
Global Distribution and Epidemiologic Associations of *Escherichia coli* Clonal Group A, 1998–2007

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Analyze the prevalence of trimethoprim/sulfamethoxazole resistance among *Escherichia coli* clonal group A (CGA) isolates
- Distinguish geographic locations with the highest prevalence of CGA
- Assess variables that significantly affect the prevalence of CGA
- Evaluate temporal trends in the prevalence of CGA

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Escherichia coli clonal group A (CGA) was first reported in 2001 as an emerging multidrug-resistant extraintestinal pathogen. Because CGA has considerable implications for public health, we examined the trends of its global distribution, clinical associations, and temporal prevalence for the years 1998–2007. We characterized 2,210 *E. coli* extraintestinal clinical isolates from 32 centers on 6 continents by CGA status for comparison with trimethoprim/sulfamethoxazole (TMP/SMZ) phenotype, specimen type, inpatient/outpatient source, and adult/child host; we adjusted for clustering by center. CGA prevalence varied greatly by center and continent, was strongly associated with TMP/SMZ resistance but not with other epidemiologic variables, and exhibited no temporal prevalence trend. Our findings indicate that CGA is a prominent, primarily TMP/SMZ-resistant extraintestinal pathogen concentrated within the Western world, with considerable pathogenic versatility. The stable prevalence of CGA over time suggests full emergence by the late 1990s, followed by variable endemicity worldwide as an antimicrobial drug-resistant public health threat.

Extraintestinal infections caused by *Escherichia coli* are a substantial source of illness, death, and increased health care costs and have become increasingly challenging to manage because of the rising prevalence of resistance to first-line antimicrobial drugs (1). The resistance problem is now recognized as having a prominent clonal component attributable in large part to the emergence and dissemination of specific antimicrobial drug-resistant clonal groups of extraintestinal pathogenic *E. coli* (2–6).

One such emergent antimicrobial drug-resistant extraintestinal pathogenic *E. coli* clonal group is clonal group A (CGA) (2). Most traditionally recognized extraintestinal pathogenic *E. coli* clonal groups derive from *E. coli* phylogenetic group B2; however, CGA derives from phylogenetic group D (7), and, according to multilocus sequence typing (MLST), CGA corresponds with clonal complex 69 (8,9).

CGA first came to attention during the late 1990s as a prominent cause of trimethoprim/sulfamethoxazole (TMP/SMZ)-resistant urinary tract infections among otherwise healthy women across the United States (2,10). Isolates of CGA typically exhibit a fairly conserved virulence genotype that includes P fimbriae (with the F16 structural subunit variant), group 2 capsule (with the K52 capsular antigen), and the aerobactin and yersiniabactin siderophore systems. They also commonly exhibit resistance to multiple antimicrobial agents other than TMP/SMZ, including tetracycline, chloramphenicol, streptomycin, and spectinomycin, with the corresponding resistance genes carried either on a large conjugative plasmid (2) or within a genomic resistance module (11).

CGA has been recognized primarily as a cause of community-acquired cystitis and pyelonephritis in adult women mainly in the United States (2,10,12,13). It is largely unknown to what extent CGA might have broader pathogenic capabilities with respect to anatomic site of infection (urine vs. nonurine), site of acquisition (hospital vs. community), and host age (adult vs. child). Likewise, although a global survey of *E. coli* clinical isolates from 2001 found CGA was significantly associated with the United States (14), assessment of its distribution beyond the United States has been limited (5). Furthermore, no recent data are available regarding whether the overall prevalence of CGA is rising, stable, or waning, as can occur on a local level for CGA and other extraintestinal pathogenic *E. coli* clonal groups (3,13). Therefore, because of the major public health implications of CGA, we assessed the prevalence of this *E. coli* clonal group during 1998–2007 in multiple locales in the United States and internationally, paying specific attention to specimen type, inpatient versus outpatient status of host, and host age.

Methods

Strains

Sets of unpublished human clinical extraintestinal *E. coli* isolates were obtained from 32 clinical microbiology laboratories and affiliated repositories worldwide (online Technical Appendix, wwwnc.cdc.gov/EID/pdfs/11-0488-Techapp.pdf). Submitters were asked to provide ≈25 consecutive TMP/SMZ-resistant extraintestinal *E. coli* isolates and 25 concurrent TMP/SMZ-susceptible extraintestinal *E. coli* controls (1 per patient), or more, as available. When possible, isolates were to be distributed evenly by inpatient versus outpatient source and, within each of these categories, by specimen type (urine vs. other). Information was requested about the adult (age ≥18 years) versus child (age <18 years) status of the hosts and the local overall prevalence of TMP/SMZ-resistant *E. coli*.

Isolates were submitted to the research laboratory (J.R.J.) in agar stabs and frozen at –80°C in 15% glycerol pending further analysis. Selected isolates underwent additional screening, by breakpoint agar dilution and disk diffusion, for confirmation of TMP/SMZ phenotype.

Molecular Analysis

Major *E. coli* phylogenetic group (A, B1, B2, D) was defined by triplex PCR (15). Group D isolates were assessed for CGA (i.e., clonal complex 69) status in a staged fashion. First, all were screened by PCR for CGA-associated single-nucleotide polymorphisms (SNPs) in *fumC* (16). All *fumC* SNP-positive isolates (which included all CGA isolates, plus any non-CGA isolates containing

the same *fumC* SNPs) then underwent pulsed-field gel electrophoresis (PFGE) analysis of *Xba*I-restricted total DNA (17). Those with $\geq 94\%$ PFGE profile similarity to a known CGA isolate (determined on the basis of previous *fumC* and *gyrB* SNP analysis or 7-locus MLST) (5) were defined as CGA because this degree of PFGE similarity reliably predicts identity by MLST (J.R. Johnson, unpub. data). The *fumC* SNP-positive isolates without a PFGE profile match of $\geq 94\%$ to a known CGA isolate were individually screened by PCR for CGA-associated SNPs in *gyrB*. If the isolates were positive for *gyrB* SNPs and for the CGA-associated *fumC* SNPs, which together provide highly accurate identification of CGA isolates, they were defined as CGA isolates (5,6,16).

Statistical Analysis

Unpaired and paired comparisons of proportions were tested by using the Fisher exact and McNemar tests, respectively. Selected variables were assessed as predictors of CGA status by using generalized linear models based on the generalized estimating equation (GEE; logistic GEE regression) to account for clustering by locale, supplemented by univariable and multivariable logistic regression analysis, as needed. Statistical analyses were conducted by using SPSS version 19.0 (IBM, Somers, NY, USA).

Results

Study Population

A total of 2,210 *E. coli* clinical isolates from 32 globally dispersed centers were studied (Table 1); the isolates differed from those used in a prior global survey (14). Each center provided a median of 54 isolates (range 24–320). All centers but 1 provided TMP/SMZ-susceptible and TMP/SMZ-resistant isolates in approximately equal numbers. The median year of isolation was 2002 (range 1998–2007). Seventeen centers provided isolates for the first half of the study period only (1998–2002); 12 centers provided isolates for the last half of the study period only (2003–2007); and 3 centers provided isolates for both halves of the study period.

The 32 centers were in 19 countries, each represented by a single center, except the United States, which was represented by 14 centers. The 6 inhabited continents were each represented by multiple centers, as follows: Africa, 2; Asia, 4; Australia/New Zealand, 2; Europe, 5; North America, 15; and South/Central America, 4. Of the 15 centers in North America, 1 was in Canada and 14 in the United States (5 in Minnesota and 9 in other states).

Of the 32 centers, 31 reported the age (i.e., adult vs. child) of the patients from whom the clinical specimens were obtained. All 31 centers provided isolates derived from specimens from adults (n = 1,909), and 19 centers also

provided isolates derived from specimens from children (n = 250). Of the 32 centers, 31 provided urine-source isolates (n = 1,511); 28 centers also provided isolates from other (nonurine) sources (n = 653). Outpatient versus inpatient source for clinical samples was reported by 29 centers, all of which provided isolates from outpatient specimens (n = 1,135); 26 centers also provided isolates from inpatient specimens (n = 926). As reported by 31 centers, the prevalence of *E. coli* TMP/SMZ susceptibility, by center, ranged from 36% to 90% (median 78%).

Phylogenetic Group and CGA Status versus TMP/SMZ Phenotype

Within the total group of isolates, phylogenetic group distribution was significantly associated with TMP/SMZ phenotype (Table 2). Although the susceptible (n = 1,083) and resistant (n = 1,127) populations exhibited the same rank order for phylogenetic group prevalence (i.e., B2 > D > A > B1), absolute prevalences differed greatly by TMP/SMZ phenotype. That is, among susceptible isolates, group B2 predominated overwhelmingly, being nearly 3 \times as prevalent as group D. In contrast, among resistant isolates, phylogenetic groups B2 and D were closely matched (approximately one third of isolates each). Accordingly, group D was strongly associated with TMP/SMZ resistance.

Molecular typing identified 144 CGA isolates (Table 1), which accounted for 6.5% of all isolates and 25.2% of the group D isolates (Table 2). CGA was strongly associated with TMP/SMZ resistance, accounting for 10.1% of resistant isolates overall but for only 2.8% of susceptible isolates (p < 0.001) (Table 2). Even within phylogenetic group D, CGA was nearly 2 \times as prevalent among resistant as among susceptible isolates (29.8% [114/383] vs. 16.0% [30/188], p < 0.001) (Table 2).

CGA Status in Relation to Geography

Of the 32 centers, 26 provided at least 1 CGA isolate (Table 1). The prevalence of CGA by center varied greatly, ranging from 0% to 34% (median 5%) for TMP/SMZ-resistant isolates and from 0% to 9.4% (median 1.4%) for TMP/SMZ-susceptible isolates. In all but 2 centers, CGA was at least as prevalent among TMP/SMZ-resistant as among TMP/SMZ-susceptible isolates; in 5 of the centers, the difference in prevalence was statistically significant. The 5 centers with the highest prevalence of CGA isolates (2 in the United States, 3 in other countries) had $\geq 20\%$ CGA prevalence among resistant isolates, and another 5 (1 United States, 4 in other countries) had 10%–19% prevalence. At the other extreme, 6 centers (3 in the United States, 3 in other countries) had no CGA isolates.

The prevalence of CGA also varied substantially by continent, in a resistance-dependent manner (Table 3). Among TMP/SMZ-susceptible isolates the prevalence of

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Table 1. Origin and epidemiologic background of 2,210 extraintestinal *Escherichia coli* isolates from 32 globally distributed centers and susceptibility to trimethoprim/sulfamethoxazole, 1998–2007*

Continent, location†	Year(s) of isolation	Total no. isolates	S, %	Source, no. isolates					No. CGA isolates/total no. (%)	
				Specimen type		Setting		Child‡	R	S
				Urine	Nonurine	In	Out			
Africa										
Ile-Ife, Nigeria	2004	41	NK	41	0	22	19	4	3/36 (8)	0/5 (0)
Lusaka, Zambia	2001	51	59	4	37	NK	NK	0	0/31 (0)	0/20 (0)
Asia										
Chandigarh, India	2006	50	60	37	13	34	16	9	0/36 (0)	0/14 (0)
Kitakyushu, Japan	2001–2005	56	80	37	19	36	20	7	1/29 (3)	0/27 (0)
Singapore	2002	50	60	43	7	NK	NK	0	1/25 (4)	0/25 (0)
Taiwan	1998–2004	320	46	256	64	66	254	73	8/161 (5)	8/159 (5)
Australia/New Zealand										
Canberra, Australia	1998–2001	121	80	50	71	0	121	5	10/60 (17)	3/61 (5)
Palmerston North, New Zealand	2006	51	78	36	15	18	33	3	1/24 (4)	0/27 (0)
Europe										
Zagreb, Croatia	2001–2002	91	81	44	47	58	33	0	8/46 (17)	1/45 (2)
Athens, Greece	2003–2005	149	66	96	53	92	57	3	15/75 (20)	1/74 (1)
Varese, Italy	2006	51	75	35	16	31	20	3	0/26 (0)	0/25 (0)
Santander, Spain	2003	53	70	35	18	19	34	9	0/26 (0)	2/27 (7)
Bellinzona, Switzerland	2006	54	75	36	18	34	20	2	3/27 (11)	0/27 (0)
North America										
Calgary, Alberta, Canada	2001	54	78	36	18	34	20	10	6/27 (22)	1/27 (4)
United States										
Denver, CO	2001	100	78	50	50	50	50	0	17/50 (34)	3/50 (6)
West Haven, CT	2006	34	76	24	10	17	17	0	0/16 (0)	0/18 (0)
Chicago, IL	2001	60	74	40	20	37	23	0	0/30 (0)	0/30 (0)
Lexington, KY	2001	60	80	40	20	7	53	5	3/30 (10)	1/30 (3)
Petoskey, MI	2001	45	89	NK	NK	NK	NK	0	5/21 (24)	0/24 (0)
Duluth, MN	2001	50	90	39	11	8	42	0	4/26 (15)	0/24 (0)
Minneapolis, MN†	2001	66	87	56	10	15	51	0	1/26 (4)	1/40 (3)
Minneapolis, MN†	2001	46	90	38	8	21	25	0	0/18 (0)	0/28 (0)
Northfield, MN	2001	24	95	24	0	0	24	0	1/12 (8)	0/12 (0)
St. Louis Park, MN	2001	64	83	64	0	0	64	7	9/32 (28)	3/32 (9)
Fargo, ND	2001	54	90	49	5	5	49	11	1/27 (4)	1/27 (4)
Philadelphia, PA	2006	94	78	87	7	13	81	0	2/22 (9)	0/72 (0)
Houston, TX	2001	60	65	40	20	35	25	9	1/30 (3)	1/30 (3)
Salt Lake City, UT	2001	47	85	31	16	24	23	4	1/21 (5)	1/26 (4)
South/Central America										
Concepción, Chile	2006	51	57	36	15	33	18	NK	5/24 (21)	1/27 (4)
Cali, Columbia	2005–2006	51	52	36	15	27	24	16	3/24 (13)	1/27 (4)
Panama City, Panama	2007	54	36	36	18	19	35	52	1/27 (4)	1/27 (4)
Lima, Peru	2002–2006	58	82	39	19	30	28	18	4/58 (7)	Not done

*S, susceptible to trimethoprim/sulfamethoxazole; in, inpatient; out, outpatient; CGA, clonal group A; R, resistant to trimethoprim/sulfamethoxazole; NK, not known.

†A list of the 32 centers is provided in the online Technical Appendix (wwwnc.cdc.gov/EID/pdfs/11-0488-Techapp.pdf). Note that 2 centers were located in Minneapolis.

‡<18 y of age.

CGA was uniformly low, regardless of continent (median prevalence 3.0%, range 0%–3.8%), whereas among TMP/SMZ-resistant isolates it was substantially higher in the Western world (Australia/New Zealand, Europe, North America, and South/Central America; median prevalence 13.1%, range 9.7%–13.2%), compared with Africa and Asia (4.2% and 4.0%, respectively) (Table 3).

Accordingly, data for Africa and Asia were combined for comparison with data from other regions. Among TMP/

SMZ-susceptible isolates, CGA was similarly prevalent among the isolates from Africa and Asia combined and the isolates from other areas (3.3% vs. 2.8%, $p>0.10$). In contrast, among TMP/SMZ-resistant isolates, CGA was significantly more prevalent among isolates from areas other than Africa and Asia than it was among isolates from Africa and Asia (12.5% vs. 4.0%, $p<0.001$) (Table 3). Likewise, CGA was significantly associated with TMP/SMZ resistance among the isolates from areas other than

Table 2. Phylogenetic group distribution and clonal group A status of extraintestinal *Escherichia coli* isolates from 32 globally distributed centers, 1998–2007*

Phylogenetic group and clonal group A status	No. clonal group A isolates/total no. isolates (%)			p value†
	Total, n = 2,210	TMP/SMZ susceptible, n = 1,083	TMP/SMZ resistant, n = 1,127	
<i>E. coli</i> phylogenetic group				
A	345 (15.6)	141 (13.0)	204 (18.1)	0.001
B1	223 (10.1)	121 (11.2)	102 (9.1)	
B2	1,071 (48.5)	633 (58.4)	438 (38.9)	<0.001
D	571 (25.8)	188 (17.4)	383 (34.0)	<0.001
Clonal group A	144 (6.5)	30 (2.8)	114 (10.1)	<0.001

*TMP/SMZ, trimethoprim/sulfamethoxazole.
†p values, by Fisher exact test, for TMP/SMZ-susceptible vs. -resistant isolates are shown where p<0.05; otherwise, p>0.10.

Africa and Asia (p<0.001) but not among the isolates from Africa and Asia (p>0.10) (Table 3).

CGA Status versus Other Variables

We also examined the prevalence of CGA in relation to other variables, after stratification for TMP/SMZ phenotype (Table 4). For each variable (i.e., specimen type, host age group, host inpatient/outpatient status, and year isolate was obtained from patient specimen), CGA was significantly more prevalent among TMP/SMZ-resistant than TMP/SMZ-susceptible isolates. In contrast, for a given TMP/SMZ phenotype, the prevalence of CGA varied minimally in relation to the other variables. Specifically, CGA was similarly (and, in some instances, slightly more) prevalent among isolates from nonurine versus urine specimens, children versus adults, inpatients versus outpatients, the first half versus the second half of the study period (Table 4), and centers with isolates with a below-median versus above-median prevalence of TMP/SMZ resistance (not shown). This finding suggested that continent and TMP/SMZ status were closely associated with CGA status, whereas other study variables were not.

Logistic GEE Models and Multivariable Analysis

To account for possible confounding of these associations because of clustering by center, we used

logistic GEE regression models to assess associations of CGA with TMP/SMZ phenotype, continent (as Africa/Asia vs. other), and the other nongeographic variables. Univariable analyses identified the same significant associations (or lack thereof) with CGA as noted initially; only TMP/SMZ phenotype and continent were confirmed as significant correlates of CGA status (Table 5).

Accordingly, we constructed a multivariable logistic GEE regression model based on TMP/SMZ phenotype and continent to assess the independent association of these 2 variables with CGA status. However, the model did not run to completion, possibly because of small numbers in certain cells (not shown). Univariable logistic regression analysis yielded results for these 2 variables separately that were similar to those obtained with the (univariable) generalized linear models (Table 5), which provided evidence that clustering by center had little effect on the associations. Therefore, a multivariable logistic regression model was constructed with TMP/SMZ phenotype and continent as the candidate predictor variables. This model yielded results similar to those of the univariable models, which provided evidence that the associations of CGA with TMP/SMZ phenotype and continent are largely independent of each other (Table 5).

Table 3. Prevalence of clonal group A, by region and TMP/SMZ phenotype, among 2,210 extraintestinal *Escherichia coli* isolates from 32 globally distributed centers, 1998–2007*

Region	No. clonal group A isolates/total no. (%)			p value†
	Total	TMP/SMZ susceptible	TMP/SMZ resistant	
Overall	144/2,210 (6.5)	30/1,083 (2.8)	114/1,127 (10.1)	<0.001
Africa	3/92 (3.3)	0/21 (0)	3/71 (4.2)	
Asia	18/476 (3.8)	8/225 (3.6)	10/251 (4.0)	
Australia/New Zealand	14/172 (8.1)	3/88 (3.4)	11/84 (13.1)	0.025
Europe	30/398 (7.5)	4/198 (2.0)	26/200 (13.0)	<0.001
North America	63/858 (7.3)	12/471 (2.5)	51/387 (13.2)	<0.001
South/Central America	16/214 (7.5)	3/80 (3.8)	13/134 (9.7)	
Africa/Asia combined	21/568 (3.7)	8/246 (3.3)‡	13/322 (4.0)§	
Not Africa/Asia	123/1,642 (7.5)	22/837 (2.6)‡	101/805 (12.5)§	<0.001

*TMP/SMZ, trimethoprim/sulfamethoxazole.

†p values, by Fisher exact test, for TMP/SMZ-susceptible vs. -resistant isolates are shown where p<0.05; otherwise, p>0.10.

‡For Africa/Asia vs. other, p>0.10.

§For Africa/Asia vs. other, p<0.001.

Table 4. Prevalence of clonal group A, by clinical/host variables, among 2,210 extraintestinal *Escherichia coli* isolates from 32 globally distributed centers, 1998–2007*

Clinical/host variable and year isolate obtained from patient clinical specimen	No. clonal group A isolates/total no. isolates (%)†			p value‡
	Total	TMP/SMZ susceptible	TMP/SMZ resistant	
Specimen type				
Nonurine	48/653 (7.4)	9/318 (2.8)	39/335 (11.6)	<0.001
Urine	88/1,470 (6.0)	21/739 (2.8)	67/731 (9.2)	<0.001
Host age group, y				
<18	16/250 (6.4)	4/118 (3.4)	12/132 (9.1)	0.08
≥18	122/1,909 (6.4)	25/938 (2.7)	97/971 (10.0)	<0.001
Host hospital status				
Outpatient	84/1,135 (7.4)	17/573 (3.0)	67/562 (11.9)	<0.001
Inpatient	54/926 (5.8)	13/434 (3.0)	41/488 (8.4)	<0.001
Year isolated				
1998–2002	95/1,330 (7.1)	21/661 (3.2)	74/669 (11.1)	<0.001
2003–2007	49/880 (5.6)	9/422 (2.1)	40/458 (8.7)	<0.001

*TMP/SMZ, trimethoprim/sulfamethoxazole.

†Data for each clinical variable include only isolates for which status with respect to the particular variable was known.

‡p values, by Fisher exact test, for comparisons of TMP/SMZ-susceptible vs. -resistant isolates within each subgroup. For all comparisons between subgroups within a given category (whether overall or by TMP/SMZ phenotype), $p > 0.10$.

Discussion

In this global survey for the recently recognized *E. coli* lineage CGA among extraintestinal clinical isolates from humans during 1998–2007, we identified strong associations of CGA with TMP/SMZ resistance and with regions other than Africa and Asia; this evidence indicates that CGA is primarily a TMP/SMZ-resistant pathogen concentrated within the Western world. In contrast, we found no association of CGA with other epidemiologic variables, which suggests that CGA is a similarly prominent pathogen among children and adults, among inpatients and outpatients, and within and outside the urinary tract. Finally, the fairly stable prevalence of CGA throughout the study period suggests that CGA had fully emerged by the late 1990s and now is an endemic public health threat in many centers worldwide.

The observed overall association of CGA with TMP/SMZ resistance is consistent with the findings of multiple studies (2,10,12–14,18–20). However, we did not find this association in Africa and Asia. Overall prevalence of CGA was also lowest in these regions. Taken together, these findings suggest that the TMP/SMZ-resistant variants of CGA had a selective advantage in the Western world but not in Asia and Africa, which led to the lineage's expansion in Europe, the Americas, and Australia but not in Asia and Africa. Why such an expansion seemingly has not occurred in Africa and Asia is unclear. One possibility is that TMP/SMZ-resistant CGA isolates emerged first in the Western world and have had insufficient time to diffuse to and expand within Africa and Asia. Alternatively, Africa and Asia may already have had an abundance of successful endemic TMP/SMZ-resistant clones competing with CGA for the same niche, effectively excluding it, or conditions in Africa and Asia may be somehow less permissive to the dispersal and expansion of this clonal group. Further

comparisons of the TMP/SMZ-resistant populations from Africa and Asia versus other locales could be informative in this regard.

Clear-cut variation in the prevalence of CGA was evident at the continent level. However, marked differences also were apparent even among closely located centers, as noted in our smaller global survey (14). For example, whereas 1 Minneapolis center had no CGA isolates, another center had a high prevalence of CGA. To what extent these differences are real, rather than a reflection of the inherent imprecision of small samples, is unclear. However, because different hospitals in the same locale often serve different patient populations and may draw from different catchment areas, the possibility of true variation by hospital is plausible. The determinants of this local variation, if real, would be potentially useful to discover as a step toward developing preventive measures. The center with the highest prevalence was in Denver, Colorado, USA, which also was the site of a previous survey with a high CGA prevalence; that survey involved different isolates than those included here (12). This consistency across studies suggests that Denver may be a focus of high-level endemicity for CGA.

CGA has been reported primarily as a urine pathogen among ambulatory women (2,10,13,19,20), which might be interpreted as indicating that urine is the favored niche or context of the clonal group. However, CGA has been reported in other clinical contexts, including, for example, as a cause of community-acquired pneumonia in a male renal transplant recipient (21). We found no association of CGA with urine versus nonurine (extraintestinal) source, inpatient versus outpatient host status, and host age (child vs. adult). This absence of discernible niche specialization suggests that CGA is a generalist, able to cause different types of infection in diverse host populations, in the hospital

Table 5. Generalized linear modeling and logistic regression analysis of TMP/SMZ phenotype and region as predictors of clonal group A status among extraintestinal *Escherichia coli* isolates from 32 globally distributed centers, 1998–2007*

Method, type of model, variable†	OR (95% CI)	p value
GEE‡		
Univariable		
TMP/SMZ resistance	3.90 (2.04–7.46)	<0.001
Africa/Asia	0.39 (0.18–0.89)	0.02
Logistic regression		
Univariable		
TMP/SMZ resistance	4.14 (2.74–6.26)	<0.001
Africa/Asia	0.43 (0.26–0.69)	<0.001
Multivariable		
TMP/SMZ resistance	3.95 (2.62–5.96)	<0.001
Africa/Asia	0.47 (0.30–0.76)	0.002

*TMP/SMZ, trimethoprim/sulfamethoxazole; OR, odds ratio; CI, confidence interval; GEE, generalized estimating equation.

†Univariable models, but not multivariable models, included the following as candidate predictor variables, each of which yielded a p value >0.10: specimen type (urine vs. nonurine), host age group (<18 vs. ≥18), host hospital status (inpatient vs. outpatient), local prevalence of TMP/SMZ resistance, and year isolate obtained.

‡Because the multivariable GEE model that used TMP/SMZ phenotype and Africa/Asia as candidate predictor variables could not run to completion, logistic regression analysis was used instead.

and community alike. In terms of niche specialization, CGA is analogous to *E. coli* O18:K1:H7, which, although best known as an agent of neonatal meningitis, is also a prominent cause of acute cystitis in women (22,23). The pathogenic versatility of CGA has no doubt contributed to its epidemiologic success.

We found no evidence of a time trend for the prevalence of CGA, even with locale taken into account, which suggests that CGA had already emerged and established widespread endemicity by 1998, the start of the study period. Overall, CGA was not as prevalent in this study as it was in the initial reports from the mid- to late 1990s (2,10). This discrepancy could reflect selection bias rather than a true prevalence decrease by the time of the present study (i.e., our study included all patient specimens sent to clinical microbiology laboratories; the early studies included specimens from women with acute cystitis and uncomplicated pyelonephritis).

Even in regions in which prevalence was highest, CGA accounted for only a minority of TMP/SMZ-resistant isolates. This finding suggests that other resistant clonal groups are likely present, some of which could be similarly or more prominent compared with CGA (3,5,6,13,20,24,25). Identification of such clonal groups and investigation of their epidemiology could help clarify the basis for the non-CGA component of TMP/SMZ resistance in *E. coli*, which represents a major ongoing public health threat.

Study limitations must be acknowledged. First, lack of information regarding the infected host (e.g., clinical symptoms, underlying health status, and sex) limits our

understanding of the study population and precludes assessment of these variables in relation to CGA status. Second, variability by center in the completeness of epidemiologic data reporting reduced power for analyses involving those variables and may have introduced unrecognized bias. Third, limited sampling of certain geographic regions (especially Africa and Australia/New Zealand) and host groups (children) constrained the inferences that could be drawn about those variables. Fourth, uncertainty regarding how closely each site followed the requested selection criteria allowed for possibly biased sample distribution by site.

Study strengths also must be acknowledged. First, the large sample size enhanced statistical power and permitted subgroup analyses that were not possible in previous studies. Second, the broad geographic distribution and multicenter design improved generalizability and allowed analyses by region. Third, the availability of basic epidemiologic data for most isolates enabled statistical analysis of these variables. Fourth, the predominantly prospective, consecutive sampling would be expected to provide a more broadly representative sample than a sample limited to a specific syndrome or host group. Fifth, the combined use of univariable and multivariable modeling, including adjustment for clustering, enabled optimal assessment of associations between individual variables and CGA.

In summary, our global survey for CGA during 1998–2007 identified strong associations of CGA with TMP/SMZ resistance and non-African/Asian origin but not with other epidemiologic variables—evidence that suggests CGA is a similarly prominent extraintestinal pathogen among children and adults, for inpatients and outpatients, and within and outside the urinary tract. The fairly stable prevalence of CGA through the 10-year study period suggests that CGA had fully emerged by the late 1990s and now is endemic worldwide as an antimicrobial drug-resistant public health threat.

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