI. These UTI were excluded from the analysis because they could not be accurately classified by onset type or by UTI disease and their 30-day clinical outcome could not be accurately assessed. The median age of women with a UTI that was excluded because of incomplete KPNC membership was eight years younger than the median age of women with a UTI for which complete membership information was available.

UTI that were treated with a drug that was purchased before the UTI event or outside the Kaiser system would have no study-defined treatment data in the Pharmacy Information Management System (PIMS). No treatment data were available for 22% of the primary UTI that had complete membership information (range 20% – 24% annually over the eight years); these UTI were excluded from the analyses presented in Chapters 5 and 6. The median age of women with UTI that were excluded due to missing treatment information was approximately six months younger than the median age of women with UTI who had PIMS treatment data available. Therefore, a total of forty-two percent of the primary UTI that were initially identified were excluded because of missing treatment data or incomplete membership information (range 40% – 44% annually over the study period). The results of the cohort study will be biased to the extent that excluded UTI events differed from those remaining in the study. The cohort study under-represents UTI in younger women who had interrupted healthcare insurance or who changed health insurance systems. In addition, this study under-represents UTI in woman who did not have pharmacy coverage through KPNC.

Serial Cross-sectional Study

The smaller, more costly, university health service based study, which sampled all urine specimens from female patients presenting to the university health service clinic with symptoms suggestive of UTI, allowed the molecular characterization of *E. coli* isolates and eliminated any sampling bias due to practitioner urine culture ordering practices. In addition, all laboratory procedures in this smaller study were performed by the same team over a reasonably short period of time, thus reducing laboratory biases, i.e. inter-operator biases, and biases due to run-to-run variations and variations in procedures, reagents, instruments, and testing systems which occur over extended periods of time. The relatively small size of the cross-sectional samples reduced the precision of antimicrobial resistance prevalence estimates and limited the study's statistical power to detect small temporal changes in antimicrobial resistance.

Major Findings

The cohort study revealed that the distribution of etiological agents causing community-acquired UTI in Northern California remains consistent with the findings of contemporaneous surveys in North America [9, 11] and in Europe [89, 104]. *E. coli* was the predominant uropathogen; approximately 85% of UCA-UTI were caused by *E. coli* and 12% were caused by

other enteric bacilli. The prevalence of trimethoprim/sulphamethoxazole (TMP/SMX) resistance was higher among *E. coli* (19%) than it was among the other gram negative uropathogens (6%). On the other hand, resistance to nitrofurantoin was minimal among *E. coli* (2%), but much more common among the other gram negative uropathogens (64%), many of which have intrinsic resistance to this drug. Estimates of proportions and trends in the antimicrobial resistance of uropathogenic *E. coli* were consistent between the two studies. Seventy-three percent of all uropathogens and 80% of *E. coli* isolated from CA-UTI remain susceptible to both TMP/SMX and nitrofurantoin. Importantly, contrary to expectation, we found no evidence to support the hypothesis that resistance to the first line UTI treatment antimicrobial, TMP/SMX, was increasing among uropathogens isolated from CA-UTI in northern California. Resistance to TMP/SMX among uropathogens peaked in 1998 and 1999 (19% among all uropathogens, 21% among *E. coli*) and then stabilized, with minor fluctuations, below 20% during the next six years. Resistance to nitrofurantoin among *E. coli* remained stable at ≤ 2%, but rose among other gram negative rods from 53% in 1998 to 77% in 2005. However, 95% of TMP/SMX resistant uropathogens (97% of TMP/SMX resistant *E. coli*) remained susceptible to nitrofurantoin. Significantly, while ciprofloxacin resistance among *E. coli* uropathogens remained at or below 3% in both populations, it steadily increased over the eight years of the study. Among uropathogens in the KPNC population, ciprofloxacin resistance rose from 0.7% (0.4% among *E. coli*) in 1998 to 2.6% in 2005 (2.8% among *E. coli*). Notably, 63% of ciprofloxacin-resistant uropathogens and 71% of ciprofloxacin-resistant *E. coli* were additionally resistant to TMP/SMX, nitrofurantoin or cefazolin.

As expected, the KPNC clinical laboratory data, which were found to over-represent uropathogens from women 15 to 20 years old, women treated with an antimicrobial other than TMP/SMX, women with CCA-UTI and women who subsequently failed treatment, resulted in more precise but higher estimated prevalences of resistance among *E. coli* isolates than did our smaller study, which cultured urine specimens from all women presenting with UTI symptoms.

The Infectious Diseases Society of America (IDSA) recommends that surveillance be established to monitor resistance to TMP/SMX among *E.coli* from women with UCA-UTI. The IDSA also advises that TMP/SMX be replaced as the first line antimicrobial for empirical treatment of UCA-UTI when community estimates of the prevalence of resistance to TMP/SMX among *E.coli* from women with UCA-UTI exceed 20%. Estimates of community levels of TMP/SMX resistance based on *E.coli* from all women with CA-UTI may be misleadingly high due to the inclusion of isolates from women with CCA-UTI, which are more likely to be resistant to TMP/SMX. Our linked data-base cohort study had the advantage of providing pharmacy and administrative data that allowed the identification of the subset of CA-UTI from women who had no evidence of a complicated UTI. This restricted population provided a less biased estimate of antimicrobial resistance to commonly prescribed empirical treatment drugs among uropathogens from UCA-UTI. Estimates of TMP/SMX resistance among *E. coli* isolated from women with UCA-UTI ranged from 14% - 17% (12% to 15% among all uropathogens) over the eight years of the study.

Importantly, between 1998 and 2005, practitioners within the KPNC system were increasingly replacing TMP/SMX with ciprofloxacin as empirical treatment for women with CA-UTI. Although there was an increase of 19% in the proportion of women with CA-UTI who

received ciprofloxacin treatment, there was only a 2% decrease in the proportion of women who received a treatment drug to which their infecting uropathogen was resistant. More importantly, the dramatic increase in the use of ciprofloxacin to treat UCA-UTI (13% of treatments in 1998 to 30% in 2005) was accompanied by no detectable change in the proportion of women returning to the KPNC system for further care of their UTI within the 30-day risk period. Treatment failure (17.8%) decreased by less than 1% over the eight years of the study. In addition, 72% of all ciprofloxacin-treated culture-confirmed UCA-UTI were infected with a uropathogen that was susceptible to TMP/SMX, nitrofurantoin and to cefazolin, suggesting that a large proportion of the ciprofloxacin-treated CA-UTI could have been treated successfully with an older narrow spectrum antimicrobial agent.

The use of cephalexin for the treatment of UTI remains problematic. Twelve percent of KPNC women with a UCA-UTI received empirical cephalexin treatment and 19% of them failed treatment. Cephalexin was found to be the least effective of the four drugs commonly used for the treatment of UCA-UTI and its use was associated with a 7% increase in the risk of treatment failure (adjusted RR 1.07, 95% CI 1.03 – 1.11) compared to the use of TMP/SMX, nitrofurantoin or ciprofloxacin. The increased risk of treatment failure associated with cephalexin treatment was more pronounced in the smaller population of women known to be infected with a uropathogen that tested susceptible to TMP/SMX, nitrofurantoin, ciprofloxacin, cephalothin, and cefazolin (adjusted RR 1.25 95% CI 1.14 – 1.38). The inability of clinical laboratories to perform standardized and approved cephalexin susceptibility testing severely hampers evidence –based decision-making for the use of this drug. The results from the cohort study clearly demonstrate that neither cephalothin susceptibility testing (the CLSI recommended proxy susceptibility test for cephalexin) nor cefazolin susceptibility testing (the other first generation cephalosporin with a standardized and approve susceptibility test protocol) adds information that is useful in predicting clinical outcome in patients treated with cephalexin. On the other hand, TMP/SMX, nitrofurantoin and ciprofloxacin susceptibility testing were shown to add information that was useful for predicting treatment outcome. U.S. federal approval and CLSI standardization of a cost-efficient methodology for clinical testing of cefazolin susceptibility is overdue.

The consistency of the estimated antimicrobial resistance prevalences among the two studies and between the 14 KPNC regions suggests that these estimates could be plausibly generalized to the larger population of northern California women with CA-UTI. We also believe that our evaluation of the utility of proxy susceptibility testing to predict outcomes of cephalexin treatment would be valid outside our study population. On the other hand, prescribing practices may differ significantly among practitioners in different health systems, making generalizations about antimicrobial choice and subsequent treatment outcomes less certain.

Genotyping of *E. coli* uropathogens isolated during the cross-sectional studies revealed that over 75% of *E. coli* CA-UTI were associated with an ERIC2-PCR defined clonal group. Importantly, antimicrobial resistance was concentrated within a small number of specific clonal groups. Four large clonal groups were responsible for 52% of the CA-UTI that were resistant to TMP/SMX, nitrofurantoin or ciprofloxacin, and a previously unrecognized clonal group, CgA, was responsible for 11% of *E. coli* isolates and 49% of TMP/SMX resistance during the first

study period. This same clonal group was responsible for 12% of the *E. coli* CA-UTI, 60% of the ciprofloxacin resistance, 34% of the TMP/SMX resistance, 25% of the nitrofurantoin resistance, and 18% of the cefazolin resistance observed during the last two sampling periods. Notably, no initially pan-susceptible clonal groups gained resistance over time.

The results of the cross-sectional study suggest that fluctuations in the prevalence of CA-UTI caused by TMP/SMX resistant *E. coli* cannot be solely explained by UTI treatment practices and may be related to the introduction of resistant clonal groups into a community through contaminated food or other sources. Further evidence of this can be seen in our cohort study where the significant and steady decrease in the use of TMP/SMX over the eight years of our study was not associated with a detectable sustained decrease in TMP/SMX resistance.

Of interest is the striking increase in nitrofurantoin resistance among *Klebsiella pneumoniae*, the second most common uropathogen isolated during the cohort study. The proportion of *Klebsiella pneumoniae* strains resistant to nitrofurantoin more than doubled from 2003 to 2004 and 2005, while the proportion of CA-UTI treated with nitrofurantoin varied only 1.4% over the eight years of the study (range 8.9% - 10.3%). This suggests that the introduction of a resistant clone, as was observed with the CgA strain of *E. coli,* or the spread of a mobile resistant gene element may have occurred during this time period. The computer algorithms developed for the cohort study could be efficiently automated to provide on-going surveillance to detect changes that would signal the need for further study to evaluate possible outbreaks and to modify treatment guidelines or current strategies to preserve treatment effectiveness. Had a surveillance system been in place during the study period, the observed increase in resistance to nitrofurantoin among *Klebsiella pneumoniae* isolates would have been detected early enough to retain the laboratory isolates necessary to perform genotyping analysis and to evaluate the mechanism(s) of nitrofurantoin resistance and its dissemination among the *Klebsiella pneumoniae* strains causing CA-UTI.

Conclusions

In conclusion, these studies have shown that, in two representative northern California populations, TMP/SMX resistance among *E. coli* causing CA-UTI was not increasing over the time period studied. Furthermore, in the KPNC population, where the laboratory sample could be restricted to *E. coli* uropathogens from women with uncomplicated CA-UTI, the proportion of *E. coli* that was resistant to TMP/SMX (annual range 14 – 17%) remained below the IDSA-recommended critical value of 20% for replacing TMP/SMX as first line empirical treatment. Our studies suggest that TMP/SMX and nitrofurantoin remain viable treatment options for women with uncomplicated community-acquired UTI.

The use of cephalexin as treatment for UCA-UTI is less effective than treatment with TMP/SMX or nitrofurantoin and is hampered by the lack of a reliable susceptibility testing protocol.

The sustained increase in the use of ciprofloxacin and the accompanying decrease in the use of TMP/SMX as empirical treatment for CA-UTI in the KPNC population have not been accompanied by sustained decreases in treatment failure, microbiologically inappropriate

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treatment or TMP/SMX resistance among uropathogens, but have been accompanied by a small but steady increase in ciprofloxacin resistance among uropathogens.

Importantly, genotyping of *E.coli* from women with CA-UTI suggests that the prevalence of antimicrobial drug resistance in a community is strongly affected by the clonal composition (i.e. the relative proportions of pan susceptible vs. drug resistant strains) of the uropathogens that are circulating at any point in time. Which strains are present in a community may be less influenced by individual antimicrobial use and clinician prescribing practices than previously believed and restrictions on human antibiotic use at the community level may have less of an impact than expected on the prevalence of drug- resistant CA-UTI.

Large health maintenance organizations that have integrated electronic patient data can efficiently monitor changes in antimicrobial treatment drug use as well as changes in the antimicrobial resistance of uropathogens from well-characterized populations. Ongoing surveillance, once established, coupled with targeted uropathogen genotyping studies, can provide the data necessary to detect outbreaks of resistant uropathogens and to maintain up-to-date treatment recommendations and antimicrobial use policies that balance the ability to successfully treat individual patients with the need to maintain the usefulness of board spectrum antimicrobials, such as ciprofloxacin.

Additional studies are needed to identify common sources of antimicrobial resistant uropathogens and to delineate individual risk factors for drug resistant CA-UTI. In addition, the development of rapid point-of-care tests to identify uropathogens known to be have intrinsic antimicrobial resistance, such as *Proteus* species, to identify multi-drug resistant *E. coli* clones, such as CgA, or to identify individual antimicrobial resistance genes would improve treatment selection decisions and clinical outcomes and may prevent the unnecessary use of broad spectrum antimicrobials. Furthermore, improvements in local treatment practices must be accompanied by nationwide interventions that target sources of drug resistant uropathogens, such *E. coli* and *Klebsiella pneumoniae*.

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Appendices

Figures

Figure 1:   Populations of Kaiser Permanente Northern California Women, ages 15 – 60 years, with Urinary Tract Infections, 1998 – 2005.

Figure 1
Populations of Women
Identified in KPNC
Administrative Databases

318,499 Women
With Primary UTI
1998 – 2005
Median age at ID **34.7** years

244,846 Women
With UTI with complete
Membership data
Median age at ID **36.7** years

Excluded
73,653 Women
Incomplete Membership data
Median age at ID **29.6** years

197,191 Women
With Complete Treated UTI
Median age at ID **36.8** years

Excluded
47,655 Women
With no Complete Treated UTI
Median age at ID **36.2** years

176,391 Women
With Community-acquired
UTI (CA-UTI)
Median age at ID **37.9** years

Excluded
20,800 Women
Hospital/Healthcare Onset only
Median age at ID **36.5** years

64,896 Women
with Culture-Confirmed
Complete Treated CA-UTI
Median age at ID **36.2** years

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Figure 2: **Populations of Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, 1998 – 2005**

Figure 2
Populations of Primary UTI
Identified in KPNC
Administrative Data Bases

397,174 Primary UTI
Median age at UTI **35.6 yrs**
in 318,449 Women

302,787 UTI
Complete Membership Data
Median age at UTI 37.8 yrs
in 244,846 Women

Excluded
94,387 UTI
Incomplete Membership
Median age at UTI **29.9 yrs**
in 90,347 Women

234,685 UTI
Treated within 2 days
Median age at UTI **37.9 yrs**
in 197,191 Women

Excluded
68,102 UTI
No treatment captured
Median age at UTI **37.5 yrs**
in 62,387 Women

205,677 UTI
Community-acquired (CA-UTI)
Median age at UTI **37.9 yrs**
in 176,391 Women

Excluded
29,008 UTI
Hospital/healthcare acquired
Median age at UTI **37.5 yrs**
in 27,781 Women

134,240 CA-UTI
Uncomplicated (UCA-UTI)
Median age at UTI 36.3 yrs
in 121,743 Women

71,437 CA-UTI
Complicated (CCA-UTI)
Median age at UTI **41.0 yrs**
in 63,479 Women

43,055 UCA-UTI
Culture Confirmed
Median age at UTI 34.8 yrs
in 41,318 Women

26,439 CCA-UTI
Culture Confirmed
Median age at UTI 41.1 yrs
in 24,963 Women

Figure 3: **Populations of Urine Cultures submitted to the Kaiser Permanente Northern California Regional Clinical Microbiology Laboratory by Women, ages 15 – 60 years, with Urinary Tract Infections: 1998 – 2005**

Figure 3
Populations of Urine Cultures Identified in the KPNC Laboratory Database

507, 125 urine cultures
in 243,440 women
1998 – 2005 ages 15 - 60
238,548 positive (45%)

EXCLUDED
282,227 urine cultures
Not associated with the diagnosis of a primary UTI

224, 898 urine cultures
Collected within 2 days of a primary UTI
in 195,808 women
152,314 (68%) positive cultures

EXCLUDED
4653 urine cultures
in women from outside the KP system

169, 280 urine cultures
with complete membership information
in 147,835 women
114,699 (68%) positive cultures

EXCLUDED
50, 965 urine cultures
from primary UTI
with incomplete information

144,854 urine cultures
in 129,119 women
with Community-acquired UTI
98,266 positive (68%)

EXCLUDED
24,426 urine cultures
in women with
Hospital or Healthcare associated UTI

88,057 Urine cultures
in 82,220 Women
with Uncomplicated Community-acquired UTI
59,706 positive cultures (68%)

56,797 Urine cultures
in 51,762 Women
With Complicated Community-acquired UTI
38,560 positive cultures (68%)

Figure 4: **Populations of Isolates from Urine Cultures submitted to the Kaiser Permanente Northern California Regional Clinical Microbiology Laboratory by Women, ages 15 – 60 years, with Urinary Tract Infections: 1998 – 2005**

Figure 4
Populations of Isolates from Urine Cultures in KPNC Women with Community-acquired UTI

99,241 Isolates
From 98,266 urine cultures
in 89,397 women
with Community-acquired UTI (CA-UTI)
Median age at UTI 37.0 yrs

60,203 Isolates
From 59,706 urine cultures
in 56,426 women
with **Uncomplicated CA-UTI**
Median age at UTI 34.5 yrs

39,038 Isolates
From 38,560 urine cultures
in 35,614 women
with **Complicated CA-UTI**
Median age at UTI 40.6 yrs

EXCLUDED
838 Isolates
Staphylococcus saprophyticus
From 808 urine cultures
in 837 women
Median age at UTI 23.2 yrs

EXCLUDED
384 Isolates
Staphylococcus saprophyticus
From 377 urine cultures
in 383 women
Median age at UTI 26.5 yrs

59,365 Isolates
From 58,898 urine cultures
in 55,686 women
with **Uncomplicated CA-UTI**
Median age at UTI 34.7 yrs

38,654 Isolates
From 38,183 urine cultures
in 35,276 women
with **Complicated CA-UTI**
Median age at UTI 40.7 yrs

Figure 5:   Populations of Culture-Confirmed Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, 1998 - 2005

Figure 5
Populations of Culture-Confirmed Community-acquired UTI (CA-UTI)

69,494 Culture-Confirmed CA-UTI
in 64,896 women
Median age at UTI 37.4 yrs

43,055 Culture Confirmed Uncomplicated UTI (UCA-UTI)
in 41,318 Women
Median age at UTI 34.8 yrs

26,439 Culture Confirmed Complicated CA-UTI
in 24,963 Women
Median age at UTI 41.1 yr

Excluded
316 UCA-UTI Infected
with >1 uropathogen
In 316 women
Median age at UTI 34.4 yrs

42,437 UCA-UTI
With a single uropathogen
Treated with mono-therapy
in **40,754** Women
Median age at UTI 34.8 yr

Excluded
302 UCA-UTI
Treated with combination therapy
In 301 Women
Median age at UTI 34.3 yrs

37,549 *E. Coli* UCA-UTI
Treated with mono-therapy
in **36,188** Women
Median age at UTI 34.9 yr

4,076 *E. Coli* UCA-UTI
Treated with cephalexin mono-therapy
in **4,076** Women
Median age at UTI 29.4 yr

**Figure 6:   Etiology of Community-acquired Urinary Tract Infections in Kaiser
Permanente Northern California Women, ages 15 – 60 years, 1998 – 2000**
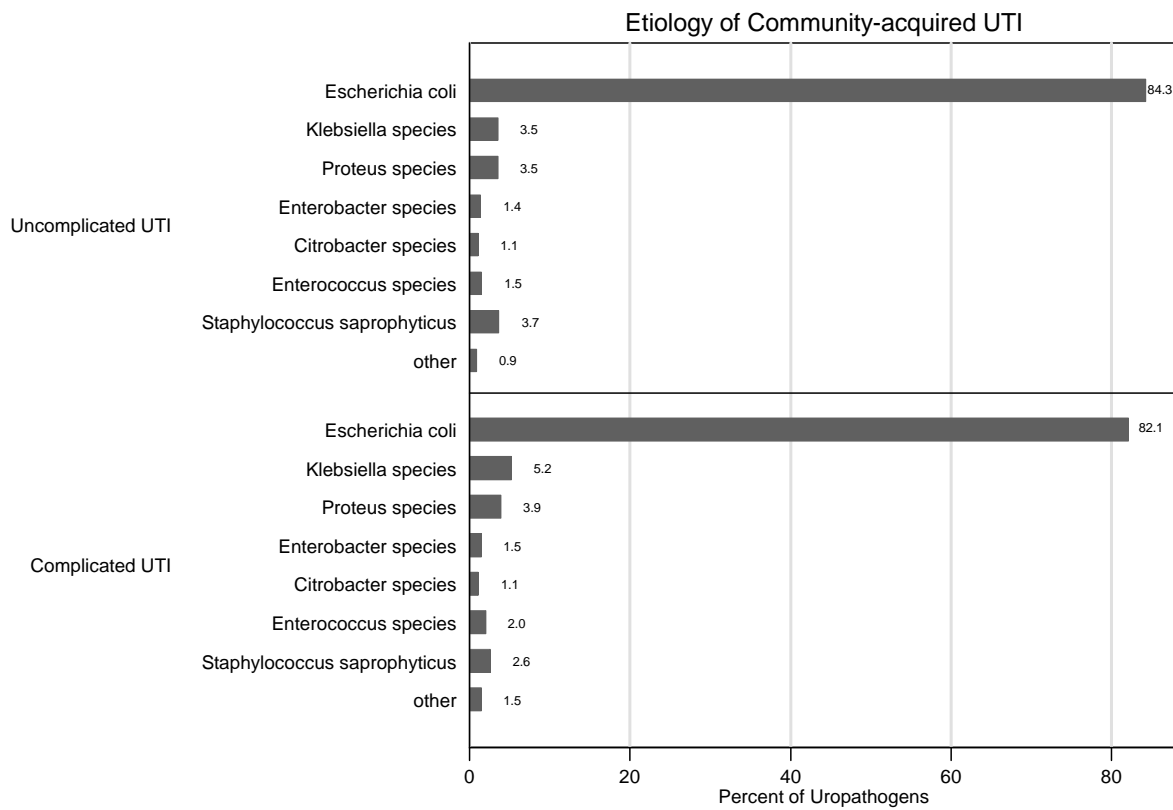
KPNC Laboratory Data 1998 - 2000

Figure 7: **Antimicrobial Resistance of Community-Acquired *Escherichia coli* and Other Uropathogenic Gram Negative Bacilli isolated from Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Year of UTI Onset**
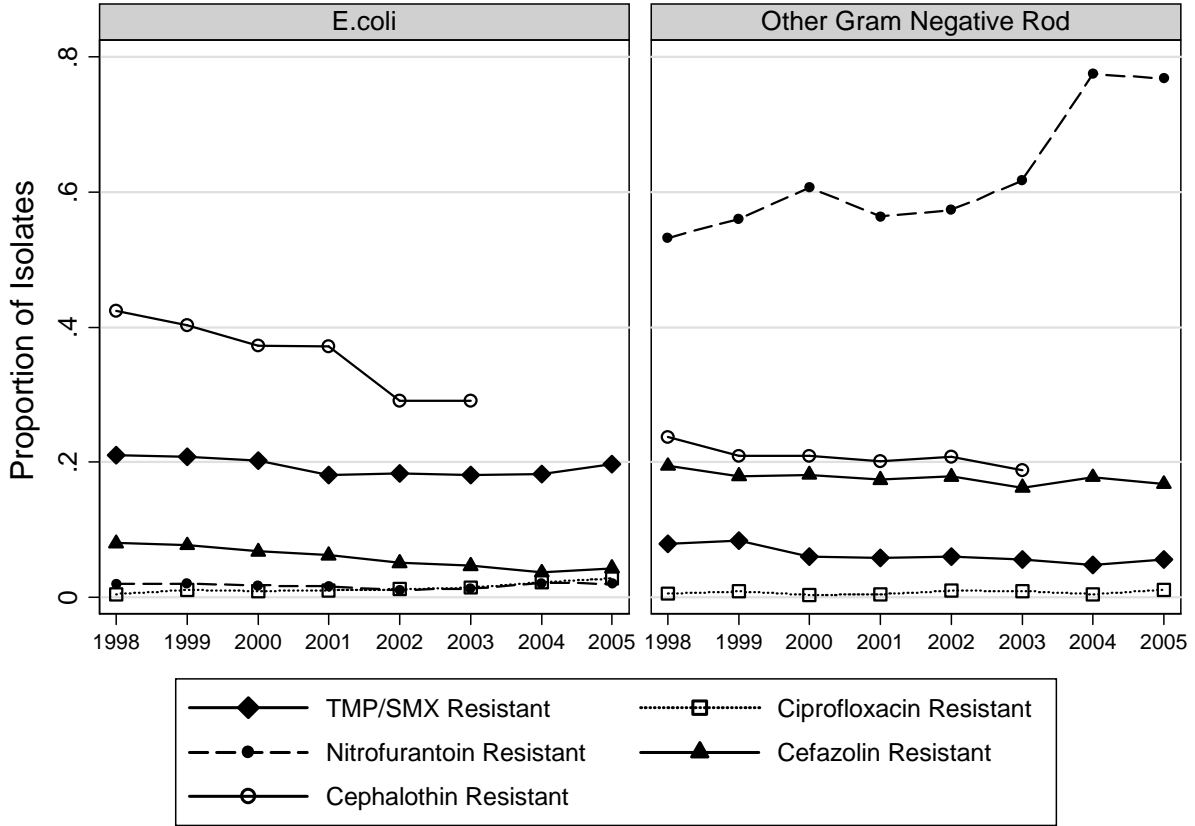
Figure 8: **Antimicrobial Resistance of Community-Acquired *Staphylococcus saprophyticus* and Other Uropathogenic Gram Positive Cocci isolated from Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Year of UTI Onset.**

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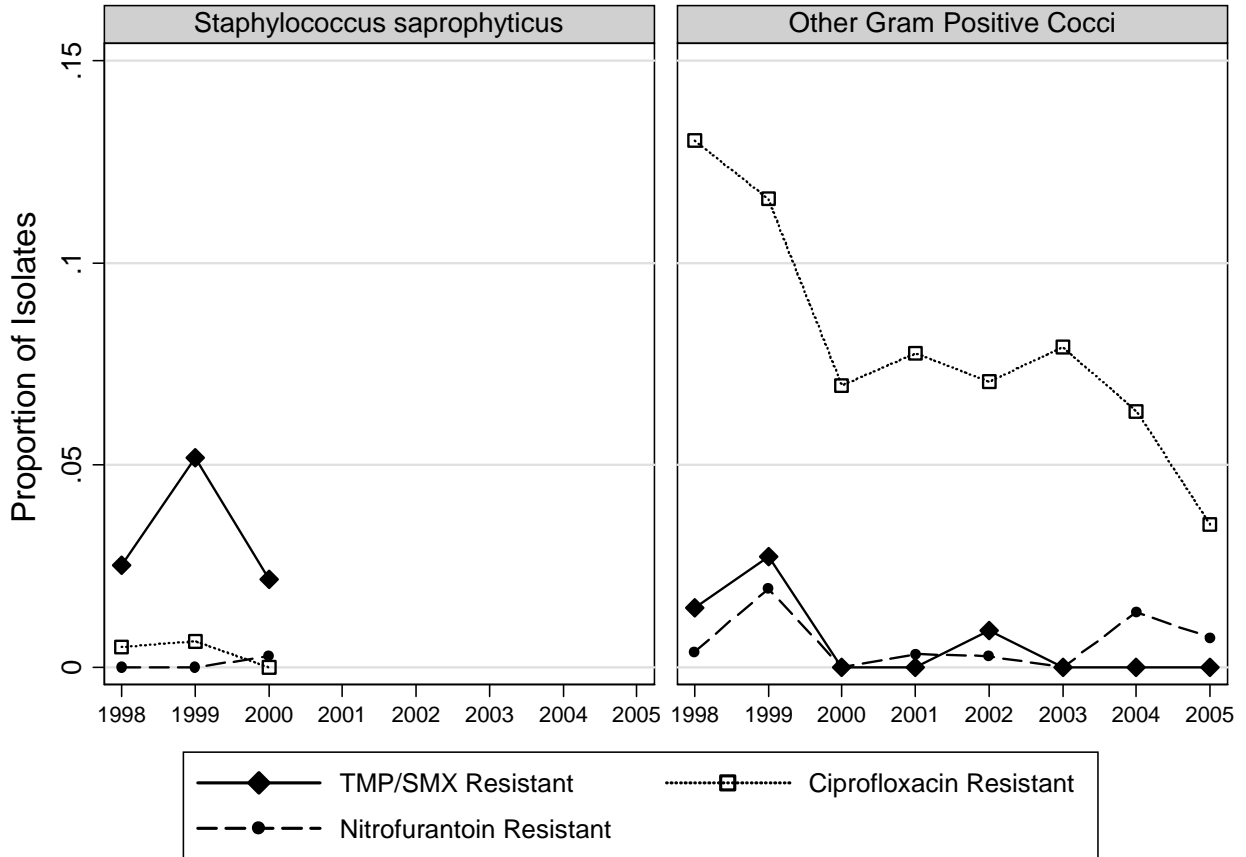
Figure 9: **Antimicrobial Resistance of** *Escherichia coli* **isolated from Uncomplicated and Complicated Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Year of UTI Onset**
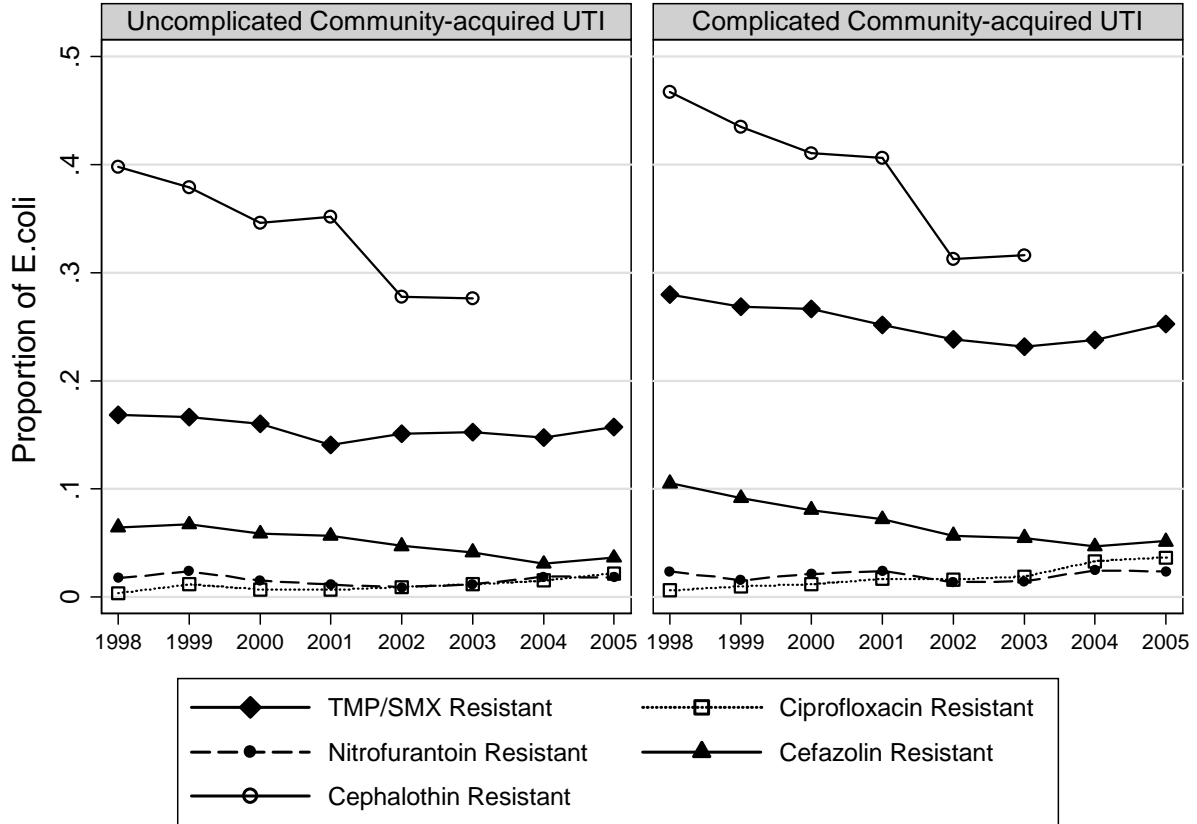
Figure 10: Antimicrobial Resistance of Uropathogens isolated from Uncomplicated and Complicated Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Age Group
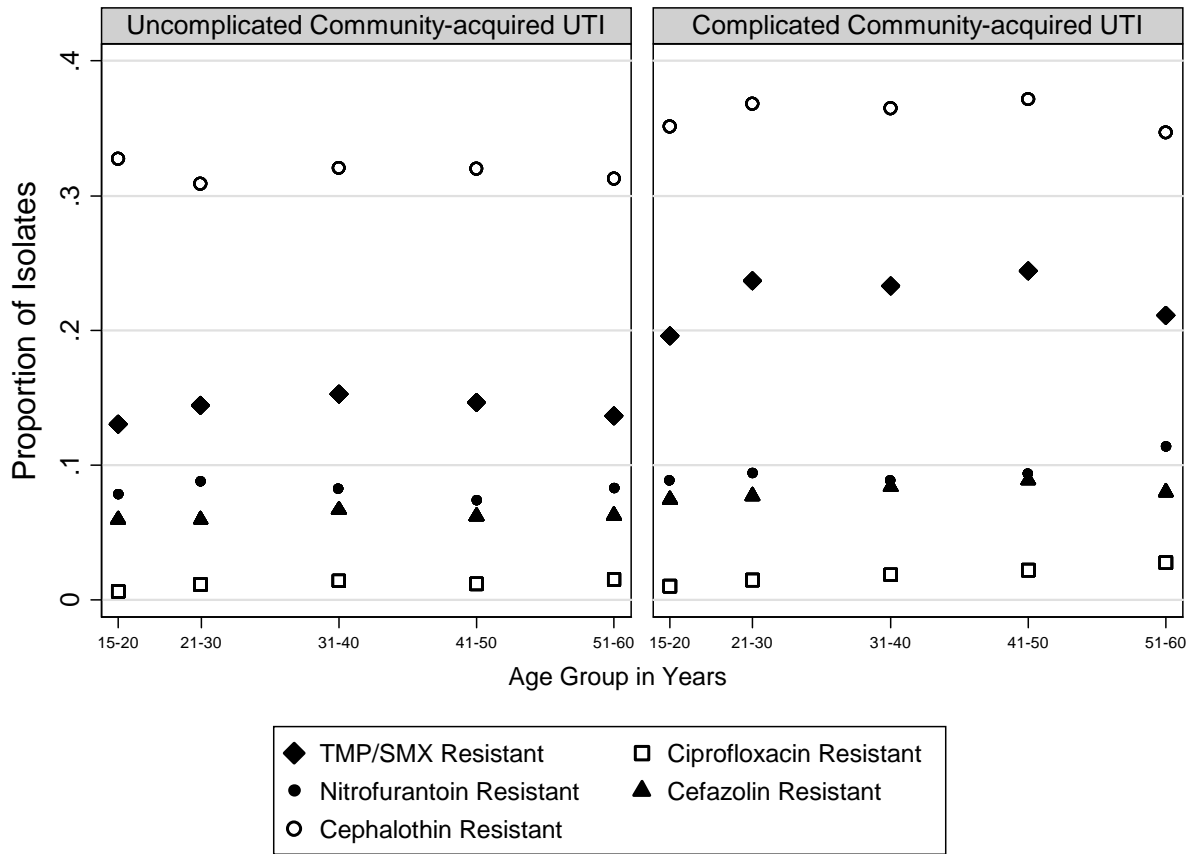
Figure 11: **Antimicrobial Resistance of *Escherichia coli* and Other Gram Negative Uropathogens isolated from Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Age Group**
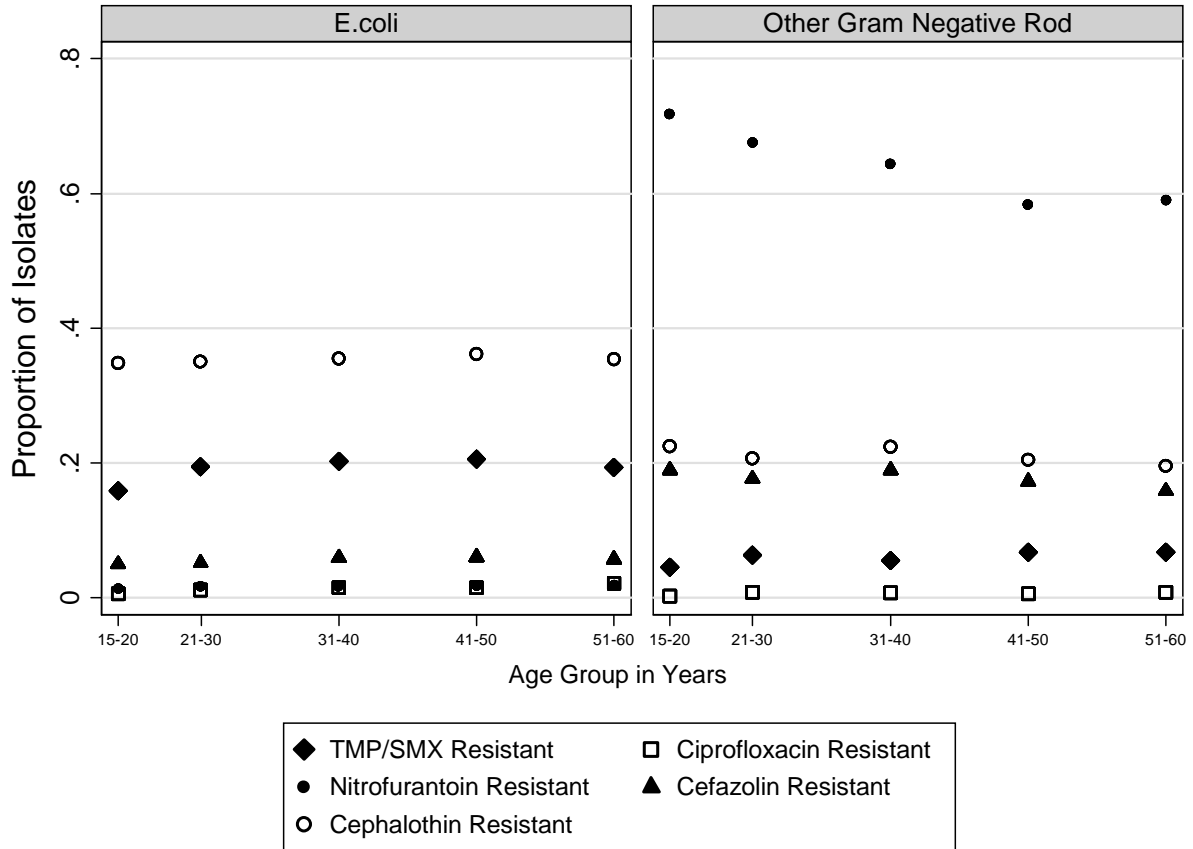
Figure 12: Common Antimicrobial Agents used to treat Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, ages 15 – 60 years, by Year of UTI Onset.
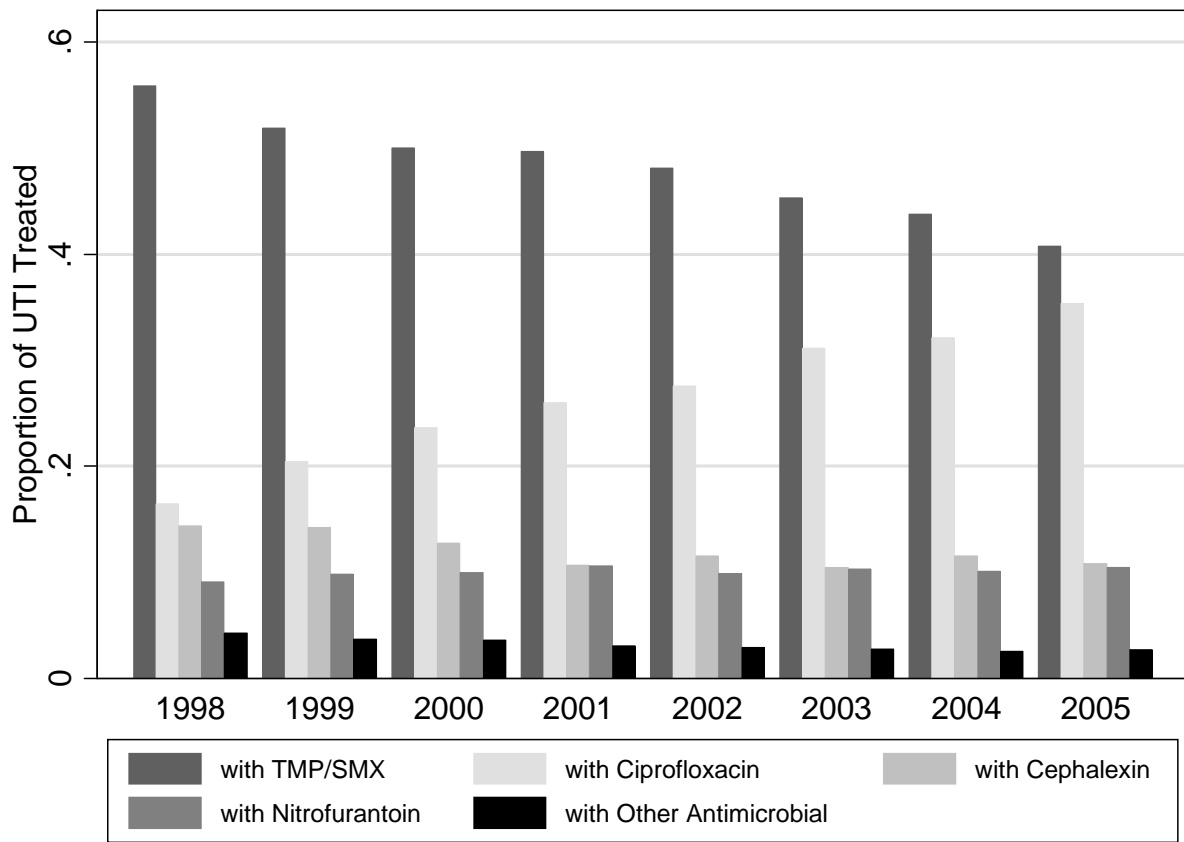
Figure 13: Common Antimicrobial Agents used to treat Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, 1998 – 2005, By Age Groups

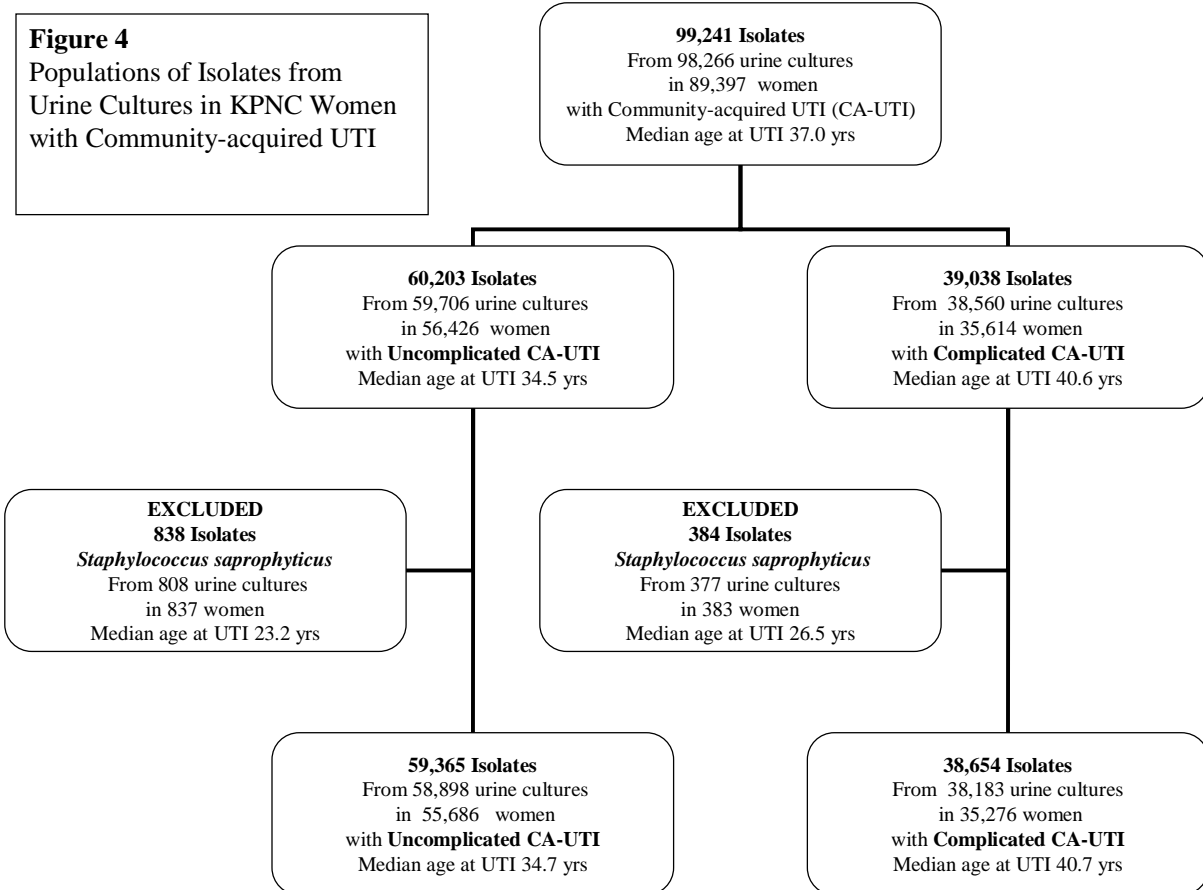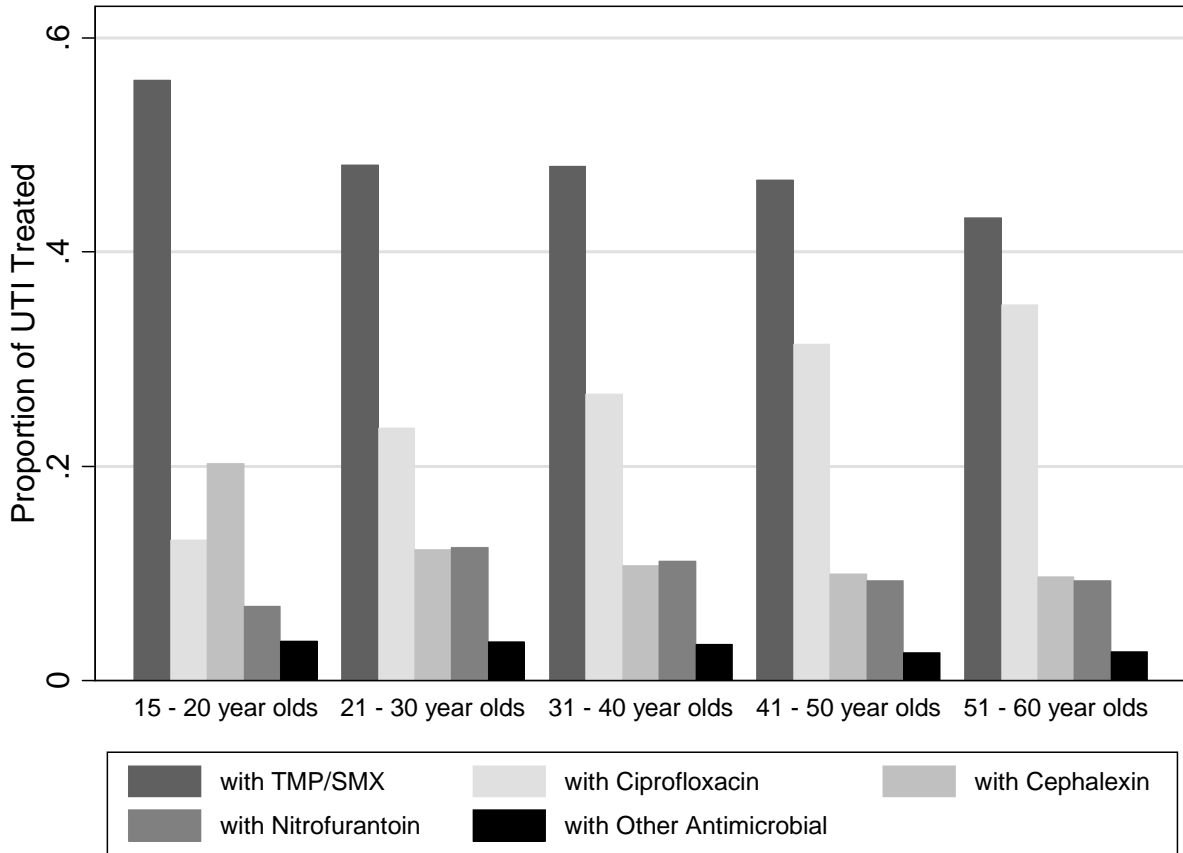**Figure 14: Common Antimicrobial Agents used to treat Uncomplicated and Complicated Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, Ages 15 – 60 years, 1998 – 2005.**
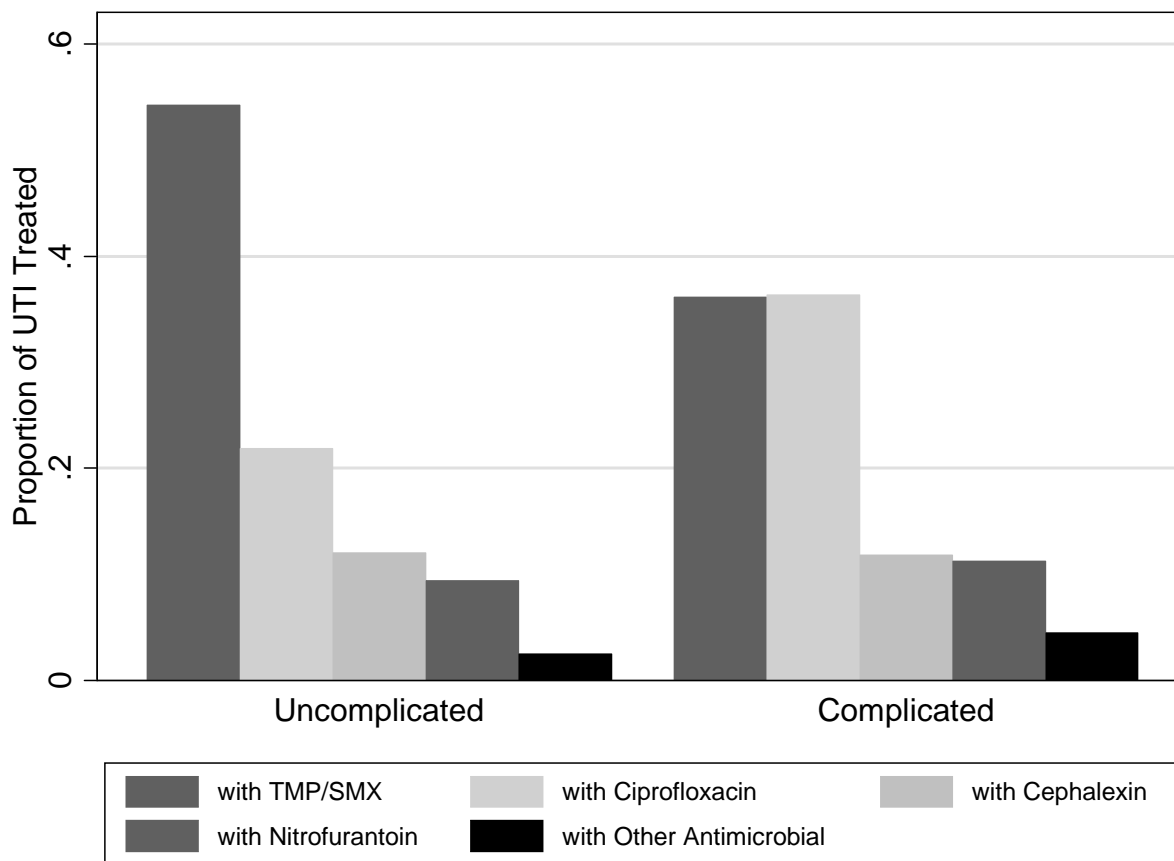
Figure 15: Common Antimicrobial Agents used to treat Uncomplicated and Complicated Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, Ages 15 – 60 years, by Year of UTI Onset
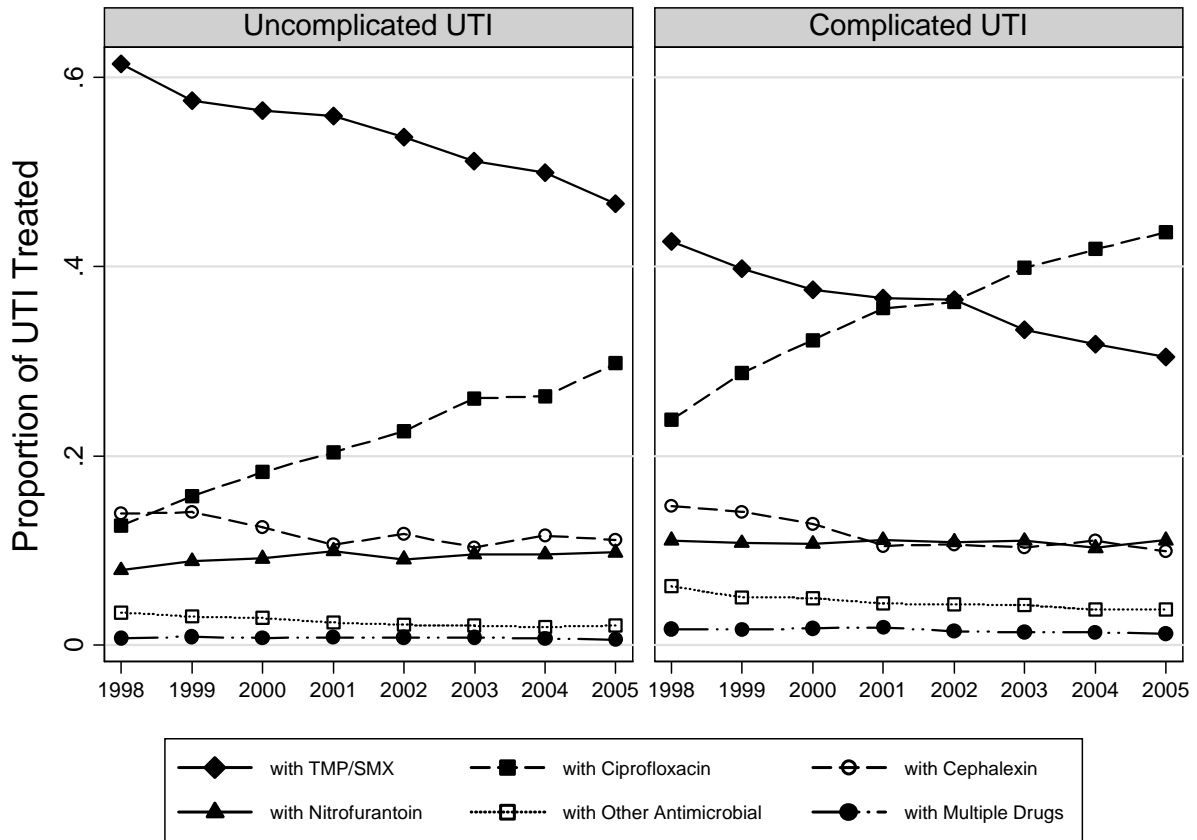
Figure 16: Proportions of Community-Acquired UTI in Kaiser Permanente Northern California Women, Ages 15 – 60, with TMP/SMX Treatment, with Ciprofloxacin Treatment, with Microbiologically Inappropriate Treatment, with a TMP/SMX Resistant Uropathogen and with a Ciprofloxacin Resistant Uropathogen, by Year of UTI Onset.
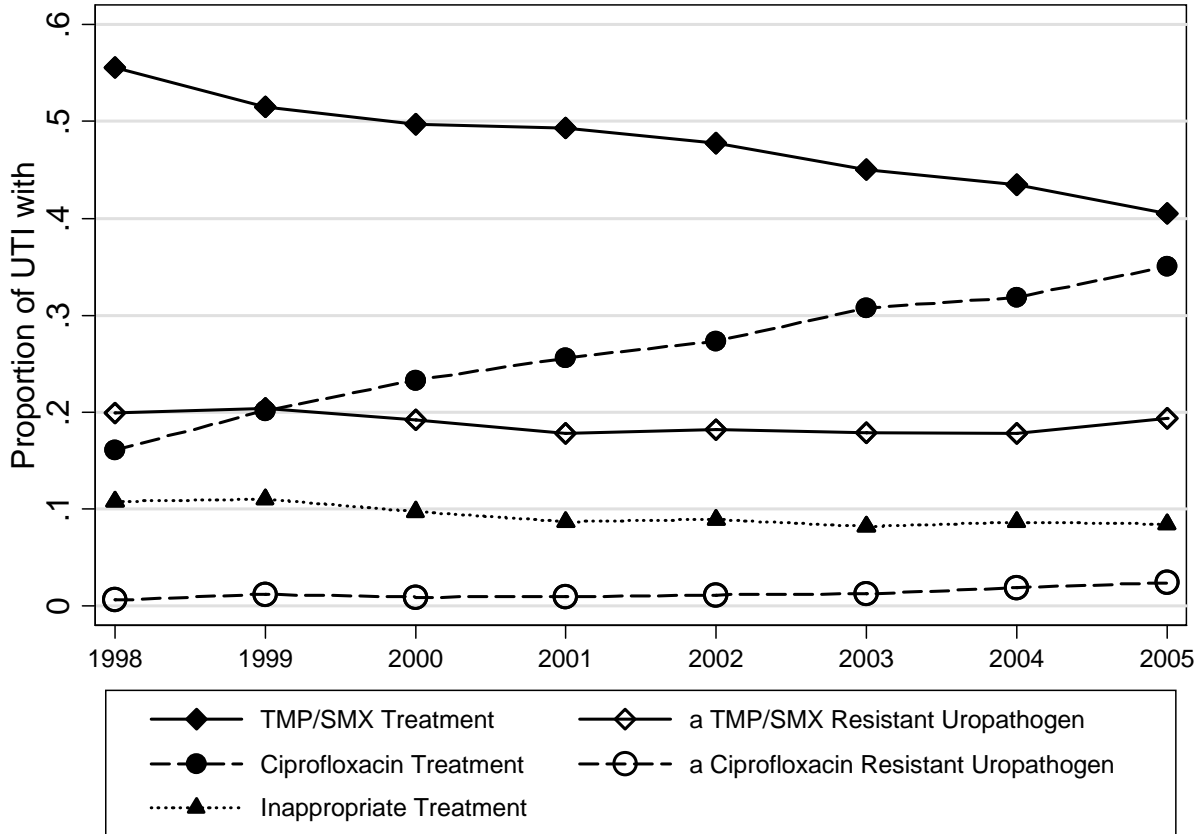
Figure 17: **Proportions of Uncomplicated Community-Acquired UTI in Kaiser Permanente Northern California Women, Ages 15 – 60, with TMP/SMX Treatment, with Ciprofloxacin Treatment, with Microbiologically Inappropriate Treatment, with a TMP/SMX Resistant Uropathogen, with a Ciprofloxacin Resistant Uropathogen, and with Treatment Failure, By Year of UTI Onset.**
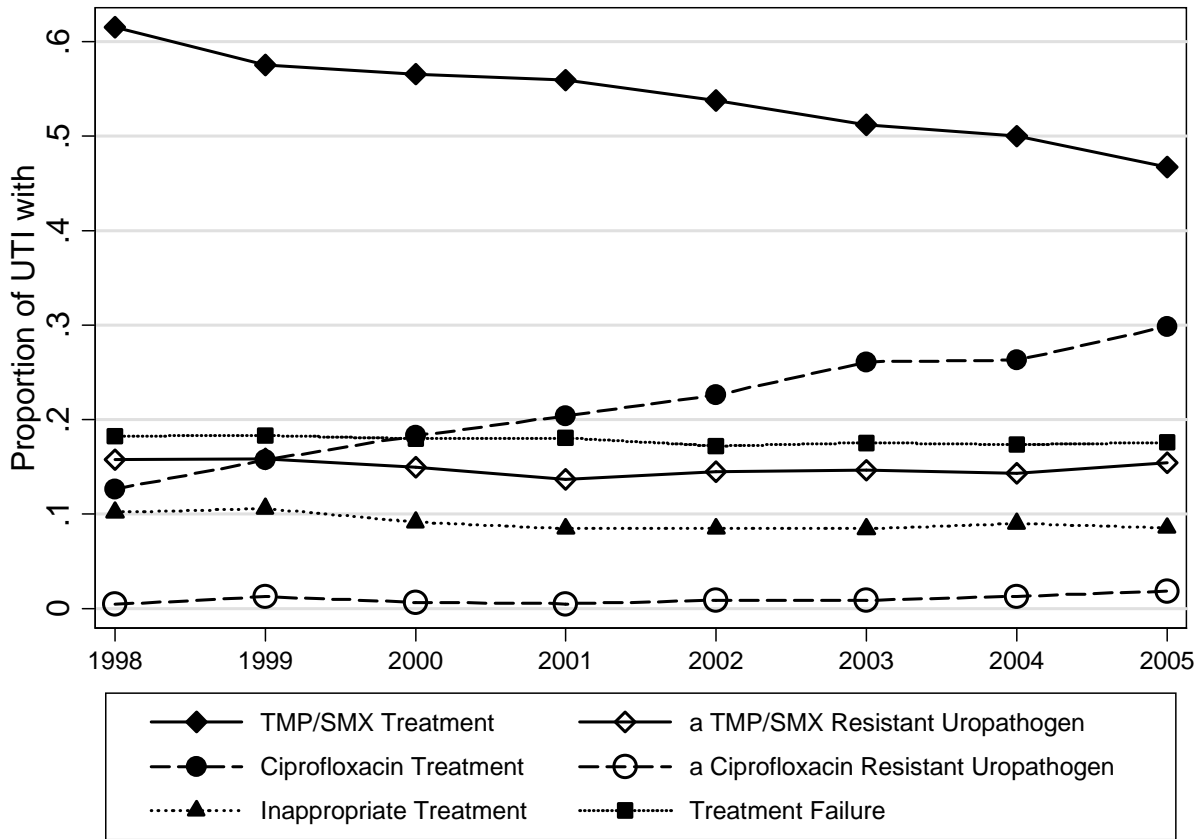
Tables

Table 1:   Kaiser Permanente Northern California Health Plan (KPNC) Administrative Databases

Abbreviation	Database Name	Database Contents
ADT	Admission Discharge and Transfer System	Data from hospitalization records at KPNC hospitals
AOMS	Authorized Outside Medical Services system	Data related to pre-authorized utilization with non-KP providers
CATS	Claims Adjudication and Tracking System	Data relating to non pre-authorized use of non KPNC providers
OSCR	Outpatient Services Clinical Record	Data relating to office visits with KPNC providers
LURS	Laboratory Utilization Reporting System	Data from the KPNC Regional Clinical Microbiology Laboratory
PIMS	Pharmacy Information Management System	Data from outpatient medication fills at KPNC pharmacies

Table 2:   Urinary Tract Infection (UTI) Classification

UTI Classification	Definition	Notes
Primary UTI	First UTI in calendar year with no UTI in previous 365 days	Subject may have up to 8 Primary UTI during study period
Duplicate UTI event	UTI event occurring between UTI date and treatment date or UTI event occurring <3 days after a primary UTI event with no treatment date	Additional information on Primary UTI event
Recheck UTI event	UTI event occurring 1 – 30 days after the treatment date (or UTI date in untreated) of a Primary UTI event	Marker for Treatment Failure
Recurrent UTI event	UTI event occurring within 31-365 days of treatment date (or UTI date in untreated) of a Primary UTI event	

Table 3:   Urinary Tract Infection Onset Definitions Based on Date of ICD-9 Code or Urine Culture

UTI Onset:	Timing of ICD-9 Code or Urine Culture
Hospital-acquired	≥ 48 hours after a hospital admission date ≤ 28 days after a hospitalization lasting >48 hours ≤ 28 days after an outpatient surgery ≤ 28 days after a hospitalization ≤ 48 hours long with a surgical ICD-9 code ≤ 28 days after peritoneal or hemodialysis
Healthcare-associated	≤ 365 days after a hospitalization lasting >48 hours ≤ 365 days after an outpatient surgery ≤ 365 days after a hospitalization ≤ 48 hours long with a surgical ICD-9 code ≤ 365 days after peritoneal or hemodialysis ≤ 365 days after any other hospitalization but not including the current hospital stay During a skilled nursing facility stay ≤ 365 days after the end of a skilled nursing facility stay
Community-acquired	Does not meet preceding definitions

Table 4:   Indications of Complicated Urinary Tract Infection

	One ICD-9 or Pharmacy Information Management System Antimicrobial Prescription Code	Time period
Pyelonephritis	590	0-2 days after UTI date
Healthcare Complications		365 days before UTI date through 30 days after
Surgery Complications	579.3, 996.9 – 998.9	
Dialysis/catheter Complications	996, 999	
Device reaction	996.60– 996.63, 996.66 – 996.69	
Post OP Infection	998.5, 998.8, 996.6	
Pregnancy	630 – 677	180 days before UTI date through 30 days after
Concurrent Bacterial Infection	001–139, 320, 324, 357, 370.8, 372, 380-384, 390-393, 421-422, 424.9-424.99, 440.24, 460-466.19, 472.1, 473-475, 478, 481-486, 490-491.9, 494, 511.1, 513.0, 522-523, 526-528, 533.90, 535, 540-542, 566-567.31, 569,572 .0,573.2, 577, 597,611, 614 – 616.4, 680– 686, 711,730, 785, 788.7, 790.7, 795, 879.9, 882.1, 910-919.9, 995– 999.3	30 days before UTI date through 30 days after
Previous Antibiotic Use	PIMS code for antimicrobial drug	30 days before through UTI date
ICD-9 for Antibiotic poisoning	960.0 – 961.9	
Genito–urinary Abnormality		1/1/1997 through 30 days after UTI date
Urinary calculi	592, 594	
Stricture	593,598	
Neurogenic bladder	344.61	
Congenital urologic abnormality	589, 593, 599, 753	
Surgical urologic abnormality	997.5	
Incontinence	788	
Obstruction	137.2, 596	
Urinary Malignancy	188 – 189, 233, 236, 239	
Renal disease	250, 283, 285,403–405, 580–583,584–588,591	
Other cystitis	595.1, 595.3, 595.81, 595.4, 595.82, 585.89	
Immune deficiency		1/1/1997 through 30 days after UTI date
Malignancy	140 – 239, 380.14	
Immune disorder	042, 079.53, 279-289, 710.0, 799.9	
Organ transplant	996.80 – 996.89	
Diabetes	250 – 253, 337.1, 355.9, 357.2,358.1,362, 713.5,791.0	1/1/1997 through 30 days after UTI date

Table 5:   Etiology of Community-acquired Urinary Tract Infections (CA-UTI) in Kaiser Permanente Northern California Women, Ages 15 – 60

	All CA-UTI	Complicated CA-UTI	Uncomplicated CA-UTI
Number of 1998 – 2000 Uropathogens	**33,316**	**13,398**	**19,918**
Percentage of 1998 - 2000 Uropathogens			
Staphylococcus saprophyticus	3.7	2.6	3.7
Number of 1998 – 2005 Cultures	**98,266**	**38,560**	**59,706**
Number of 1998 – 2005 Uropathogens	**98,019***	**38,654***	**59,365***
Percentage of 1998 - 2005 Uropathogens*			
Escherichia coli	85.7	83.4	87.1
Klebsiella species	4.5	5.8	3.7
Proteus species	4.0	4.2	3.9
Enterococcus	1.9	2.4	1.7
Enterobacter species	1.5	1.5	1.4
Citrobacter species	1.2	1.2	1.2
Staphylococcus aureus	0.7	0.9	0.6
Pseudomonas species	0.2	0.3	0.2
Other Uropathogen	0.3	0.4	0.2

* *Staphylococcus saprophyticus* isolates excluded

Table 6: **Community-acquired Uropathogens from Kaiser Permanente Northern California Women, Ages 15 – 60, 1998 – 2005 by Age Group**

	Patient Age at UTI				
	15 - 20 years	21 - 30 years	31 - 40 years	41 - 50 years	51 - 60 years
Complicated UTI					
Number of 1998 - 2000 Uropathogens	**1,735**	**2,727**	**2,988**	**3,205**	**2,743**
Percentage of 1998 - 2000 Uropathogens					
Staphylococcus saprophyticus	6.6	4.1	1.6	1.6	0.8
Number of 1998 - 2005 Uropathogens*	**4,051**	**7,124**	**8,380**	**9,402**	**9,697**
Percentage of 1998 - 2005 Uropathogens*					
Escherichia coli	86.8	84.0	83.6	83.7	81.1
Proteus species	4.6	4.8	3.8	3.6	4.6
Klebsiella species	3.1	4.0	4.8	6.8	8.3
Enterococcus	1.9	2.7	3.1	2.0	2.0
Enterobacter species	1.8	1.6	1.4	1.3	1.4
Citrobacter species	0.7	1.2	1.2	1.2	1.2
Staphylococcus aureus	0.8	0.9	1.2	0.8	0.7
Pseudomonas species	0.2	0.4	0.4	0.3	0.3
Other Uropathogen	0.1	0.4	0.5	0.4	0.5
Uncomplicated UTI					
Number of 1998 - 2000 Uropathogens	**4,278**	**4,151**	**4,398**	**4,242**	**2,849**
Percentage of 1998 - 2000 Uropathogens					
Staphylococcus saprophyticus	6.9	5.0	2.6	2.0	0.9
1998 - 2005 Uropathogens* (N)	**12,238**	**12,675**	**12,765**	**12,542**	**9,145**
Percentage of 1998 - 2005 Uropathogens*					
Escherichia coli	88.5	86.2	86.7	88.0	86.0
Proteus species	4.3	4.6	3.9	3.2	3.6
Klebsiella species	2.6	3.1	3.5	4.2	5.5
Enterobacter species	1.5	1.5	1.6	1.4	1.1
Enterococcus	1.4	2.0	2.0	1.3	1.6
Citrobacter species	0.8	1.5	1.2	1.1	1.4
Staphylococcus aureus	0.7	0.8	0.7	0.6	0.2
Pseudomonas species	0.1	0.1	0.2	0.1	0.2
Other Uropathogen	0.1	0.2	0.2	0.1	0.3

* *Staphylococcus saprophyticus* isolates excluded

Table 7:   Antimicrobial Susceptibility to Common Treatment Antimicrobials among Community-acquired Uropathogens from Kaiser Permanente Northern California Women, Ages 15 – 60, 1998 – 2005

	All Tested	*Escherichia coli*	Other Gram Negative Rods	Gram Positive Cocci
All Community-acquired UTI				
Women (N)	**88,362**	**77,271**	**11,012**	**2,557**
Median Age at UTI	37.2	37.0	38.9	35.3
Positive Cultures (N)	**97,081**	**83,874**	**11,366**	**2,597**
Isolates (N)	**98,019**	**83,929**	**11,478**	**2,612**
Susceptibility Results	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Susceptible*	71.1 (70.8 - 71.4)	76.5 (76.1 - 76.8)	29.5 (28.6 - 30.3)	97.3 (96.0 - 98.7)
TMP/SMX Resistant	17.6 (17.3 - 17.8)	19.2 (19.0 - 19.5)	6.1 (5.7 - 6.6)	0.7 (0.01- 1.4)
Ciprofloxacin Resistant	1.5 (1.4 - 1.6)	1.4 (1.3 - 1.5)	0.7 (0.5 - 0.9)	8.2 (7.1 - 9.4)
Nitrofurantoin Resistant	8.8 (8.6 - 8.9)	1.7 (1.6 - 1.8)	63.4 (62.5 - 64.3)	0.6 (0.3 - 0.9)
Cefazolin Resistant **	7.0 (6.8 - 7.2)	5.6 (5.5 - 5.8)	17.6 (16.9 - 18.3)	4.1 2.60 - 5.6)
Cephalothin Resistant ***	33.5 (33.1 - 33.8)	35.4 (35.0 - 35.8)	21.0 (20.1 - 21.9)	5.9 (3.9 - 7.7)
Complicated Community-acquired UTI				
Women (N)	**35,276**	**30,164**	**4,952**	**1,230**
Median Age at UTI	40.7	40.5	43.5	37.5
Positive Cultures (N)	**38,183**	**32,206**	**5,104**	**1,251**
Isolates (N)	**38,654**	**32,227**	**5,170**	**1,257**
Susceptibility Results	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Susceptible*	65.1 (64.6 - 65.6)	70.2 (69.7 - 70.7)	30.1 (28.9 - 31.5)	96.6 (94.4 - 98.8)
TMP/SMX Resistant	22.7 (22.3 - 23.1)	25.2 (24.8 - 25.7)	7.8 (7.0 - 8.5)	2.7 (1.5 - 4.0)
Ciprofloxacin Resistant	2.0 (1.9 - 2.1)	2.0 (1.8 - 2.1)	0.9 (0.7 - 1.2)	8.4 (6.8 - 10.2)
Nitrofurantoin Resistant	9.7 (9.4 - 10.0)	2.0 (1.8 - 2.2)	61.7 (60.3 - 63.1)	0.9 (0.3 - 1.4)
Cefazolin Resistant **	8.2 (7.9 - 8.5)	6.8 (6.5 - 7.1)	17.5 (16.5 - 18.6)	4.7 (2.4 - 6.9)
Cephalothin Resistant ***	36.1 (35.6 - 36.7)	38.8 (38.2 - 39.4)	21.3 (19.9 - 22.6)	5.6 (2.9 - 8.1)
Uncomplicated Community-acquired UTI				
Women (N)	**55,686**	**49,120**	**6,157**	**1,336**
Median Age at UTI	34.7	34.7	35.0	32.7
Positive Cultures (N)	**58,898**	**51,668**	**6,262**	**1,346**
Isolates (N)	**59,365**	**51,702**	**6,308**	**1,355**
Susceptibility Results	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Susceptible*	75.0 (74.6 - 75.3)	80.4 (80.0 - 80.7)	28.9 (27.7 - 30.0)	97.9 (96.3 - 99.6)
TMP/SMX Resistant	14.3 (14.0 - 14.5)	15.5 (15.2 - 15.8)	4.8 (4.3 - 5.3)	0.7 (0.0 - 1.6)
Ciprofloxacin Resistant	1.2 (1.1 - 1.3)	1.1 (1.0 - 1.2)	0.5 (0.3 - 0.7)	8.0 (6.4 - 9.6)
Nitrofurantoin Resistant	8.1 (7.9 - 8.3)	1.5 (1.4 - 1.6)	64.8 (63.6 - 66.0)	0.4 (0.0 - 0.7)
Cefazolin Resistant **	6.2 (6.0 - 6.4)	4.9 (4.7 - 5.1)	17.7 (16.7 - 18.6)	3 .6 (1.7 - 5.5)
Cephalothin Resistant ***	31.8 (31.4 - 32.3)	33.4 (32.9 - 33.8)	20.8 (19.6 - 22.0)	6.2 (3.3 - 9.0)

*   Susceptible = tested and susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin

**   Proxy for Cephalexin susceptibility testing

*** Based on 1998 - 2003 data

Table 8: **Susceptibility to Common Treatment Antimicrobials among Community-acquired Uropathogens from Kaiser Permanente Northern California Women, Ages 15 – 60, 2005**

All 2005 Community-acquired Urinary Tract Infections

	Escherichia coli		Other Gram Negative Rods	
	Number tested	% (95% CI)	Number tested	% (95% CI)
TMP/SMX Susceptible	11,956	80.3 (79.6 - 81.0)	1,681	94.5 (93.4 - 95.6)
Ciprofloxacin Susceptible	11,958	97.2 (96.9 - 97.5)	1,707	98.9 (98.4 - 99.4)
Nitrofurantoin Susceptible	11,954	97.9 (97.7- 98.2)	1,665	23.2 (21.2 - 25.2)
Cefazolin Susceptible **	11,958	95.8 (95.4 - 96.1)	1,666	83.2 (81.5 -85.0)

2005 Complicated Community-acquired Urinary Tract Infections

	Escherichia coli		Other Gram Negative Rods	
	Number tested	% (95% CI)	Number tested	% (95% CI)
TMP/SMX Susceptible	4,905	74.7 (73.5 - 75.9)	836	92.8 (91.1 - 94.6)
Ciprofloxacin Susceptible	4,905	96.4 (95.8 - 96.9)	851	98.6 (97.8 - 99.4)
Nitrofurantoin Susceptible	4,905	97.7 (97.3 - 98.1)	826	22.8 (19.9 - 25.6)
Cefazolin Susceptible **	4,905	94.9 (94.2 - 95.5)	828	82.7 (80.2 - 85.3)

2005 Uncomplicated Community-acquired Urinary Tract Infections

	Escherichia coli		Other Gram Negative Rods	
	Number tested	% (95% CI)	Number tested	% (95% CI)
TMP/SMX Susceptible	7,051	84.2 (83.4 - 85.1)	845	96.1 (94.8 - 97.4)
Ciprofloxacin Susceptible	7,053	97.8 (97.5 - 98.2)	856	99.2 (98.6 - 99.8)
Nitrofurantoin Susceptible	7,049	98.2 (97.9 - 98.5)	839	23.6 (20.7 - 26.5)
Cefazolin Susceptible **	7,053	96.4 (95.9 - 96.8)	838	83.8 (81.3 -86.3)

* Susceptible = tested and susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin
** Proxy for Cephalexin susceptibility testing

Table 9: **Treated Community-acquired Urinary Tract Infections (CA-UTI) in Kaiser Permanente Northern California Women**

	Treated CA-UTI	Microbiologically Investigated CA-UTI	Complicated CA-UTI	Uncomplicated CA-UTI (UCA-UTI)
Number of Women	**176,391**	**100,010**	**63,479**	**121,743**
Median Age at UTI	37.9	37.1	41.0	36.3
Number of CA-UTI	**205,677**	**109,484**	**71,437**	**134,240**
	N (%)	N (%)	N (%)	N (%)
Age at UTI Onset				
15 – 20 years	28,363 (14)	18,775 (17)	6,471 (9)	21,892 (16)
21 - 30 years	42,490 (21)	22,004 (20)	13,257 (19)	29,233 (22)
31 - 40 years	47,081 (23)	23,609 (22)	15,947 (22)	31,134 (23)
41 - 50 years	49,185 (24)	24,819 (23)	18,329 (26)	30,856 (23)
51 - 60 years	38,558 (19)	20,277 (19)	17,433 (24)	21,125 (16)
Year of UTI Onset				
1998	24,755 (12)	11,816 (11)	7,689 (11)	17,066 (13)
1999	23,465 (11)	11,810 (11)	7,938 (11)	15,527 (12)
2000	23,881 (12)	12,712 (12)	8,578 (12)	15,303 (11)
2001	25,465 (12)	13,263 (12)	8,730 (12)	16,735 (12)
2002	25,599 (12)	13,544 (12)	8,845 (12)	16,754 (12)
2003	26,746 (13)	14,792 (14)	9,086 (13)	17,660 (13)
2004	27,483 (13)	15,527 (14)	9,844 (14)	17,639 (13)
2005	28,283 (14)	16,020 (15)	10,727 (15)	17,556 (13)
UTI Disease				
Uncomplicated	134,240 (65)	67,725 (62)		134,240 (100)
Complicated	71,437 (35)	41,759 (38)	71,437 (100)	
Treatment Drug				
TMP/SMX	97,973 (48)	46,699 (43)	25,516 (36)	72,457 (54)
Cephalexin	24,297 (12)	14,922 (14)	8,292 (12)	16,005 (12)
Nitrofurantoin	20,176 (10)	12,313 (11)	7,757 (11)	12,419 (9)
Ciprofloxacin	54,684 (27)	30,751 (28)	25,617 (36)	29,067 (22)
Other Drug	6451 (3)	3,651 (3)	3,170 (4)	3,281 (2)
Multiple Drugs	2096 (1)	1,148 (1)	1,085 (2)	1,011 (1)
Urine Culture				
Submitted	109,484 (53)	109,484 (100)	41,759 (58)	67,725 (50)
Culture-confirmed	69,494 (34)	69,494 (100)	26,439 (37)	43,055 (32)

Table 10: Culture-confirmed Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women

	Culture-Confirmed Complicated CA-UTI*	Culture-Confirmed Uncomplicated CA-UTI* (UCA-UTI)	Single drug Treated UCA-UTI caused by a Single Pathogen	Single drug Treated *Escherichia coli* UCA-UTI
Number of Women	24,963	41,318	40,754	36,188
Median Age at UTI	41.1	34.8	34.8	34.9
Number of CA-UTI*	26,439	43,055	42,437	37,549
	N (%)	**N (%)**	**N (%)**	**N (%)**
Age at UTI Onset				
15 - 20 years	2,848 (11)	9,435 (22)	9,297 (22)	8,216 (22)
21 - 30 years	4,757 (18)	8,771 (20)	8,635 (20)	7,571 (20)
31 - 40 years	5,554 (21)	8,922 (21)	8,809 (21)	7,814 (21)
41 - 50 years	6,634 (25)	9,356 (22)	9,233 (22)	8,252 (22)
51 - 60 years	6,646 (25)	6,571 (15)	6,463 (15)	5,696 (15)
Year of UTI Onset				
1998	2,930 (11)	4,749 (11)	4,670 (11)	4,023 (11)
1999	3,087 (12)	4,418 (10)	4,337 (10)	3,765 (10)
2000	3,253 (12)	4,812 (11)	4,754 (11)	4,130 (11)
2001	2,938 (11)	5,283 (12)	5,200 (12)	4,577 (12)
2002	3,157 (12)	5,472 (13)	5,384 (13)	4,849 (13)
2003	3,350 (13)	6,031 (14)	5,948 (14)	5,356 (14)
2004	3,614 (14)	6,268 (15)	6,199 (15)	5,533 (15)
2005	4,110 (16)	6,022 (14)	5,945 (14)	5,316 (14)
UTI Disease				
Uncomplicated		43,055 (100)	42,437 (100)	37549 (100)
Complicated	26,439 (100)			
Treatment Drug				
TMP/SMX	8,707 (33)	21,226 (49)	21,079 (50)	18,651 (50)
Cephalexin	3,234 (12)	6,354 (15)	6,309 (15)	5,569 (15)
Nitrofurantoin	3,193 (12)	4,714 (11)	4,663 (11)	4,097 (11)
Ciprofloxacin	9,674 (37)	9,344 (22)	9,279 (22)	8,290 (22)
Other Drug	1,240 (5)	1,115 (3)	1,107 (3)	942 (3)
Multiple Drugs	391 (1)	302 (1)		
Escherichia coli* CA-UTI	22,857 (86)	38,085 (88)	37,549 (88)	37,549 (100)
UTI with uropathogens testing	**N (% of tested)**	**N (% of tested)**	**N (% of tested)**	**N (% of tested)**
Susceptible^	16,569 (64)	31,933 (75)	31,669 (75)	30,072 (80)
TMP/SMX Resistant	6,570 (25)	6,340 (15)	6,223 (15)	6,043 (16)
Ciprofloxacin Resistant	487 (2)	429 (1)	415 (1)	379 (1)
Nitrofurantoin Resistant	2,308 (9)	3,234 (8)	3,058 (7)	494 (1)
Cefazolin Resistant	2,121 (8)	2,670 (6)	2,577 (6)	1,809 (5)

^ Tested susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin

* CA-UTI = Community-acquired Urinary Tract Infection

Table 11:   Treatment Failure in Kaiser Permanente Northern California Women with Uncomplicated Community-acquired Urinary Tract Infections

Number of Women		121,743
Number of Uncomplicated Community-acquired UTI (UCA-UTI)		134,240

	Treatment Failure (95% CI)	**Adjusted RR* (95% CI)**
1998 - 2005 UCA-UTI	17.8% (17.6 - 18.0)	**1.00**
Year of UTI Onset		
1998	18.2% (17.7 - 18.8)	**1.00**
1999	18.3% (17.7 - 18.9)	1.01 (0.97 - 1.06)
2000	18.0% (17.3 - 18.7)	1.00 (0.96 - 1.05)
2001	18.0% (17.4 - 18.6)	1.01 (0.97 - 1.06)
2002	17.2% (16.6 - 17.8)	0.97 (0.92 - 1.02)
2003	17.5% (17.0 - 18.1)	0.99 (0.95 - 1.04)
2004	17.3% (16.8 - 17.9)	0.98 (0.94 - 1.02)
2005	17.5% (17.0 - 18.1)	0.99 (0.95 - 1.04)
Age at UTI Onset		
15 - 20 years	18.1% (17.6 - 18.6)	**1.00**
21 - 30 years	16.4% (16.0 - 16.9)	0.93 (0.89 - 0.97)
31 - 40 years	17.3% (16.8 - 17.7)	0.98 (0.95 - 1.02)
41 - 50 years	18.1% (17.7 - 18.5)	1.04 (1.00 - 1.08)
51 - 60 years	19.5% (19.0 - 20.0)	1.12 (1.08 - 1.17)
Treatment Drug		
Ciprofloxacin	15.8% (15.3 - 16.2)	**1.00**
Nitrofurantoin	17.2% (16.6 - 17.9)	1.10 (1.05 - 1.16)
TMP/SMX	17.9% (17.7 - 18.2)	1.15 (1.12 - 1.19)
Cephalexin	19.2% (18.6 - 19.8)	1.19 (1.13 - 1.24)
Multiple Drugs	18.9% (16.5 - 21.3)	1.20 (1.05 - 1.37)
Other Drug	26.1% (24.6 - 27.6)	1.68 (1.58 - 1.79)
Culture-Confirmed UTI	22.6% (22.2 - 23.0)	1.48 (1.45 - 1.52)
UTI with uropathogens testing		
Susceptible^	17.3% (16.9 - 17.7)	0.45 (0.43 - 0.46)^^
TMP/SMX Resistant	48.2% (46.9 - 49.4)	2.74 (2.65 - 2.83)**
Ciprofloxacin Resistant	50.3% (45.6 - 55.1)	2.29 (2.07 - 2.52)**
Nitrofurantoin Resistant	27.2% (25.7 - 28.7)	1.23 (1.16- 1.31)**
Cefazolin Resistant	31.9% (30.2 - 33.7)	1.47 (1.38- 1.55)**
Cephalothin Resistant	28.2% (27.4 - 29.1)	1.38 (1.33 - 1.44)**

*   Relative risks, adjusted for treatment, age group, year, region, and clustering within the individual

^   Tested susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin

^^   Relative to UCA - UTI with uropathogens testing resistant to at least one treatment antimicrobial

**   Relative to UCA - UTI with uropathogens testing susceptible to the drug tested

Table 12: Treatment Failure in Kaiser Permanente Northern California Women with Uncomplicated Community-acquired Urinary Tract Infections, by Treatment Drug and Age Group

	Age Group at UCA-UTI Onset in Years					
	15 - 60 years	15 - 20 years	21 - 30 years	31 - 40 years	41 - 50 years	51 - 60 years
Number of UCA-UTI	134,240	21,892	29,233	31,134	30,856	21,125
Treatment Drug	Treatment Failure (95% CI)	Treatment Failure (95% CI)	Treatment Failure (95% CI)	Treatment Failure (95% CI)	Treatment Failure (95% CI)	Treatment Failure (95% CI)
TMP/SMX	18% (17.7 - 18.2)	18% (17.0 - 18.3)	17% (16.2 - 17.4)	18% (17.1 - 18.3)	18% (17.7 - 18.9)	20% (19.0 - 20.5)
Nitrofurantoin	17% (16.6 - 17.9)	16% (14.3 - 18.3)	15% (14.1 - 16.6)	16% (15.0 - 17.6)	18% (17.0 - 19.9)	21% (19.2 - 22.9)
Cephalexin	19% (18.6 - 19.8)	19% (18.2 - 20.5)	18% (16.3 - 18.9)	17% (16.1 - 18.7)	20% (18.7 - 21.6)	23% (21.2 - 24.9)
Ciprofloxacin	16% (15.3 - 16.1)	16% (14.0 - 17.0)	14% (13.2 - 15.0)	16% (14.9 - 16.6)	16% (15.2 - 16.8)	17% (16.2 - 18.1)

Table 13: Relative Treatment Effectiveness of Common Antimicrobial Treatment Drugs in Kaiser Permanente Northern California Women with Uncomplicated Community-acquired Urinary Tract Infections (UCA-UTI)

UCA-UTI	Susceptible* UTI		TMP/SMX R-UTI**		Ciprofloxacin R-UTI		Nitrofurantoin R-UTI		Cefazolin R-UTI	
	N (% of tested) 31,669 (75)		N (% of tested) 6,091 (15)		N (% of tested) 406 (1)		N (% of tested) 2,972 (7)		N (% of tested) 2,577 (6)	
Treatment Failure (TF)	% TF	(95%CI)	% TF	(95%CI)	% TF	(95%CI)	% TF	(95%CI)	% TF	(95%CI)
All UCA-UTI	17.3%	(16.9 - 17.7)	48.4%	(47.1 - 49.6)	51.1%	(46.2 - 55.9)	27.1%	(25.5 - 28.7)	31.8%	(30.0 - 33.6)
TMP/SMX Treated	15.0%	(14.4 - 15.6)	77.6%	(76.1 - 79.2)	52.9%	(45.7 - 60.2)	20.2%	(18.2 - 22.2)	31.4%	(8.80 - 33.9)
Cephalexin Treated	21.0%	(19.9 - 22.2)	27.5%	(24.5 - 30.4)	30.0%	(16.8 - 43.2)	28.4%	(24.2 - 32.6)	54.1%	(48.9 - 59.2)
Nitrofurantoin Treated	16.6%	(15.3 - 17.8)	19.7%	(16.7 - 22.7)	23.3%	(16.6 - 40.1)	65.3%	(60.2 - 70.4)	24.6%	(19.4 - 29.6)
Ciprofloxacin Treated	17.5%	(16.6 - 18.4)	20.0%	(18.1 - 21.9)	67.6%	(58.7 - 76.4)	19.2%	(16.3 - 22.3)	18.9%	(15.7 - 22.0)
Relative Risk of Treatment Failure	RR ***	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
TMP/SMX Treated	1.00		3.96	(3.40 - 4.63)	1.88	(1.21 - 2.91)	1.09	(0.91 - 1.31)	1.72	(1.43 - 2.08)
Cephalexin Treated	1.38	(1.28 - 1.48)	1.42	(1.17 - 1.71)	1.04	(0.58 - 1.89)	1.51	(1.21 - 1.89)	3.00	(2.44 - 3.66)
Nitrofurantoin Treated	1.09	(1.00 - 1.19)	1.00		1.00		3.43	(2.87 - 4.11)	1.31	(1.00 - 1.72)
Ciprofloxacin Treated	1.15	(1.07 - 1.23)	1.00	(0.84 - 1.20)	2.36	(1.53 - 3.66)	1.00		1.00	

* UTI with single uropathogens reported as susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin
**R-UTI = UCA-UTI caused by a single uropathogen reported as intermediate or resistant susceptibility
***RR = Risk Relative, adjusted for age group, year, region, and clustering within the individual

Table 14: **Cephalexin-treated Uncomplicated Community-acquired Urinary Tract Infections in Kaiser Permanente Northern California Women, Ages 15 – 60, 1998 – 2005**

	Cephalexin Treated UCA-UTI (cUCA-UTI)	cUCA-UTI caused by a Single Uropathogen	Study Population*
Number of Women	15,595	6,231	4,036
Median Age at UTI	31.7	28.3	29.4
Number of UTI	**16,005**	**6,309**	**4,076**
	N (%)	**N (%)**	**N (%)**
Age at UTI Onset			
15 - 20 years	4,502 (28)	2,320 (37)	1,419 (35)
21 - 30 years	3,286 (21)	1,170 (19)	745 (18)
31 - 40 years	3,156 (20)	1,018 (16)	670 (16)
41 - 50 years	3,023 (19)	1,051 (17)	738 (18)
51 - 60 years	2,038 (13)	750 (12)	504(12)
Year of UTI Onset			
1998	2,369 (15)	698 (11)	584 (14)
1999	2,180 (14)	697 (11)	617 (15)
2000	1,903 (12)	787 (12)	673 (17)
2001	1,774 (11)	735 (12)	655 (16)
2002	1,967 (12)	859 (14)	781 (19)
2003	1,823 (11)	802 (13)	689 (17)
2004	2,040 (13)	911 (14)	72 (2)**
2005	1,949 (12)	820 (13)	5 (0.2)**
Treatment Failure	3,077 (19)	1,472 (23)	995 (24)
Urine Culture Submitted	9,728 (61)		
Culture-confirmed cUCA-UTI	6,354 (40)		
with one uropathogen	6,309 (39)	6,309 (100)	4,076 (100)
with two uropathogens	45 (0.3)		

*   cUCA-UTI with a single *E.coli* isolate that was tested for susceptibility to both cephalothin and cefazolin
** Routine testing of cephalothin was discontinued in 2004

Table 15: Antimicrobial Susceptibility to Common Treatment Antimicrobials among Community-acquired Uropathogens from Cephalexin -Treated Kaiser Permanente Northern California Women, Ages 15 – 60, 1998 – 2005

	Cephalexin treated UCA-UTI		
	All Cephalexin treated UCA-UTI		Study Population*
Uropathogen	*Escherichia coli*	Other Uropathogen	*Escherichia coli*
Number of Isolates	5,609	790	4,076
Susceptibility Testing Performed	N (%)	N (%)	N (%)
Cephalothin	4,102 (73)	527 (67)	4,076 (100)
Cefazolin	5,609 (100)	704 (90)	4,076 (100)
Cephalothin and Cefazolin	4,102 (73)	525 (66)	4,076 (100)
Susceptibility Testing Results	N (%Tested)	N (%Tested)	N (%Tested)
Susceptible^	4,570 (82)	244 (34)	3,318 (81)
TMP/SMX Resistant	839 (15)	35 (5)	614 (15)
Ciprofloxacin Resistant	46 (1)	6 (1)	36 (1)
Nitrofurantoin Resistant	67 (1)	412 (53)	42 (1)
Cephalothin Resistant	1,385 (34)	124 (23)	1,377 (34)
Cefazolin Resistant	239 (4)	144 (19)	187 (5)

^ Tested susceptible to TMP/SMX, ciprofloxacin, nitrofurantoin, and cefazolin or oxacillin
* UCA-UTI with a single *E.coli i*solate that was tested for susceptibility to both cephalothin and cefazolin

Table 16: Performance of Antimicrobial Susceptibility Testing to Predict Treatment Failure among Cephalexin-Treated Uncomplicated Community-acquired Urinary Tract Infections caused by *Escherichia coli* in Kaiser Permanente Northern California Women, ages 15 - 60 years, 1998 - 2005.

Treatment	Antimicrobial Susceptibility test	E.coli UCA-UTI N (%)	Treatment Failure (95% CI)	Sensitivity	Specificity	Positive Predicitive Value	Negative Predicitive Value	Likelihood Ratio + (95%CI)	Likelihood Ratio - (95%CI)	Diagnostic OR** LR+/LR- (95%CI)
Cephalexin	Cephalothin	4,076 (100)	24.4 (23.1 - 25.7)	43.4%	69.3%	31.4%	79.1%	1.42 (1.30 - 1.55)	0.816 (0.77 - 0.87)	1.74 (1.49 - 1.98)
	Susceptible	2,699 (66)	20.9 (19.3 - 22.4)							
	Resistant	1,377 (34)	31.4 (28.9 - 33.8)							
Cephalexin	Cefazolin	4,076 (100)	24.4 (23.1 - 25.7)	10.3%	97.2%	54.5%	77.0%	3.72 (2.81 - 4.91)	0.923 (0.90 - 0.94)	4.04 (2.80 - 5.28)
	Susceptible	3,889 (95)	23.0 (21.6 - 24.3)							
	Resistant	187 (5)	54.5 (47.3 - 61.7)							

** Adjusted for age group and clustering within the individual, 95% Confidence Intervals calculated by bootstrapping

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Table 17: Performance of Antimicrobial Susceptibility Testing to Predict Treatment Failure among Cephalexin-Treated Uncomplicated Community-acquired Urinary Tract Infections caused by Escherichia coli in Kaiser Permanente Northern California Women, ages 15 - 60 years, 1998 - 2005.

Treatment	Antimicrobial Susceptibility test	Escherichia coli UCA-UTI N (%)	Treatment Failure (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Likelihood Ratio Positive (95%CI)	Likelihood Ratio Negative (95%CI)	Diagnostic OR** LR+/LR- (95%CI)
Cephalexin	Cephalothin	4,076 (100)	24.4% (23.9 - 25.7)	43.4%	69.3%	31.4%	79.1%	1.42 (1.3 - 1.6)	0.816 (0.77 - 0.87)	1.74 (1.49 - 1.99)
	Susceptible	2,699 (66)	20.9% (19.3 - 22.4)							
	Resistant	1,377 (34)	31.4% (28.9 - 33.8)							
Cephalexin	Cefazolin	5,569 (100)	22.9% (21.8 - 24.0)	9.7%	97.5%	53.4%	78.4%	3.9 (3.0 - 5.0)	0.926 (0.91 - 0.94)	4.19 (3.04 - 5.34)
	Susceptible	5,337 (96)	21.6% (20.5 - 22.7)							
	Resistant	232 (4)	53.5% (47.0 - 60.0)							
TMP/SMX	TMP/SMX	18,651 (100)	24.3% (23.7 - 24.9)	47.7%	95.6%	77.7%	85.1%	10.9 (10.0 - 11.8)	0.547 (0.53 - 0.56)	20.16 (18.14 - 22.18)
	Susceptible	15,866 (85)	14.9% (14.4 - 15.5)							
	Resistant	2,785 (15)	77.7% (76.2 - 79.3)							
Nitrofurantoin	Nitrofurantoin	4,096 (100)	17.6% (16.4 - 18.7)	5.2%	99.6%	72.5%	83.1%	12.4 (6.8 - 22.8)	0.952 (0.94 - 0.97)	12.99 (1.50 - 24.49)
	Susceptible	4,045 (98.8)	16.9% (15.7 - 18.0)							
	Resistant	51 (1.2)	72.5% (59.9 - 85.2)							
Ciprofloxacin	Ciprofloxacin	8,290 (100)	18.2% (17.3 - 19.0)	4.8%	99.5%	69.2%	82.5%	10.1 (6.7 - 15.3)	0.957 (0.95 - 0.97)	10.53 (5.50 - 15.55)
	Susceptible	8,186 (98.8)	17.5% (16.7 - 18.3)							
	Resistant	104 (1.2)	69.2 % (60.2 - 78.3)							

** Adjusted for age group and clustering within the individual, 95% Confidence Intervals calculated by bootstrapping

Table 18:   Antimicrobial Susceptibility of Escherichia coli causing Community-acquired Urinary Tract Infections (CA-UTI) in University Health Clinic Women

	Period I [*] 10/11/99 - 1/31/00	Period II [*] 10/11/00 - 1/31/01	Period III 10/11/03 - 1/31/04	Period IV 10/11/04 - 1/31/05
Number of Women	434	414	456	363
Median age at UTI (range)	22 (17 - 68)	22 (13 - 48)	22 (18 - 60)	23 (18 - 68)
Number of CA-UTI	505	468	532	415
Number of *Escherichia coli*	228	206	230	116
	N (%)	N (%)	N (%)	N (%)
Susceptibility Testing Results				
Pan - Susceptible[**]	NA[***]	NA	108 (47)	61 (53)
Multi-drug Resistant[^]	NA	NA	84 (36)	33 (24)
TMP/SMX Resistant	47 (21)	38 (18)	37 (16)	19 (16)
Ciprofloxacin Resistant	2 (1)	6 (3)	2 (1)	3 (3)
Nitrofurantoin Resistant	4 (2)	1 (1)	2 (1)	2 (2)
Cephalothin Resistant	NA	NA	79 (34)	33 (28)
Ampicillin Resistant	NA	NA	80 (35)	28 (24)[^^]

[*]   Results previously published in Manges et al.

[**]   Tested susceptible to 29 antibiotics

[***]   NA = results not available

[^]   Multi-drug Resistant defined as nonsusceptible to ≥ 2 of the 11 classes of drugs tested.

[^^]   Statistically significant change in proportion between periods III and IV $p \leq 0.05$

Table 19:   ERIC2-PCR Grouping and TMP/SMX Resistance of *Escherichia* coli causing Community-acquired Urinary Tract Infections in University Health Clinic Women

	Period I 10/11/99 - 1/31/00	Period II 10/11/00 - 1/31/01	Period III 10/11/03 - 1/31/04	Period IV 10/11/04 - 1/31/05
***Escherichia coli* (*E. coli*) (N)**	228	206	230	116
Clonal groups detected (N)	3	6	30	24
With TMP/SMX Resistant *E. coli* (N)	2	5	7	8
ERIC2 PCR *E. coli* (N)	96*	142*	230	116
	N (%)	**N (%)**	**N (%)**	**N (%)**
Nonclonal Group	63 (66)	105 (74)	55 (24)	30 (26)
Clonal Group	33 (34)	37 (26)	175 (76)	86 (74)
Major Clonal Group				
CgA	25 (26)	7 (5)	30 (13)	10 (9)
CgC	6 (7)	6 (3)	31 (13)	18 (16)
CgH	0 (0)	17 (12)	24 (10)	9 (8)
Cg3	NA**	NA	15 (7)	5 (4)
TMP/SMX Resistant *E. coli* (N)	47	38	37	19
	N (%)	**N (%)**	**N (%)**	**N (%)**
Nonclonal Group	22 (47)	26 (68)	9 (24)	6 (32)
Clonal Group	25 (25)	12 (32)	28 (76)	13 (68)
Major Clonal Group				
CgA	23 (49)	4 (11)	15 (41)	4 (21)
CgC	0 (0)	0 (0)	5 (14)	0 (0)
CgH	0 (0)	3(8)	2 (5)	1 (5)
Cg3	NA	NA	0 (0)	0 (0)

* All TMP/SMX isolates and a randomly selected subset of TMP/SMX susceptible isolates were typed

** NA = results not available

Table 20: Temporal clustering of ERIC2-PCR Clonal Groups of *Escherichia coli* causing Community-acquired Urinary Tract Infections in University Health Clinic Women

ERIC2-PCR Clonal group	*Escherichia coli*	Period I 10/11/99 - 1/31/00		Period II 10/11/00 - 1/31/01		Period III 10/11/03 - 1/31/04		Period IV 10/11/04 - 1/31/05	
	N	Clusters*	Women	Clusters	Women	Clusters	Women	Clusters	Women
	N	N	N	N	N	N	N	N	N
CgA	72	5	11	ND	0	6	13	0	0
CgC	61	ND**	ND	1	2	6	13	3	7
CgH	50	ND	ND	2	5	3	6	1	2
Cg1	12	ND	ND	ND	ND	0	0	1	2
Cg3	21	ND	ND	ND	ND	4	9	0	0
Cg5	12	ND	ND	ND	ND	1	2	0	0

* Occurrence of ≥ 2 patients presenting to the clinic on the same day infected by the same ERIC2 clonal group

** None Detected = < 100% of isolates typed