MAJOR ARTICLE

Population-Based Epidemiologic Analysis of Acute Pyelonephritis

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(See the editorial commentary by Foxman et al. on pages 281–3)

Background. Acute pyelonephritis is a potentially severe disease for which there are few population-based studies. We performed a population-based analysis of trends in the incidence, microbial etiology, antimicrobial resistance, and antimicrobial therapy of outpatient and inpatient pyelonephritis.

Methods. A total of 4887 enrollees of Group Health Cooperative, based in Seattle, Washington, who received an *International Classification of Diseases, Ninth Revision, Clinical Modification,* diagnosis of acute pyelonephritis from 1997 through 2001 were identified using computerized records. Diagnoses were linked to urine culture and antibiotic prescription data. Case patients ($n = 3236$) included subjects who had received an inpatient or culture-confirmed outpatient diagnosis of acute pyelonephritis.

Results. Among the female population, annual rates of outpatient and inpatient pyelonephritis were 12–13 cases per 10,000 population and 3–4 cases per 10,000 population, respectively; among the male population, the rates were 2–3 cases per 10,000 population and 1–2 cases per 10,000 population, respectively. Rates were relatively stable from year to year. Incidence was highest among young women, followed by infants and the elderly population. The ratio of outpatient to inpatient cases was highest among young women (ranging from 5:1 to 6:1). *Escherichia coli* caused 80% of cases of acute pyelonephritis in women and 70% of cases in men and was less dominant in older age groups. Among *E. coli* strains, the rate of ciprofloxacin resistance increased from 0.2% of isolates to 1.5% of isolates ($P = .03$), and the rate of trimethoprim-sulfamethoxazole resistance decreased from 25% of isolates to 13% of isolates ($P < .01$) from 1997 to 2001. Among outpatient cases, the rate of fluoroquinolone use increased from 35% to 61%, whereas the rate of trimethoprim-sulfamethoxazole use decreased from 53% to 32% over the 5-year period ($P < .01$).

Conclusions. This comprehensive, population-based analysis adds to our limited knowledge of the epidemiology of acute pyelonephritis, especially among outpatients, in whom the majority of cases now occur.

Acute pyelonephritis is a severe form of urinary tract infection (UTI) with symptoms that range from mild discomfort to life-threatening illness or death [1]. Complications may result in chronic renal scarring and impairment of renal function [2–6], especially in children. The annual societal cost of treatment of acute pyelonephritis was recently estimated to be $2.14 billion in the United States [7]. Despite the morbidity related to this disease, epidemiological data on incidence and causal organisms are limited. Earlier studies have focused primarily on disease associated with hospitalization [8–12]. To our knowledge, only 2 population-based studies have included outpatients [13, 14]. However, outpatient treatment is increasingly advocated and practiced in most populations [15–22].

There are also relatively few data available on the antimicrobial-resistance patterns of bacterial strains causing acute pyelonephritis. Because resistance to trimethoprim-sulfamethoxazole among *Escherichia coli* strains causing acute cystitis and pyelonephritis is increasing and is associated with treatment failure [23–27], guidelines recommend the use of alternative agents for treatment of UTI when drug resistance may be likely [15]. Consequently, fluoroquinolones are becoming the predominant therapy for UTI in many areas, and an increased incidence of fluoroquinolone resistance may soon follow [28–30].

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We undertook this study to better describe the epidemiology of acute pyelonephritis in a well-defined US population over a 5-year period, including the incidence and microbial etiology among both outpatients and inpatients. Trends in antimicrobial resistance and antimicrobial use for therapy of pyelonephritis were also evaluated.

METHODS

Study setting. Group Health Cooperative (GH; Seattle, WA) is a health maintenance organization serving >525,000 enrollees in Washington and Idaho. The age, sex, and racial distribution (82% white and 5% Hispanic) of the enrollees are similar to those of the communities that GH serves. Eighty-two percent of GH enrollees are college-educated, which is a slightly larger percentage than that for the surrounding population of King County, Washington (where 63% of the population is college-educated).

Study subjects and case definitions. Subjects included all GH enrollees with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis of acute pyelonephritis recorded in the GH computerized database during the period 1997–2001. Codes 590.1 (acute pyelonephritis, without lesion of renal medullary necrosis), 590.11 (acute pyelonephritis, with lesion of renal medullary necrosis), and 590.8 (pyelonephritis, unspecified) were included. We did not distinguish between primary and secondary diagnoses. The age, sex, date of diagnosis, and treatment setting of each subject were gathered from the computerized record.

The case definition of acute pyelonephritis differed for outpatient and inpatient cases. Outpatients were subjects who received an ICD-9-CM diagnosis of acute pyelonephritis in the outpatient setting, including the emergency department, in combination with urine culture confirmation. Inpatients were subjects who received an ICD-9-CM diagnosis of acute pyelonephritis in the inpatient setting (i.e., at GH or an affiliate hospital) with or without confirmation by culture. Subjects who were initially seen as outpatients and were later hospitalized were considered to be inpatients. Date of diagnosis was designated as the date of the first recorded outpatient or inpatient ICD-9-CM code, and recurrent episodes were not included. Because we did not access patient charts, we did not further characterize patients as to risk factors for disease, such as pregnancy, diabetes, or urologic abnormalities.

Culture, susceptibility, and treatment data. Case patients were linked in the computerized record to urine cultures containing $\geqslant 10^3$ cfu/mL of a uropathogen (i.e., a gram-negative rod, *Staphylococcus saprophyticus, Enterococcus* species, or *Staphylococcus aureus*) within 7 days before or 2 days after the date of diagnosis. Culture confirmation was used to provide more specificity to the outpatient diagnoses by eliminating subjects whose pyelonephritis diagnosis was recorded at unrelated visits. If >1 organism was present in a urine culture, the uropathogen with the highest colony count was identified as the etiologic agent. Automated culture data from the inpatient laboratories of affiliate hospitals were generally not available.

GH interpretations of antimicrobial susceptibility were used. Reported MIC values were interpreted according to the National Committee for Clinical Laboratory Standards guidelines [31]. Isolates with intermediate resistance were categorized as resistant to the antimicrobial in question.

All antibiotics prescribed to outpatients within 7 days before and 2 days after receipt of a diagnosis of pyelonephritis were identified from GH computerized pharmacy records. Treatment of inpatients was not included in this analysis, because automated data from affiliate hospitals were unavailable.

Data analysis. We undertook 4 major analyses: trends in incidence, microbial etiology, antimicrobial resistance, and antimicrobial therapy. Denominator data for incidence rates used GH enrollment at the midpoint of each year. The χ^2 test and χ^2 test for trend were used to compare proportions, rates, and trends, with significance levels set at P values of $\leqslant .01$. Statistical analyses were conducted using SAS software, version 9.1 (SAS), and Epi Info (Centers for Disease Control and Prevention).

RESULTS

Study population. There were 4887 subjects with 10,330 ICD-9-CM diagnoses of acute pyelonephritis from January 1997 through December 2001. Of these, 2408 subjects (87% of whom were female) had culture-confirmed outpatient pyelonephritis and were included in these analyses (excluding 1651 outpatients without culture confirmation). A total of 828 subjects (79% of whom were female) had inpatient pyelonephritis; of these, 331 (40%) had culture confirmation.

Trends in incidence. Annual incidence rates of outpatient, inpatient, and total pyelonephritis from 1997 through 2001 are presented in figure 1. Over the 5-year period, rates of outpatient (12–13 cases per 10,000 population) and inpatient (3–4 cases per 10,000 population) pyelonephritis in the female population were several times higher than the respective rates in the male population (2–3 cases per 10,000 population and 1–2 cases per 10,000 population, respectively). Rates were relatively stable over time.

Among the female population, the incidence of outpatient pyelonephritis was elevated in girls aged 0–4 years but then decreased until a dramatic peak occurred in women aged 15–35 years (figure 2). Rates remained elevated but gradually decreased in older age groups until they again began to increase after 50 years of age. The highest incidence of inpatient pyelonephritis occurred in girls aged 0–4 years. Rates then decreased among individuals in early adolescence, followed by a small peak in women aged 15–35 years; rates gradually increased among patients aged >50 years, reaching a third peak at ~80

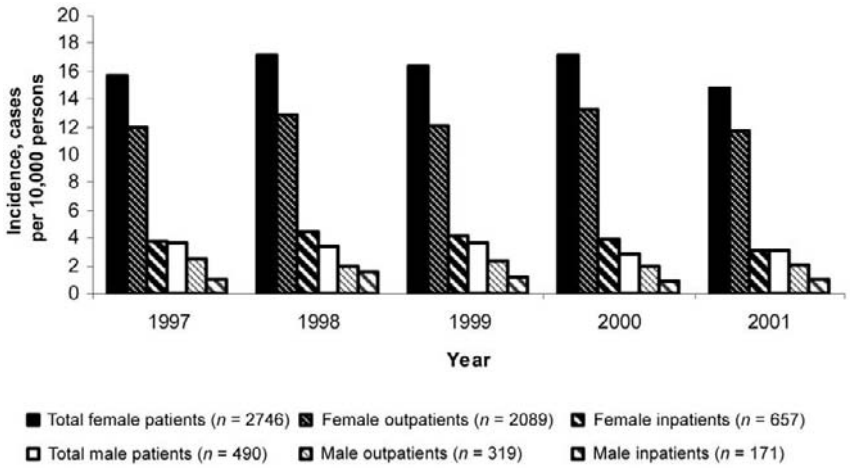

Figure 1. Annual incidence of acute pyelonephritis per 10,000 population, 1997–2001 ($P = .33$ for all female patients, $P = .97$ for female outpatients, $P = .05$ for female inpatients, $P = .08$ for all male patients, $P = .22$ for male outpatients, and $P = .21$ for male inpatients, by χ^2 test for trend).

years of age. Outpatient rates were higher than inpatient rates among females of all age groups except young girls, most of whom were hospitalized. Among girls aged 0–4 years, 34% of outpatients and 57% of inpatients were aged <1 year.

Incidence rates of acute pyelonephritis were lower in the male population than in the female population for nearly every age group, although the difference in rates appeared to diminish at older ages. Males experienced a peak rate of outpatient pyelonephritis at 0–4 years of age, which was followed by a gradual increase in rates with older age, particularly after 35 years of age, that reached a separate, higher peak rate at 85 years of age. The highest rates of inpatient pyelonephritis also occurred in young boys and in the elderly population. After 0–4 years of age, rates were low until 50 years of age, after which they gradually increased. The incidence of inpatient pyelonephritis did not peak in the teenage years in boys as it did in girls. As observed in the female population, outpatient disease predominated in all age groups except for the youngest boys. Among boys aged 0–4 years, 80% of outpatients and 84% of inpatients were aged <1 year.

The ratio of outpatients to inpatients appeared to increase over time for girls aged 0–14 years ($P = .05$) and women aged 15–54 years ($P = .17$; figure 3). The ratio was highest for women aged 15–54 years (from 5:1 to 6:1). The ratio for boys aged 0–14 years ranged from 0.1 to 1.0, that for men aged 15–54 years ranged from 3 to 12, and that for men aged ⩾55 years ranged from 1 to 3 without a strong linear trend.

Acute pyelonephritis occurred most frequently during the months of July and August in the female population and during the months of August and September in the male population (figure 4). These month-to-month variations were statistically significant in adult women ($P < .01$, by χ^2 test).

Trends in microbial etiology. The distribution of causative uropathogens was similar for outpatients and inpatients (table 1). *E. coli* caused 81%–84% of pyelonephritis events among the female population. In the male population, a smaller percentage of pyelonephritis events (71%–74%) was associated with *E. coli* ($P < .01$, by χ^2 test for the difference between female and male patients), and uropathogens, such as *Klebsiella, Citrobacter,* and *Enterococcus* species, played a larger role. *S. saprophyticus* was isolated from a small percentage of female patients (2.8% of outpatients) and male patients (2.9% of inpatients and 0.9% of outpatients). There were no annual or monthly trends in the percentages of *E. coli*-associated pyelonephritis.

A lower percentage of pyelonephritis cases due to *E. coli* occurred in older patients, compared with younger age groups (table 2); this trend was statistically significant for female patients ($P < .01$). Other organisms were more frequently isolated

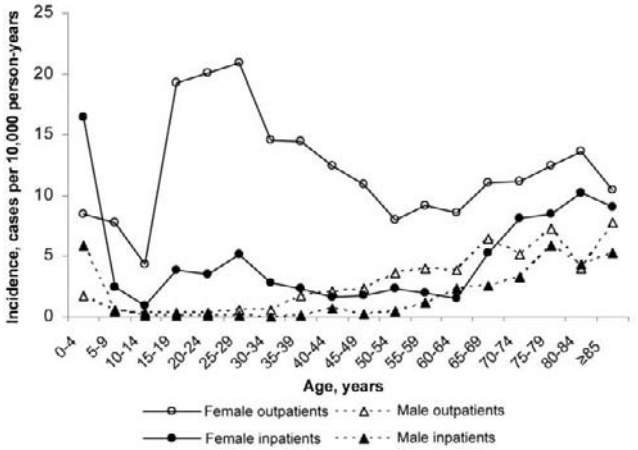

Figure 2. Incidence of outpatient and inpatient pyelonephritis per 10,000 person-years, 1997–2001.

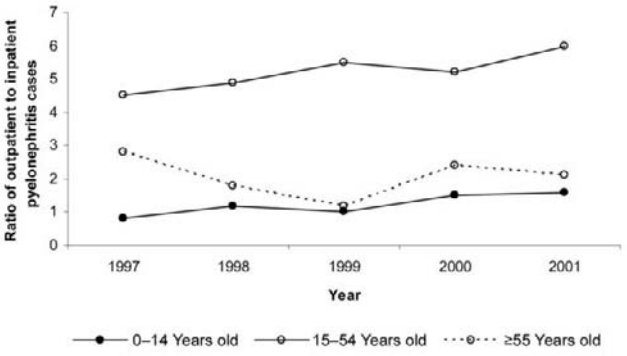

Figure 3. Ratio of outpatient to inpatient pyelonephritis cases in female patients, by age group, 1997–2001 ($P = .05$ for patients aged 0–14 years, $P = .17$ for patients aged 15–54 years, and $P = .93$ for patients aged ⩾55 years, by χ^2 test for trend).

in persons ⩾55 years of age, including *Klebsiella* and *Enterococcus* species, in particular. Among male patients, isolation of *S. saprophyticus* occurred predominantly among boys aged 0–14 years (6.8%). *E. coli* remained the predominant uropathogen in girls and boys aged <1 year.

Trends in antimicrobial resistance. Antimicrobial resistance data were available for pathogens isolated from 2137 (89%) of the outpatients and 303 (92%) of the inpatients with culture-confirmed cases. Uropathogen antimicrobial-resistance patterns were similar when stratified by treatment setting or by sex, and the data for all groups combined are shown in table 3. A trend of increasing resistance to cephalothin from 1997 through 2001 was noted ($P < .01$). The rate of fluoroquinolone resistance among *E. coli* strains was low, but it increased to 1.5% in 2001 ($P = .03$). Nonsignificant trends of decreasing rates of resistance among *E. coli* isolates were seen with gentamicin ($P = .05$) and nitrofurantoin ($P = .02$). Notably, the rate of *E. coli* with resistance to trimethoprim-sulfamethoxazole decreased significantly in 2001, from 23%–26% to 13% ($P < .01$). Yearly drug-resistance trends for *E. coli* and non–*E. coli* organisms combined also are presented in table 3. The rate of infection due to fluoroquinolone-resistant *E. coli* strains was lowest (0.0%) in girls and boys aged 0–14 years and highest (1.3%) in women and men aged ⩾55 years ($P = .01$).

Trends in antimicrobial therapy. There were 2318 outpatients (96%) with prescription data available. Thirty-six percent of outpatients were prescribed multiple antibiotics. Seventy-three percent received oral antibiotics alone, 24% received oral and intravenous antibiotics, and 3% received intravenous antibiotics alone.

Several trends in antimicrobial use for outpatient treatment of acute pyelonephritis were noted (table 4). The frequency of fluoroquinolone use increased from 35% of outpatients in 1997 to 61% in 2001 ($P < .01$). There was a simultaneous decrease in the use of trimethoprim-sulfamethoxazole, from 53% of outpatients in 1997 to 32% in 2001 ($P < .01$). Third-generation cephalosporin use for the treatment of outpatient pyelonephritis nearly doubled over time, whereas the use of first generation cephalosporins and nitrofurantoin decreased ($P < .01$).

Subjects aged 0–14 years with outpatient pyelonephritis were most frequently prescribed trimethoprim-sulfamethoxazole (rate of trimethoprim-sulfamethoxazole use, 61%). These subjects were rarely given fluoroquinolones. In contrast, fluoroquinolone use predominated for treatment of outpatient pyelonephritis among subjects aged 15–54 years (rate of fluoroquinolone use, 52%) and subjects ⩾55 years of age (rate of fluoroquinolone use, 53%; $P < .01$, for trend with older age groups). The rate of trimethoprim-sulfamethoxazole use decreased with age.

DISCUSSION

To date, surprisingly few studies describe the epidemiology of acute pyelonephritis, which is a relatively common disease that causes substantial short-term morbidity and can lead to death or long-term complications. Still fewer studies are population based. Thus, our understanding of the societal impact of this disease is limited.

This study demonstrates that, over a recent 5-year interval in a large US population, cases of acute pyelonephritis were predominantly managed in the outpatient setting, particularly those cases occurring among young women. Earlier case series suggest that women with milder disease are largely treated as outpatients [16–19]. In a population-based study of acute pyelonephritis in South Korea, the incidence of disease among young adult women was 5 times greater among outpatients than among inpatients, which is similar to our results [14]. As in South Korea, elderly men and women at GH tended to receive outpatient treatment. Young children, however, were mostly hospitalized. The observed (nonsignificant) trend toward increasing outpatient treatment of girls likely reflects the

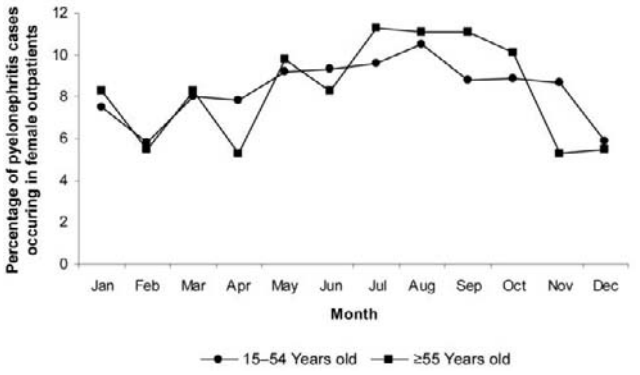

Figure 4. Percentage of pyelonephritis cases occurring in female outpatients, by month and age group, 1997–2001 ($P < .01$ for each age group, by χ^2 test).

Table 1. Uropathogens isolated at time of acute pyelonephritis, 1997–2001.

Pathogen	Percentage of isolates			
	Female outpatients (n = 2089)	Male outpatients (n = 319)	Female inpatients (n = 262)	Male inpatients (n = 69)
Escherichia coli[a]	81.6	74.0	84.5	71.0
Klebsiella species	2.6	6.0	3.4	7.3
Proteus species	1.2	2.2	1.9	1.5
Enterobacter species	1.3	1.9	1.9	0
Pseudomonas species	0.5	1.9	1.2	1.5
Citrobacter species	0.3	2.2	0.4	2.9
Enterococcus species	1.0	4.4	1.5	4.4
Staphylococcus saprophyticus	2.8	0.9	0	2.9
Staphylococcus aureus	0.2	0.6	0.4	1.5
Other	8.5	5.9	4.8	7.0

[a] $P < .01$ for comparison between female and male patients (outpatients and inpatients combined), $P = .27$ for comparison between female outpatients and female inpatients, and $P = .61$ for comparison between male outpatients and male inpatients, by χ^2 test.

treatment of older children. There are published data that suggest that children may be treated safely as outpatients [22], although hospitalization of young infants is recommended [32].

Overall rates of acute pyelonephritis at GH were 15–17 cases per 10,000 females and 3–4 cases per 10,000 males and were stable from year to year. Incidence varied substantially by sex and age. These incidence patterns likely reflect sex- and age-specific risk factors for UTI [13, 32–38]. We demonstrated a high incidence of disease among children aged 0–4 years, which is an age group that, to our knowledge, has not been evaluated by other population-based studies. Very young children, especially infants, are at increased risk of pyelonephritis, primarily because of predisposing structural or anatomic factors [32]. The large peak of cases occurring in young women is likely to be related to sexual intercourse, contraceptive use, and pregnancy [9, 13], whereas the increasing occurrence of acute pyelonephritis in men after middle age may be mostly attributable to obstructive uropathy [38]. The prevalence of diabetes also likely influenced the observed age distribution of disease [14].

An increased incidence of acute pyelonephritis in the late summer was seen for adult women. Seasonal trends have been noted in other studies of acute pyelonephritis [8, 14] and cystitis [39]. Such seasonal variation in UTI incidence has not yet been adequately explained, but may be attributable to changes in host behavior, environmental, or microbial factors [14]. The hypothesis that uropathogenic *E. coli* may be acquired via food may be consistent with a seasonal pattern [40].

As we have previously documented in premenopausal

Table 2. Uropathogens isolated at time of acute pyelonephritis among both inpatients and outpatients, 1997–2001.

Pathogen	Percentage of isolates, by patient sex and age					
	Female patients			Male patients		
	0–14 years (n = 301)	15–54 years (n = 1598)	⩾55 years (n = 452)	0–14 years (n = 59)	15–54 years (n = 139)	⩾55 years (n = 190)
Escherichia coli[a]	88.0	82.4	76.1	78.0	79.1	67.9
Klebsiella species	1.7	1.9	6.2	1.7	2.2	10.5
Proteus species	1.0	1.1	1.8	1.7	2.9	1.6
Enterobacter species	0.7	1.4	1.6	0.0	2.9	1.1
Pseudomonas species	2.3	0.3	0.4	0.0	2.2	2.1
Citrobacter species	0.7	0.2	0.4	1.7	2.2	2.6
Enterococcus species	0.7	0.6	2.6	1.7	2.2	6.8
Staphylococcus saprophyticus	0.3	3.4	0.4	6.8	0.7	0.0
Staphylococcus aureus	0.0	0.3	0.2	3.4	0.7	0.0
Other	4.6	8.4	10.3	5.0	4.9	7.4

[a] For female patients, $P < .01$, by χ^2 test for trend, for trend of decreasing percentage with older age group; for male patients, $P = .04$, by χ^2 test for trend, for trend of decreasing percentage with older age group.

Table 3. Urinary isolates from female and male outpatients and inpatients with acute pyelonephritis resistant to selected antimicrobial agents, 1997–2001.

	Percentage of isolates with resistance									
	1997		1998		1999		2000		2001	
Antimicrobial agent	*E. coli* isolates (n = 416)[a]	All isolates (n = 464)[a]	*E. coli* isolates (n = 399)[a]	All isolates (n = 438)[a]	*E. coli* isolates (n = 450)[a]	All isolates (n = 494)[a]	*E. coli* isolates (n = 447)[a]	All isolates (n = 495)[a]	*E. coli* isolates (n = 388)[b]	All isolates (n = 423)[c]
Ampicillin	44	46	44	45	42	45	45	46	40	42
Cefotaxime	0.5	0.4	0.0	0.0	0.2	0.4	0.0	0.4	0.8	0.7
Cephalothin	34	32	32	33	41	40	53	52	49	49
Ciprofloxacin	0.2	1.7	0.3	1.8	0.4	1.2	0.2	2.0	1.5	3.4
Gentamicin	1.9	1.9	0.8	0.7	0.9	0.8	0.7	0.6	0.5	1.3
Nitrofurantoin	1.7	6.0	1.8	5.6	1.3	5.2	0.7	5.2	0.3	3.1
TMP-SMX	25	24	26	24	25	25	23	21	13	13

NOTE. Significance of linear trends from 1997 to 2001 for *E. coli* isolates, by antimicrobial agent, are as follows: ampicillin, $P = .32$; cefotaxime, $P = .82$; cephalothin, $P < .01$; ciprofloxacin, $P = .03$; gentamicin, $P = .05$; nitrofurantoin, $P = .02$; TMP-SMX, $P < .01$. Significance of linear trends from 1997 to 2001 for all isolates, by antimicrobial agent, are as follows: ampicillin, $P = .41$; cefotaxime, $P = .40$; cephalothin, $P < .01$; ciprofloxacin, $P = .09$; gentamicin, $P = .37$; nitrofurantoin, $P = .06$; TMP-SMX, $P < .01$. All P values were determined by χ^2 test for trend. *E. coli, Escherichia coli;* TMP-SMX, trimethoprim-sulfamethoxazole.

[a] The n values varied slightly by antibiotic; values for ampicillin are presented.

[b] The n values are 254 for cefotaxime and cephalothin and range from 388 to 407 for other antibiotics.

[c] The n values are 271 for cefotaxime, 279 for cephalothin, and range from 423 to 453 for other antibiotics.

women [13], *E. coli* was the leading cause of acute pyelonephritis. Of interest, the distribution of causative uropathogens did not appear to differ greatly between outpatients and inpatients and was similar to what was found in an earlier study of cystitis at GH [23]. It may be that host and other factors play a larger role in hospitalization and severity of disease [16, 18]. An unexpected finding was the frequency with which *S. saprophyticus* was isolated, particularly among boys. Although known to cause 15%–20% of cases of cystitis in young women [39], *S. saprophyticus* has been occasionally identified as a cause of acute pyelonephritis in women [13, 16]. This organism has not been described as a significant cause of UTI in men.

We noted concurrent trends of increasing fluoroquinolone resistance and decreasing trimethoprim-sulfamethoxazole resistance among *E. coli* strains over time and inverse trends in fluoroquinolone and trimethoprim-sulfamethoxazole use for outpatient treatment of acute pyelonephritis. Our data suggest that increasing fluoroquinolone use for treatment of UTI and other infections may be driving resistance. Our finding that fluoroquinolone resistance was greatest in the older age groups supports this hypothesis. Fluoroquinolone resistance was lowest among children, who are rarely treated with fluoroquinolones because of the known adverse effects. Increasing rates of fluoroquinolone resistance have been documented in the United States and Europe and have correlated with increased use [28, 30]. Although decreased use of trimethoprim-sulfamethoxazole for the treatment of cystitis has been documented elsewhere [28, 29], an accompanying decrease in trimethoprim-sulfamethoxazole resistance has not. In a previous study of cystitis at GH, trimethoprim-sulfamethoxazole resistance among *E. coli* isolates increased from 9% to 18% from 1992 to 1996 [23]. Of note, national guidelines for the treatment of UTI that were

Table 4. Prescription of selected antimicrobial agents to treat outpatients with acute pyelonephritis, 1997–2001.

	Outpatients with prescription, %					
Antimicrobial agent	1997 (n = 442)	1998 (n = 477)	1999 (n = 459)	2000 (n = 479)	2001 (n = 461)	P[a]
Aminoglycoside	3.2	8.2	7.6	5.6	3.7	.60
First-generation cephalosporin	13	12	5.7	6.9	4.8	<.01
Second-generation cephalosporin	0.0	0.4	0.4	1.0	0.4	.14
Third-generation cephalosporin	12	23	26	25	23	<.01
Fluoroquinolone	35	33	52	58	61	<.01
Nitrofurantoin	9.3	9.6	5.0	3.8	5.0	<.01
Penicillin derivative	7.9	8.8	10	7.5	5.4	.11
TMP-SMX	53	52	41	35	32	<.01

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Significance of linear trends from 1997 to 2001, determined by χ^2 test for trend.

published in 1999 advocate the use of alternatives to trimethoprim-sulfamethoxazole, including fluoroquinolones, in areas with elevated levels of trimethoprim-sulfamethoxazole resistance [15], and may have influenced subsequent treatment and drug-resistance patterns at GH. We did not find an increase in third generation cephalosporin resistance, despite an increase in the use of that class of antibiotic, and there was an increase in first-generation cephalosporin resistance, despite decreased use of first-generation cephalosporin.

This study has several strengths. GH provided a large well-defined population. We included outpatients and inpatients from both sexes and included subjects with a wide age range. Culture, antimicrobial-resistance, and antimicrobial-treatment data have not been included in other population-based studies of acute pyelonephritis.

Several limitations of our study should be mentioned. ICD-9-CM diagnoses are imprecise, in that it is difficult to distinguish codes associated with true disease from those that are not. We minimized this inaccuracy by restricting our analysis to first episodes and using culture-confirmation of outpatient cases. We may not have captured a small number of outpatient cases in which a subject was discharged from the emergency department of an affiliate hospital for which culture data were unavailable. Likewise, urine culture data were available for only 40% of inpatients (including those not hospitalized at GH affiliates), and misclassification of non–culture-confirmed inpatient cases was possible. Despite these limitations, a similar case definition was found to be 98% accurate in a previous study involving young adult women at GH [13]. Although our case definition has not been verified in other population age and sex subsets, we believe that the same methodological approach would be similarly accurate in these groups, as well. Finally, our treatment data were identified by their temporal relation to ICD-9-CM diagnoses and may reflect some antibiotics prescribed for unrelated conditions. For example, nitrofurantoin use, reported in 5%–10% of cases, may have been prescribed for episodes of cystitis that later progressed to pyelonephritis. Because treatment data for inpatients treated at affiliate hospitals were incomplete, we did not include an analysis of inpatient therapy.

Finally, our incidence rates were lower than those documented in other population-based studies [8, 9, 14], potentially because our more conservative case definition excluded recurrent disease and required culture-confirmation of outpatient cases. Previous study populations may also have differed from ours with respect to other risk factors for acute pyelonephritis. A detailed risk factor analysis, including a comparison of uncomplicated and complicated disease, was not possible using the databases available for this study.

In conclusion, in a comprehensive analysis of the epidemiology of acute pyelonephritis in a defined US population, we demonstrated that the great majority of cases are now managed in the outpatient setting, and we found significant changes in antimicrobial treatment and resistance patterns over time that mirror changes in the management of cystitis. To our knowledge, this is the first population-based study to describe, in detail, trends in the incidence, etiology, antimicrobial resistance, and antimicrobial therapy of acute pyelonephritis among outpatients in the United States. Further studies should address whether subsequent drug-resistance trends warrant changes in empirical recommendations for the treatment of this important infection.

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