

The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 345

OCTOBER 4, 2001

NUMBER 14



WIDESPREAD DISTRIBUTION OF URINARY TRACT INFECTIONS CAUSED BY A MULTIDRUG-RESISTANT *ESCHERICHIA COLI* CLONAL GROUP

AMEE R. MANGES, M.P.H., JAMES R. JOHNSON, M.D., BETSY FOXMAN, PH.D., TIMOTHY T. O'BRYAN,
KATHLEEN E. FULLERTON, M.P.H., AND LEE W. RILEY, M.D.

ABSTRACT

Background The management of urinary tract infections is complicated by the increasing prevalence of antibiotic-resistant strains of *Escherichia coli*. We studied the clonal composition of *E. coli* isolates that were resistant to trimethoprim-sulfamethoxazole from women with community-acquired urinary tract infections.

Methods Prospectively collected *E. coli* isolates from women with urinary tract infections in a university community in California were evaluated for antibiotic susceptibility, O:H serotype, DNA fingerprinting, pulsed-field gel electrophoretic pattern, and virulence factors. The prevalence and characteristics of an antibiotic-resistant clone were evaluated in this group of isolates and in those from comparison cohorts in Michigan and Minnesota.

Results Fifty-five of the 255 *E. coli* isolates (22 percent) from the California cohort were resistant to trimethoprim-sulfamethoxazole as well as other antibiotics. There was a common pattern of DNA fingerprinting, suggesting that the isolates belonged to the same clonal group (clonal group A), in 28 of 55 isolates with trimethoprim-sulfamethoxazole resistance (51 percent) and in 2 of 50 randomly selected isolates that were susceptible to trimethoprim-sulfamethoxazole (4 percent, $P < 0.001$). In addition, 11 of 29 resistant isolates (38 percent) from the Michigan cohort and 7 of 18 (39 percent) from the Minnesota cohort belonged to clonal group A. Most of the clonal group A isolates were serotype O11:H(nt) or O77:H(nt), with similar patterns of virulence factors, antibiotic susceptibility, and electrophoretic features.

Conclusions In three geographically diverse communities, a single clonal group accounted for nearly half of community-acquired urinary tract infections in women that were caused by *E. coli* strains with resistance to trimethoprim-sulfamethoxazole. The widespread distribution and high prevalence of *E. coli* clonal group A have major public health implications. (N Engl J Med 2001;345:1007-13.)

Copyright © 2001 Massachusetts Medical Society.

AN estimated 11 percent of women in the United States report at least one physician-diagnosed urinary tract infection per year, and the lifetime probability that a woman will have a urinary tract infection is 60 percent.¹ The clinical management of urinary tract infection is complicated by the increasing incidence of infections caused by strains of *Escherichia coli* that are resistant to commonly used antimicrobial agents. In recent studies in the United States, the rates of resistance to trimethoprim-sulfamethoxazole among *E. coli* isolates from women with urinary tract infections ranged from 15 to 18 percent.²⁻⁴

Although urinary tract infection is not usually thought of as a disease associated with community-wide outbreaks, certain multidrug-resistant, uropathogenic lineages of *E. coli* have exhibited epidemic behavior.⁵ *E. coli* O15:K52:H1 caused an outbreak of community-acquired cystitis, pyelonephritis, and septicemia in South London in 1987 and 1988⁵ and is an endemic cause of urinary tract infection in Barcelona, Spain.⁶ This clonal group's distinctive profile of antibiotic resistance contributed to its identification in Europe.⁵

We studied the clonal composition of *E. coli* isolates from women (age range, 17 to 68 years) with uncomplicated, community-acquired urinary tract infections that were resistant to trimethoprim-sulfamethoxazole in order to ascertain whether any clonal group of *E. coli* was disproportionately represented.

From the Division of Epidemiology and Public Health Biology, School of Public Health, University of California at Berkeley, Berkeley (A.R.M., K.E.F., L.W.R.); the Medical Service, Minneapolis Veterans Affairs Medical Center, and the Department of Medicine, University of Minnesota, Minneapolis (J.R.J., T.T.O.); and the Department of Epidemiology, University of Michigan, School of Public Health, Ann Arbor (B.F.). Address reprint requests to Dr. Riley at the Division of Epidemiology and Public Health Biology, School of Public Health, University of California, 140 Warren Hall, Berkeley, CA 94720, or at lriley@uclink4.berkeley.edu.

METHODS

Study Cohorts

The study subjects included three cohorts of women (defined as those who were at least 17 years old) with urinary tract infections and a comparison group of healthy women whose stool specimens were analyzed to identify the *E. coli* isolates. The study was approved by the Committee for Protection of Human Subjects of the University of California at Berkeley; informed consent was not obtained, because the study involved neither direct interviews nor chart reviews. The California cohort consisted of women with symptoms of urinary tract infection who were seen at a university health service and were consecutively enrolled in the study between October 11, 1999, and January 31, 2000. A case of *E. coli* urinary tract infection was defined as symptoms suggestive of infection⁴ and a culture of a clean-catch urine specimen with more than 10² colony-forming units of *E. coli* per milliliter.⁷

The two comparison cohorts were women with uncomplicated cystitis who were seen at university health services in Minnesota and Michigan. For the Minnesota cohort, we analyzed all *E. coli* urinary isolates that were resistant to trimethoprim-sulfamethoxazole and 20 isolates that were susceptible to the combined drugs. The isolates were obtained from students with uncomplicated cystitis who were enrolled in a study between June 1998 and August 1999. For the Michigan cohort, we analyzed a similarly selected sample of urinary isolates from women with acute cystitis who were enrolled in a university-based study between September 1996 and May 1999.

Another comparison cohort consisted of 41 healthy residents at least two years of age (18 male subjects and 23 female subjects) of the university community in California who were free of urinary tract infection. Between August 1998 and November 2000, samples of freshly passed stool obtained from each subject monthly for six months were cultured for *E. coli*.

Isolation of *E. coli*

In California and Minnesota, urine samples were cultured on MacConkey agar. Colonies that were positive for lactose and indole were presumptively identified as *E. coli*. Culture methods for the Michigan cohort have been described previously.⁸ One putative *E. coli* colony from each urine culture was arbitrarily selected for further analyses. Five *E. coli* colonies per monthly fecal sample were selected for DNA fingerprinting with a polymerase-chain-reaction (PCR) assay.

Antibiotic Susceptibility Testing

E. coli isolates were screened for susceptibility to trimethoprim-sulfamethoxazole with the use of E-test strips (AB Biodisk, Solna, Sweden) in California, the MicroScan system (Dade Behring, Sacramento, Calif.) in Michigan, and a standard disk-diffusion assay⁹ in Minnesota. *E. coli* strain 25922 (from the American Type Culture Collection) was used as the reference strain. Susceptibility to 18 additional antimicrobial agents was assessed for selected isolates by the disk-diffusion method,¹⁰ with the use of standard interpretive criteria.⁹ Intermediate susceptibility was interpreted as full susceptibility.

DNA Fingerprinting

For each of the three cohorts of women with urinary tract infections, all isolates that were resistant to trimethoprim-sulfamethoxazole and subgroups of susceptible isolates, selected either randomly (in California and Michigan) or arbitrarily (in Minnesota), were screened with the enterobacterial repetitive intergenic consensus (ERIC2) PCR fingerprinting assay,¹¹⁻¹⁵ as previously described.¹⁶ Isolates with fingerprints that were indistinguishable on visual inspection were considered to belong to a single clonal group. Pattern A was defined by four predominant bands that were approximately 1145, 1029, 908, and 720 bp; isolates exhibiting this pattern were considered to be members of clonal group A. A pylonephritogenic isolate CFT073 (O6:K2:H1),¹⁷ provided by Dr. Harry Mobley at the University of Maryland, was used as a reference strain for each ERIC2 PCR run.

Pulsed-Field Gel Electrophoresis

The standardized protocol for molecular subtyping of *E. coli* (O157:H7) by pulsed-field gel electrophoresis (PFGE), as established by the Centers for Disease Control and Prevention,¹⁸ was used to identify a subgroup of the *E. coli* isolates that were indistinguishable by ERIC2 fingerprinting. *Xba*I-digested DNA was electrophoresed in the CHEF DR-II apparatus (Bio-Rad, Hercules, Calif.). Isolates that had indistinguishable PFGE patterns with the use of *Xba*I were reanalyzed with a second enzyme, *Apa*II. The criteria for strain relatedness established by Tenover et al. were used to compare PFGE patterns.¹⁹ The most frequently identified pattern among the California isolates was designated *Xba*I PFGE pattern A.

Virulence Genotyping

Genotypes for 31 putative virulence factors and the 12 known *papA* alleles were determined by multiplex PCR assays, supplemented by dot-blot hybridization, as previously described.²⁰⁻²²

Serotyping

Serotyping was performed on *E. coli* isolates at the *E. coli* reference center in University Park, Pennsylvania. Strains that were motile but that did not react with O or H antiserum were classified as nontypable (nt) — O(nt) and H(nt), respectively.

Conjugation Experiments

Selected wild-type isolates that were resistant to trimethoprim-sulfamethoxazole were conjugated with nalidixic acid-resistant, lactose-negative laboratory strain JM109,²³ according to a standard procedure,^{24,25} and plated on Luria-Bertani agar²⁶ containing trimethoprim-sulfamethoxazole (16 and 350 µg per milliliter, respectively) and nalidixic acid (20 µg per milliliter). The putative trans-conjugants were tested for susceptibility to 18 antimicrobial agents by a disk-diffusion method to identify markers of resistance to additional antimicrobial agents.

Statistical Analysis

Chi-square analysis with the use of generalized estimating equations based on the PROC GENMOD procedure in SAS (version 8.01, SAS Institute, Cary, N.C.) was used to account for clustered sampling in the California cohort, which included women with multiple urinary tract infections. An exchangeable correlation structure was used in the analysis. The chi-square test or Fisher's exact test was also used in analyses in which the data were restricted to the first (primary) episode of urinary tract infection during the study period.

RESULTS

Prevalence of Trimethoprim-Sulfamethoxazole Resistance

A total of 228 women (median age, 22 years) seen at the university health service in California had symptoms suggestive of acute urinary tract infection. A total of 505 consecutive urine samples from these women were cultured, 255 of which yielded more than 10² colony-forming units of *E. coli* per milliliter. Twenty-four women had repeated urinary tract infections during the study period: 21 (9 percent) had two infections, and 3 (1 percent) had three infections.

Fifty-five of the 255 *E. coli* isolates (22 percent) were resistant to trimethoprim-sulfamethoxazole (Table 1). All 55 resistant isolates, which were from 47 women, and 50 susceptible isolates, from 49 other women, were selected for further analysis. In the Minnesota cohort, 18 of 82 *E. coli* isolates (22 percent) were resistant to trimethoprim-sulfamethoxazole. All

TABLE 1. RESULTS OF FINGERPRINTING ANALYSIS OF *ESCHERICHIA COLI* ISOLATES OBTAINED FROM WOMEN WITH URINARY TRACT INFECTIONS IN CALIFORNIA, MICHIGAN, AND MINNESOTA.*

VARIABLE	CALIFORNIA	MICHIGAN	MINNESOTA
No. of isolates	255	NA	82
No. of women	228	NA	82
TMP-SMX-resistant isolates			
— no. (%)			
All isolates	55 (22)	67	18 (22)
Isolates from primary episode	47 (21)	66	—
Clonal pattern A — no./total no. (%)†			
All isolates	28/55 (51)	11/29 (38)‡	7/18 (39)
Isolates from primary episode	23/47 (49)	10/28 (36)	—

*In California and Michigan, some of the women from whom isolates were obtained had recurrent episodes of urinary tract infection. Information for all isolates and for isolates from the primary episode is presented. In Minnesota, only one isolate was obtained from each woman. Fingerprinting was analyzed with the use of the enterobacterial repetitive intergenic consensus polymerase-chain-reaction assay. NA denotes not available, and TMP-SMX trimethoprim-sulfamethoxazole.

†Clonal pattern A was defined by four predominant bands that were approximately 1145, 1029, 908, and 720 bp.

‡A subgroup of 29 TMP-SMX-resistant isolates was selected for analysis of fingerprinting.

18 resistant isolates (from 18 women), plus 20 susceptible isolates (from 20 women), were selected for further analysis. In the Michigan cohort, 29 resistant isolates (from 28 women) and 20 susceptible isolates (from 20 other women) were selected for further analysis (Table 1).

ERIC2 PCR Fingerprinting

In the California cohort, 28 of the 55 *E. coli* isolates that were resistant to trimethoprim-sulfamethoxazole (51 percent) exhibited the same four-band ERIC2 pattern and were therefore identified as belonging to clonal group A (Fig. 1 and Table 1), as compared with only 2 of 50 randomly selected susceptible isolates (4 percent; $P < 0.001$, with adjustment for clustered sampling). In the Minnesota cohort, 7 of 18 isolates that were resistant to trimethoprim-sulfamethoxazole exhibited clonal pattern A (39 percent), as compared with only 1 of 20 susceptible isolates (5 percent, $P = 0.02$). Likewise, in the Michigan cohort, 11 of 29 isolates that were resistant to trimethoprim-sulfamethoxazole exhibited clonal pattern A (38 percent), as compared with none of the 20 susceptible isolates ($P = 0.001$ by Fisher's exact test) (Fig. 1 and Table 1).

ERIC2 PCR was also used to evaluate 925 colonies of *E. coli* isolated from the stool samples obtained from the group of 41 healthy persons. Clonal group A isolates were identified in one or more fecal samples from 5 of the 18 male subjects (28 percent) and 10 of the

23 female subjects (43 percent). Thirteen of the 26 clonal group A isolates (50 percent) were resistant to trimethoprim-sulfamethoxazole (data not shown).

Results of PFGE Analysis

*Xba*I PFGE analysis was performed on 38 clonal group A isolates (23 from the California cohort and a total of 15 from the other two cohorts). Eleven of the California isolates (48 percent) had indistinguishable PFGE findings (designated *Xba*I PFGE pattern A); 7 isolates (30 percent) differed from this pattern by only one to three bands, 4 (17 percent) by four to six bands, and 1 (4 percent) by more than six bands (Fig. 2 and Table 2). *Avr*II PFGE performed on six of the isolates with *Xba*I PFGE pattern A showed that four were indistinguishable, and the other two differed by only two bands. Although none of the isolates from Michigan and Minnesota had patterns that were identical to *Xba*I PFGE pattern A of the isolates from California, two of the eight Michigan isolates and all seven Minnesota isolates had patterns that were moderately or very similar (Table 2).

Antibiotic Susceptibility

Clonal group A isolates from all three cohorts had a significantly higher prevalence of resistance to multiple antibiotics than did the comparison strains (Table 3). A pattern of resistance to six drugs was found in 8 of 19 clonal group A strains (42 percent) but in none of the other strains ($P < 0.001$).

Serotyping

Of 41 representative clonal group A isolates from the three cohorts with urinary tract infections, 32 (78 percent) exhibited one of two distinctive serotypes: O11:H(nt) or O77:H(nt). Serotype O11:H(nt) predominated among the California isolates but was rare or nonexistent among the Michigan and Minnesota isolates, whereas serotype O77:H(nt) accounted for large proportions of the Michigan and Minnesota isolates (Table 2). Three of the remaining clonal group A isolates (7 percent of the total) exhibited a unique O antigen, and 6 (15 percent of the total) could not be typed. Of the 13 clonal group A fecal isolates that were serotyped, 9 (69 percent) were O11:H(nt), 2 were other serotypes, and 2 could not be typed.

Virulence Genotyping

Clonal group A was characterized by a distinctive profile of virulence factors that included a complete copy of *pap*, the F16 *papA* allele, *papG* allele II, *intA*, *kpsMT* II, and *traT*, and the absence of *sfu/foc*, *afa/dra*, *hly*, *cnf*, *iroN*, *iss*, and *malX* (Table 3). This profile, which corresponds with that previously documented for the O15:K52:H1 clonal group,^{6,27} was consistent among isolates from all three cohorts, whether or not the strains were resistant to trimethoprim-sulfamethoxazole.

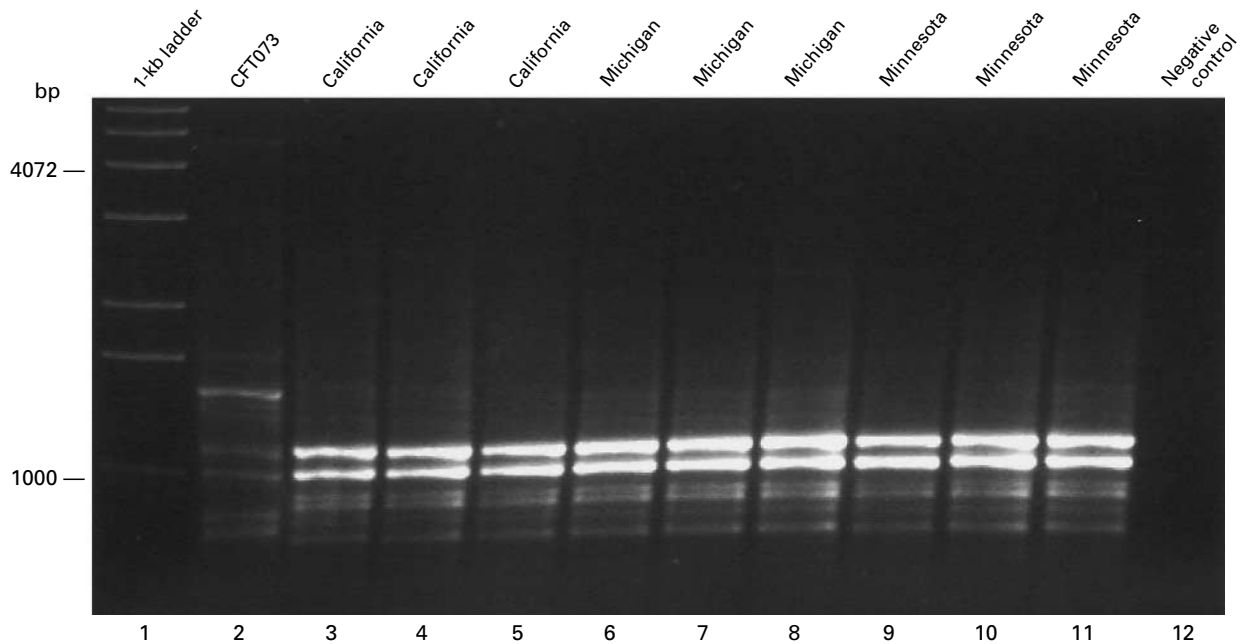


Figure 1. Fingerprint Patterns of *Escherichia coli* Isolates with Resistance to Trimethoprim–Sulfamethoxazole.

Fingerprinting was performed with the use of the enterobacterial repetitive intergenic consensus polymerase-chain-reaction assay. The *E. coli* isolates from California (lanes 3, 4, and 5), Michigan (lanes 6, 7, and 8), and Minnesota (lanes 9, 10, and 11) show the same four-band (two dark and two light) pattern (designated pattern A), indicating that they are all members of clonal group A. Lane 1 shows a 1-kb ladder, lane 2 CFT073 (the reference strain), and lane 12 a negative control.

Conjugation

JM109 transconjugants were derived from five clonal group A isolates in California that were resistant to trimethoprim–sulfamethoxazole. The transconjugants acquired resistance not only to trimethoprim–sulfamethoxazole but also to ampicillin, tetracycline, chloramphenicol, and streptomycin (data not shown).

DISCUSSION

We found that 11 percent of uncomplicated, community-acquired urinary tract infections in women seen during a four-month period at a university health service in California were caused by a single, previously unrecognized clonal group of multidrug-resistant *E. coli*, clonal group A. This clonal group accounted for 51 percent of urinary tract infections caused by *E. coli* strains that were resistant to trimethoprim–sulfamethoxazole at this health center and for high proportions of such isolates from women seen at university health centers in Michigan and Minnesota (38 and 39 percent, respectively). Although a limited number of isolates and locations were surveyed, these data suggest that a single *E. coli* clonal group may have contributed to the recently documented increase in antibiotic resistance among *E. coli* isolates from patients with urinary tract infections in some parts of

the United States.^{3,4} In the California cohort, if it had not been for this drug-resistant clonal group, the proportion of all primary episodes of urinary tract infections caused by *E. coli* strains that were resistant to trimethoprim–sulfamethoxazole would have been 11 percent instead of 21 percent.

That the *E. coli* isolates with resistance to trimethoprim–sulfamethoxazole represent a phylogenetically distinct clonal group was suggested by their similarities to one another and their differences from other strains with respect to five characteristics: the ERIC2 fingerprinting pattern; O:H serotype, with the unusual serotypes O77:H(nt) or O11:H(nt) predominating among members of clonal group A; PFGE profiles; virulence-factor profiles; and patterns of antibiotic susceptibility. Clonal group A isolates accounted for 11 percent of all urinary tract infections in California and for 9 percent in Minnesota, which represents a substantial prevalence for a single *E. coli* clonal group.^{20,27} This finding indicates that clonal group A contributes substantially not only to drug-resistant urinary tract infections but also to urinary tract infections in general.

Clonal group A appears to represent a new lineage of multidrug-resistant, uropathogenic *E. coli* rather than an established virulent clone that has acquired antibiotic resistance. In previous studies of *E. coli* iso-

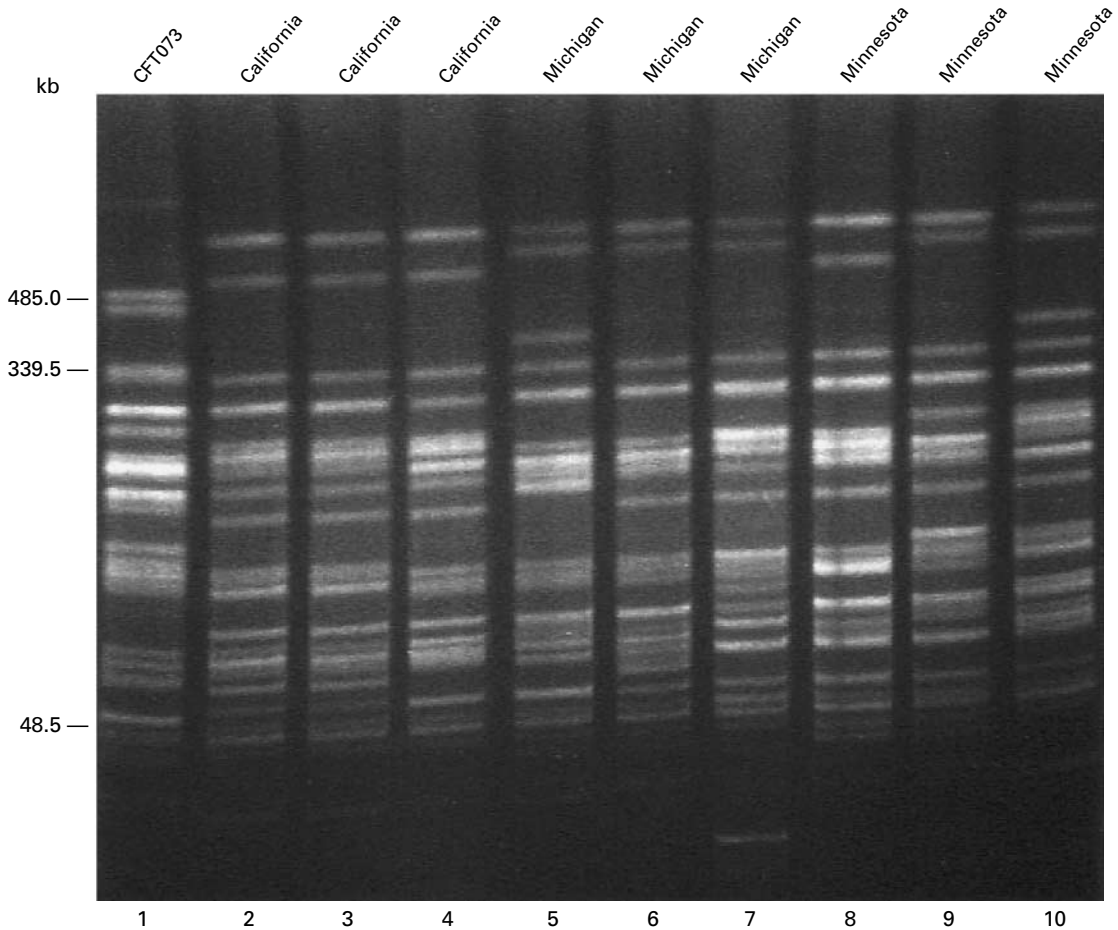


Figure 2. Molecular Subtyping of Clonal Group A Isolates with Resistance to Trimethoprim–Sulfamethoxazole. Pulsed-field gel electrophoresis with *Xba*I was used for subtyping. Lane 1 shows CFT073 (the reference strain). Clonal group A isolates from California are shown in lanes 2, 3, and 4; those from Michigan in lanes 5, 6, and 7; and those from Minnesota in lanes 8, 9, and 10.

lates from urinary tract infections, O11 and O77 somatic antigens have not been noted, and serogroups O1, O2, O4, O6, O7, O16, O18, O25, and O75 have consistently predominated, accounting for up to 81 percent of isolates.²⁷⁻³⁰

Although urinary tract infection is usually regarded as a sporadic disease caused by organisms from the host’s own fecal flora, transmission of *E. coli* between sex partners and household members has been reported.^{31,32} Nosocomial outbreaks of *E. coli* pyelonephritis have also been documented.³³ A community-wide outbreak of urinary tract infection due to a single strain occurred in South London in 1986 and 1987.⁵ In this outbreak, isolates of *E. coli* O15:K52:H1 that exhibited a distinctive multidrug-resistance phenotype similar to that of the clonal group A isolates in our study were recovered from community-acquired cases of pyelonephritis and bacteremia. This serotype was subsequently identified as a cause of endemic urinary tract infection and bacteremia in other European

TABLE 2. SEROTYPE AND PULSED-FIELD GEL ELECTROPHORETIC (PFGE) PATTERN OF SELECTED CLONAL GROUP A ISOLATES FROM CALIFORNIA, MICHIGAN, AND MINNESOTA.*

SEROTYPE AND PFGE PATTERN	CALIFORNIA	MICHIGAN	MINNESOTA
	no. of isolates (%)		
Serotype	23	11	7
O11:H(nt)	14 (61)	0	1 (14)
O77:H(nt)	6 (26)	8 (73)	3 (43)
Other or nontypable	3 (13)	3 (27)	3 (43)
PFGE pattern	23	8	7
Pattern A	11 (48)	0	0
Pattern that differed from pattern A			
By 1–3 bands	7 (30)	2 (25)	5 (71)
By 4–6 bands	4 (17)	0	2 (29)
By >6 bands	1 (4)	6 (75)	0

*Serotyping was performed on 23 of the 28 isolates in California that were resistant to trimethoprim–sulfamethoxazole and that exhibited pattern A on fingerprinting and on all such isolates in Michigan and Minnesota. Isolates from recurrent episodes of infection are included in the data for California and Michigan. PFGE was performed with *Xba*I-digested DNA; nt denotes nontypable.

TABLE 3. PREVALENCE OF ANTIBIOTIC-RESISTANCE PATTERNS AND VIRULENCE-FACTOR PROFILES OF *ESCHERICHIA COLI* ISOLATES.

ANTIBIOTIC RESISTANCE AND VIRULENCE FACTORS	CLONAL GROUP A ISOLATES	OTHER ISOLATES	P VALUE*
	no. of isolates (%)		
Antibiotic resistance			
Total isolates†	19	21	
TMP-SMZ resistance with or without resistance to other drugs	16 (84)	3 (14)	<0.001
TMP-SMZ and chloramphenicol	12 (63)	1 (5)	<0.001
TMP-SMZ and streptomycin	11 (58)	2 (10)	<0.001
TMP-SMZ and ampicillin	15 (79)	3 (14)	<0.001
TMP-SMZ, ampicillin, streptomycin, and chloramphenicol	9 (47)	1 (5)	0.003
TMP-SMZ, ampicillin, streptomycin, chloramphenicol, and tetracycline	8 (42)	0	<0.001
Virulence factors‡			
Total isolates	25	36	
<i>papA</i> F16 with or without other factors	21 (84)	0	<0.001
<i>papA</i> F16, <i>traT</i>	20 (80)	0	<0.001
<i>papA</i> F16, <i>traT</i> , <i>kpsMTII</i> , <i>iutA</i>	18 (72)	0	<0.001
<i>papA</i> F16, <i>traT</i> , <i>kpsMTII</i> , <i>iutA</i> , <i>fyuA</i>	16 (64)	0	<0.001
<i>papA</i> F16, <i>traT</i> , <i>kpsMTII</i> , <i>iutA</i> , <i>fyuA</i> , <i>ompT</i>	16 (64)	0	<0.001
<i>papA</i> F16, <i>traT</i> , <i>kpsMTII</i> , <i>iutA</i> , <i>fyuA</i> , <i>ompT</i> , <i>malX</i> (pathogenicity island) with or without other factors	12 (48)	0	<0.001
<i>malX</i> , <i>blyA</i>	0	24 (67)	<0.001
<i>malX</i> , <i>blyA</i> , <i>papA</i> , <i>papG</i>	0	13 (36)	<0.001
<i>malX</i> , <i>blyA</i> , <i>papA</i> , <i>papG</i> , <i>cnfI</i>	0	11 (31)	0.002
<i>malX</i> , <i>blyA</i> , <i>papA</i> , <i>papG</i> , <i>cnfI</i>	0	6 (17)	0.04
<i>malX</i> , <i>blyA</i> , <i>papA</i> , <i>papG</i> , <i>cnfI</i> , <i>iroN</i>	0	4 (11)	0.13
<i>malX</i> , <i>blyA</i> , <i>papA</i> , <i>papG</i> , <i>cnfI</i> , <i>iroN</i> , <i>sfu</i>	0	3 (8)	0.26

*Only one isolate per subject was included in these analyses. The P values were therefore calculated with a simple chi-square test or Fisher's exact test.

†Isolates from California, Minnesota, and Michigan were selected for inclusion in the analysis of antibiotic resistance in proportion to the prevalence of resistance to trimethoprim-sulfamethoxazole (TMP-SMZ) among clonal group A isolates as compared with that of other isolates in each cohort. The ratio of TMP-SMZ-resistant to TMP-SMZ-susceptible isolates included in the analysis was 4:1 for clonal group A and 1:6 for other strains in California, 6:2 for clonal group A and 1:6 for other strains in Minnesota, and 6:0 for clonal group A and 1:6 for other strains in Michigan. The patterns of resistance are not mutually exclusive.

‡The distribution of virulence factors was similar among clonal group A isolates from each cohort. All isolates with *papA* allele F16 were also positive for *papAH*, *papC*, *papEF*, and *papG* allele II. Independent isolates were selected from each cohort for inclusion in the analysis of virulence factors in order to provide, for clonal group A, up to six TMP-SMZ-resistant isolates and as many TMP-SMZ-susceptible isolates as were available (up to six) and, for non-clonal group A, six TMP-SMZ-resistant and six TMP-SMZ-susceptible isolates. The virulence patterns are not mutually exclusive.

countries³⁴⁻³⁶ and, more recently, in the United States.⁶ The clonal group A strains exhibit a virulence genotype that is very similar to that of the O15:K52:H1 clonal group, including the F16 *papA* allele, *papG* allele II, *iutA*, *fyuA*, *kpsMTII*, and *traT*.⁶

We identified clonal group A strains in fecal samples obtained during the study period from healthy members of the university community in California. The proportion of healthy subjects identified as having fecal colonization with clonal group A on one or more occasions is probably an overestimate of the true prevalence of this infection in the community because of the sampling strategy used. Nevertheless, this analysis does show that clonal group A was circulating in members of the community when the cases of urinary tract infection occurred.

The apparent emergence of clonal group A in three states suggests either the simultaneous expansion in multiple locations of a previously introduced endemic clonal group, possibly as a consequence of increasing antimicrobial selection pressure, or the recent introduction of the clonal group into new environments. The high degree of genetic homogeneity among the California isolates favors the latter hypothesis. One possible explanation for the observed temporal and geographic clustering of a single *E. coli* PFGE type (pattern A) in California is that the strains were spread by one or more contaminated products ingested by community residents, which is similar to the way an enteric pathogen, such as *E. coli* O157:H7, causes community-wide outbreaks after being disseminated by the consumption of contaminated foods.^{18,37} If a

large proportion of urinary tract infections caused by drug-resistant strains of *E. coli* in a community were due to the ingestion of widely consumed, contaminated foods, this would constitute a serious and novel public health problem.

Clonal group A isolates were resistant to antibiotics that are commonly used in the outpatient setting to treat urinary tract infection and a wide variety of other infections. Resistance to these agents may persist with the use of any of the antibiotics represented in the resistance phenotype. Additional studies are needed to establish the geographic and temporal distribution of this emerging *E. coli* clonal group and to determine whether it is spread by the ingestion of contaminated foods.

Supported by grants from the Alameda County District Attorney General's Fund (to Dr. Riley); the Office of Research and Development, Medical Research Service, Department of Veterans Affairs (to Dr. Johnson); the National Institutes of Health (DK-47504, to Dr. Johnson, and DK35368, to Dr. Foxman); and the National Research Initiative Competitive Grants Program and the Department of Agriculture (00-35212-9408, to Dr. Johnson).

We are indebted to Peter Dietrich, M.D., M.P.H., and the staff of the clinical laboratory at the University of California, Berkeley, Health Services, for their assistance in enrolling patients and collecting samples; to David Wang, M.D., and the nursing and laboratory staff at the Minnesota clinic; to Sharon Abbott, Jan O'Connell, and Jim Ware at the California Department of Health for technical assistance with PFGE; and to Brent Sugimoto, M.P.H., for assistance in collecting and analyzing the fecal samples.

REFERENCES

1. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol* 2000;10:509-15.
2. Kahlmeter G. The ECO-SENS Project: a prospective, multinational, multicentre epidemiological survey of the prevalence and antimicrobial susceptibility of urinary tract pathogens — interim report. *J Antimicrob Chemother* 2000;46:Suppl A:15-22.
3. Talan D, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* 2000;283:1583-90.
4. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA* 1999;281:736-8.
5. Phillips I, Eykyn S, King A, et al. Epidemic multiresistant *Escherichia coli* infection in West Lambeth Health District. *Lancet* 1988;1:1038-41.
6. Prats G, Navarro F, Mirelis B, et al. *Escherichia coli* serotype O15:K52:H1 as a uropathogenic clone. *J Clin Microbiol* 2000;38:201-9.
7. Hooton T, Stamm W. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am* 1997;11:551-81.
8. Foxman B, Gillespie B, Koopman J, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol* 2000;151:1194-205.
9. Supplemental tables: disk diffusion. NCCLS document M100-S10. Wayne, Pa.: National Committee for Clinical Laboratory Standards, 2000:14-8.
10. Performance standards for antimicrobial disk susceptibility tests. NCCLS document M2-A7. Wayne, Pa.: National Committee for Clinical Laboratory Standards, 2000:1-18.
11. Sharples GJ, Lloyd RG. A novel repeated DNA sequence located in the intergenic regions of bacterial chromosomes. *Nucleic Acids Res* 1990;18:6503-8.
12. Hulton CSJ, Higgins CF, Sharp PM. ERIC sequences: a novel family of repetitive elements in the genomes of *Escherichia coli*, *Salmonella typhimurium* and other enterobacteria. *Mol Microbiol* 1991;5:825-34.
13. Versalovic J, Koeuth T, Lupski JR. Distribution of repetitive DNA sequences in eubacteria and application to fingerprinting of bacterial genomes. *Nucleic Acids Res* 1991;19:6823-31.
14. Versalovic J, Schneid M, de Bruijn FL, Lupski JR. Genomic fingerprinting of bacteria using repetitive sequence-based polymerase chain reaction. *Methods Mol Cell Biol* 1994;5:25-40.
15. Woods CR, Versalovic J, Koeuth T, Lupski JR. Whole-cell repetitive element sequence-based polymerase chain reaction allows rapid assessment of clonal relationships of bacterial isolates. *J Clin Microbiol* 1993;31:1927-31.
16. Johnson JR, O'Bryan TT. Improved repetitive-element PCR fingerprinting for resolving pathogenic and nonpathogenic phylogenetic groups within *Escherichia coli*. *Clin Diagn Lab Immunol* 2000;7:265-73.
17. Mobley HL, Green DM, Trifillis AL, et al. Pyelonephritogenic *Escherichia coli* and killing of cultured human renal proximal tubular epithelial cells: role of hemolysin in some strains. *Infect Immun* 1990;58:1281-9.
18. Bender JB, Hedberg CW, Besser JM, Boxrud DJ, MacDonald KL, Osterholm MT. Surveillance for *Escherichia coli* O157:H7 infections in Minnesota by molecular subtyping. *N Engl J Med* 1997;337:388-94.
19. Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995;33:2233-9.
20. Johnson JR, Stell AL. Extended virulence genotypes of *Escherichia coli* strains from patients with urosepsis in relation to phylogeny and host compromise. *J Infect Dis* 2000;181:261-72. [Erratum, *J Infect Dis* 2000;181:2122.]
21. Johnson JR, O'Bryan TT, Low DA, et al. Evidence of commonality between canine and human extraintestinal pathogenic *Escherichia coli* strains that express *papG* allele III. *Infect Immun* 2000;68:3327-36.
22. Johnson JR, Stell AL, Scheutz F, et al. Analysis of the F antigen-specific *papA* alleles of extraintestinal pathogenic *Escherichia coli* using a novel multiplex PCR-based assay. *Infect Immun* 2000;68:1587-99.
23. Yanisch-Perron C, Vieira J, Messing J. Improved M13 phage cloning vectors and host strains: nucleotide sequences of the M13mp18 and pUC19 vectors. *Gene* 1985;33:103-19.
24. Hardy KG. Bacterial plasmids. Washington, D.C.: American Society for Microbiology, 1983.
25. Johnson JR, Moseley SL, Roberts PL, Stamm WE. Acrobactin and other virulence factor genes among strains of *Escherichia coli* causing urosepsis: association with patient characteristics. *Infect Immun* 1988;56:405-12.
26. Maniatis T, Fritsch EF, Sambrook J. Molecular cloning: a laboratory manual. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1982.
27. Johnson JR. Virulence factors in *Escherichia coli* urinary tract infection. *Clin Microbiol Rev* 1991;4:80-128.
28. *Escherichia coli* and urinary tract infection. In: Cook EM. *Escherichia coli* and man. Edinburgh, Scotland: Churchill Livingstone, 1974:31-46.
29. Donnenberg MS, Welch RA. Virulence determinants of uropathogenic *Escherichia coli*. In: Mobley HLT, Warren JW, eds. *Urinary tract infections: molecular pathogenesis and clinical management*. Washington, D.C.: American Society of Microbiology, 1996:135-74.
30. Bettelheim KA. *Escherichia coli* in the normal flora of humans and animals. In: Sussman M, ed. *Escherichia coli: mechanisms of virulence*. Cambridge, England: Cambridge University Press, 1997:85-109.
31. Foxman B, Zhang L, Tallman P, et al. Transmission of uropathogens between sex partners. *J Infect Dis* 1997;175:989-92.
32. Johnson JR, Brown JJ, Carlino UB, Russo TA. Colonization with and acquisition of uropathogenic *Escherichia coli* as revealed by polymerase chain reaction-based detection. *J Infect Dis* 1998;177:1120-4.
33. Tullus K, Horlin K, Svenson SB, Kallenius G. Epidemic outbreaks of acute pyelonephritis caused by nosocomial spread of P fimbriated *Escherichia coli* in children. *J Infect Dis* 1984;150:728-36.
34. Dalmau D, Navarro F, Mirelis B, Blanco J, Garau J, Prats G. *Escherichia coli* bacteraemia: serotype O15:K52:H1 as a urinary pathogen. *J Hosp Infect* 1996;34:233-4.
35. Olesen B, Kolmos HJ, Orskov F, Orskov I. A comparative study of nosocomial and community-acquired strains of *Escherichia coli* causing bacteraemia in a Danish university hospital. *J Hosp Infect* 1995;31:295-304.
36. Johnson JR, Stell A, Nowicki B, et al. Broad prevalence in the U.S. of a "European" clone of urovirulent *E. coli* O15:K52:H1. In: Abstracts of the 99th General Meeting of the American Society for Microbiology, Chicago, May 30–June 3, 1999. Washington, D.C.: American Society for Microbiology, 1999:31. abstract.
37. Dorn CR. Review of foodborne outbreak of *Escherichia coli* O157:H7 infection in the western United States. *J Am Vet Med Assoc* 1993;203:1583-7.

Copyright © 2001 Massachusetts Medical Society.