Emergence of and risk factors for ciprofloxacin-gentamicin-resistant *Escherichia coli* urinary tract infections in a region of Quebec

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BACKGROUND: An increased incidence of urinary tract infections (UTIs) caused by ciprofloxacin-gentamicin-resistant *Escherichia coli* (CiGREC) has been observed in a tertiary care centre in Sherbrooke, Quebec. The risk factors for such infections remained unclear.
METHODS: To determine risk factors for, and outcomes of, CiGREC UTIs, a case control study was conducted. Between 2000 and 2007, 93 cases and 186 controls were identified using laboratory records of patients with greater than 10^7 colony-forming units/L of *E coli* in a urinary specimen. Cases had *E coli* with minimum inhibitory concentration to ciprofloxacin of 4 mg/L or greater and minimum inhibitory concentration to gentamicin of 8 mg/L or greater (CiGREC), and controls had *E coli* with any other susceptibility pattern to ciprofloxacin and gentamicin. Clinical and laboratory data were collected. Adjusted odds ratios (AOR) and their 95% CIs were calculated by logistic regression.
RESULTS: The prevalence of CiGREC increased sixfold during the study period. Risk factors associated with CiGREC UTI were advanced age, male sex, urological abnormality, domicile outside Sherbrooke, living in a nursing home (AOR 11.73; 95% CI 3.70 to 37.15), use of fluoroquinolones (AOR 15.24; 95% CI 5.42 to 42.83) or aminoglycosides (AOR 6.59; 95% CI 1.22 to 35.61) within the previous month, and use of fluoroquinolones during the preceding one to 12 months (AOR 2.45; 95% CI 1.06 to 5.62). Compared with controls, cases were more likely not to receive an active antibiotic as empirical or definitive treatment, and were more likely to relapse.
INTERPRETATION: In the future, it may become necessary to avoid selecting as empirical therapy of urinary tract infection an antibiotic to which the patient has been recently exposed.

Key Words: *Canada; Ciprofloxacin;* Escherichia coli; *Gentamicin; Urinary tract infections*

L'émergence et les facteurs de risque des infections urinaires à *Escherichia coli* résistantes à la ciprofloxacine et à la gentamicine dans une région du Québec

HISTORIQUE : On a observé une incidence accrue d'infections urinaires (IU) à *Escherichia coli* résistantes à la ciprofloxacine et à la gentamicine (ECRCiG) dans un centre de soins tertiaires de Sherbrooke, au Québec. Les facteurs de risque de ces infections demeurent nébuleux.
MÉTHODOLOGIE : Pour déterminer les facteurs de risque et les issues des IU à ECRCiG, les auteurs ont effectué une étude cas-témoins. Entre 2000 et 2007, ils ont repéré 93 cas et 186 sujets témoins au moyen des dossiers de laboratoire des patients dont l'échantillon d'urine contenait plus de 107 unités formant des colonies/L d'*E coli*. Les cas présentaient un *E coli* à la concentration inhibitrice minimale à la ciprofloxacine de 4 mg/L ou plus et à la concentration inhibitrice minimale à la gentomicine de 8 mg/L ou plus (ECRCiG), et les sujet témoins avaient un *E coli* dont le profil de susceptibilité à la ciprofloxacine et à la gentomicine était différent. Les auteurs ont colligé les données cliniques et de laboratoire et calculé le rapport de risque rajusté (RRR) et leur 95 % IC au moyen de la régression logistique.
RÉSULTATS : La prévalence d'ECRCiG a sextuplé pendant la période de l'étude. Les facteurs de risque associés aux IU à ECRCiG étaient l'âge avancé, le sexe masculin, une anomalie urologique, le fait d'habiter à l'extérieur de Sherbrooke, le fait d'habiter dans un centre d'hébergement et de soins de longue durée (RRR 11,73; 95 % IC 3,70 à 37,15) le recours aux fluoroquinolones (RRR 15,24; 95 % IC 5,42 à 42,83) ou aux aminoglycosides (RRR 6,59; 95 % IC 1,22 à 35,61) au cours du mois précédent et aux fluoriquonolones (RRR 2,45; 95 % IC 1,06 à 5,62) au cours des un à 12 mois précédents. Par rapport aux sujets témoins, les cas étaient plus susceptibles de ne pas recevoir un antibiotique actif comme traitement empirique ou définitif et étaient également plus susceptibles de faire une rechute.
INTERPRÉTATION : À l'avenir, il deviendra peut-être nécessaire d'éviter de sélectionner, pour le traitement empirique d'une infection urinaire, un antibiotique auquel le patient a récemment été exposé.

Urinary tract infections (UTIs) are among the most common bacterial infections, leading each year to 8,000,000 visits to physicians, more than 100,000 hospital admissions and societal costs of $ 2.1 billion in the United States (1,2). In Canada, 3% of females and 0.5% of males develop a community-acquired UTI each year (3). They also are the leading cause of nosocomial infections (4). UTIs are most commonly caused by *Escherichia coli*, isolated in approximately 80% of women and approximately 70% of men with pyelonephritis (5). The recommended treatment for cystitis is a three-day course of trimethoprim-sulfamethoxazole (TMP-SMX), except in communities with high rates (greater than 10% to 20%) of resistance to TMP-SMX among uropathogens, where fluoroquinolones (FQ) should be preferred (1). Since these recommendations were issued, hospitals worldwide have reported prevalences of resistance to TMP-SMX above this threshold (4,6-13) and FQ are widely used. Mild cases of pyelonephritis caused by Gram-negative rods can be treated with a seven- to 14-day course of FQ or TMP-SMX (if susceptible), while severe cases should receive a either parenteral FQ, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside (1).

Ciprofloxacin resistance among *E coli* is increasing, with dramatic geographic variations (6-22). In Taiwan and China, more than one-third of isolates are resistant as are 10% to 25% of isolates in southern Europe (10,11,13,20). In the United

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States, Canada and Britain, *E coli* resistance to ciprofloxacin increased from 1% in the mid-1990s to 2% to 7% from 2001 to 2004 (9,11-13,23,24). In our hospital, we observed an increase in the incidence of UTI caused by ciprofloxacin-gentamicin-resistant *E coli* (CiGREC). This may have implications for the empirical management of patients with urinary tract infections, especially pyelonephritis, pending results of susceptibility testing. To delineate risk factors for, and outcomes of, CiGREC UTI, we performed a case control retrospective study.

METHODS

Setting and laboratory assays

The Centre Hospitalier Universitaire de Sherbrooke (CHUS), Hôpital Fleurimont, is a 400-bed hospital in the Estrie region of Quebec, whose laboratory processes annually approximately 16,000 urine specimens. CHUS provides all microbiological assays for residents of Sherbrooke, while sharing the workload with smaller hospitals for patients living outside Sherbrooke. The evolution of resistance to antimicrobials among all urine isolates of *E coli* obtained from January 2001 to December 2007 was reviewed. Urine specimens had been inoculated using calibrated loops on Columbia 5% sheep blood and MacConkey agars, and incubated for 18 h to 24 h before quantitative reading. After identification of *E coli* (umbilicated lactose-positive colony with positive indole reaction; if nonumbilicated, the API 20E strip was used), susceptibility tests were performed using agar dilution as per the routine procedures of the laboratory at the time. Resistance to gentamicin was defined as a minimum inhibitory concentration (MIC) 8 mg/L or greater and resistance to ciprofloxacin as MIC 4 mg/L or greater. Resistance to other antibiotics was determined using Clinical and Laboratory Standards Institute criteria except for ceftazidime and ceftriaxone, for which European (and upcoming Clinical and Laboratory Standards Institute) breakpoints were used (25,26). Phenotypic detection of extended-spectrum beta-lactamase (ESBL) was sought on isolates with MIC 2 mg/L or greater against ceftriaxone and/or ceftazidime, based on cefoxitin susceptibility and an increase of 5 mm or more in inhibition zone around cefotaxime or ceftazidime disks after adding clavulanate. Repetitive specimens showing the same organism with same antibiotic susceptibility in the same patient during a given calendar month were eliminated (27).

Selection of cases and controls

Isolates with resistance to both ciprofloxacin and gentamicin (CiGREC) were used to define cases. For each case, two controls were selected among all patients with a positive urinary culture for *E coli* showing any other susceptibility pattern to ciprofloxacin and gentamicin (sensitive to both, or resistant to only one), by systematically taking the isolates closest to the case's culture specimen, based on the specimen number. Cases and controls needed to have a bacterial count greater than 10^7colony forming units/L. Controls were unmatched to ensure determination of age- and sex-associated risk factors. Only inpatients, or outpatients seen by a CHUS physician when the UTI was documented were included, so that clinical data were recorded. Any patient could be included only once during any one-year period.

Data collection and definitions

Medical records were reviewed to collect sociodemographic, clinical, diagnostic and therapeutic data, after obtaining authorization from the direction of professional services (institutional procedure for retrospective chart reviews). Patients were considered to have only asymptomatic bacteriuria if no pyuria was documented and no symptoms recorded. Those with pyuria and/or urinary symptoms were considered to have pyelonephritis if their temperature reached 38.0°C at least once within 24 h of the positive urine culture, while those who remained afebrile were considered to have cystitis. Discharge diagnoses of current and previous admissions were used to calculate the Charlson score (28), reflecting the burden of 19 chronic comorbidities. Information concerning use of antibiotics within one year was extracted from outpatient notes, admission notes and the computerized records. Infection was considered nosocomial if acquired 48 h or longer after hospitalization, if the patient had been discharged within 14 days or transferred from another hospital. It was considered health care-associated in the presence of: hospitalization during the previous year; residence in a long-term care facility; permanent intravenous or urinary catheter; or dialysis or cancer chemotherapy within one year. All others were considered community-acquired. Patients were considered to present a urological risk factor if they had cystoscopy in the previous month, permanent urinary catheter, urolithiasis, prostate hyperplasia, prostate or bladder cancer, double-J catheter, ileal bladder, nephrostomy, vesicoureteral reflux, neurogenic bladder, urinary catheter during the hospital stay or other urinary system anomalies.

Outcomes included treatment with appropriate antibiotics; admission into the intensive care unit within 48 h of the first positive urinary culture; septic shock (administration of vasopressors within the same interval); relapses; and all-cause mortality within 30 days. Relapses were defined as a urine culture with the same pathogen (greater than 10^7 colony-forming units/L) and same susceptibility pattern, within 60 days (here, patients with asymptomatic bacteriuria, those with cystitis or pyelonephritis for whom no documentation of their initial treatment could be found, as well as patients who died before the end of this interval, were excluded). Susceptibility patterns between isolates of cases and controls were compared.

Data analysis

Data were analysed with Stata 8.0 (StataCorp LP, USA). Proportions were compared using the χ^2 test or Fisher's test. Unconditional logistic regression was used for multivariate analysis. Models were built up sequentially, starting with the variable most strongly associated with the outcome and continuing until no other variable reached significance. Then, each variable was dropped in turn to assess its effect. Different models were compared with the likelihood ratio test, keeping variables significant at the $P \leq 0.05$ level.

RESULTS

Table 1 summarizes temporal changes in resistance to antimicrobials among urinary isolates of *E coli* (regardless of bacterial counts) from 2001 to 2007. The proportion of isolates resistant to gentamicin or ciprofloxacin doubled, while the proportion of CiGREC increased sixfold. Resistance to TMP-SMX slowly increased. Resistance to third-generation

TABLE 1
Prevalence of ciprofloxacin-gentamicin-resistant *Escherichia coli* (CiGREC), and of resistance to antimicrobials, among nonrepetitive *E coli* urine isolates, 2001 to 2007

	2001	2002	2003	2004	2005	2006	2007	χ^2 for trend
Number of isolates	1412	1296	1306	1402	1525	1557	1692	
CiGREC, n (%)	7 (0.5)	7 (0.5)	9 (0.7)	17 (1.2)	19 (1.2)	35 (2.2)	48 (2.8)	≤0.001
Resistance, n (%)								
Ciprofloxacin (MIC ≥4 mg/L)	45 (3.2)	37 (2.9)	32 (2.5)	48 (3.4)	71 (4.7)	102 (6.6)	114 (6.7)	≤0.001
Gentamicin (MIC ≥8 mg/L)	27 (1.9)	28 (2.2)	21 (1.7)	34 (2.4)	29 (1.9)	48 (3.1)	73 (4.3)	≤0.001
Tobramycin (MIC ≥8 mg/L)	19 (1.3)	24 (1.9)	23 (1.8)	31 (2.2)	21 (1.4)	48 (3.1)	66 (3.9)	≤0.001
TMP-SMX (MIC ≥76 mg/L)	165 (11.7)	152 (11.7)	165 (12.6)	213 (15.2)	230 (15.1)	223 (14.3)	246 (14.5)	≤0.001
Ampicillin (MIC ≥32 mg/L)	371 (26.3)	328 (25.3)	342 (26.2)	411 (29.4)	462 (31.0)	561 (36.0)	612 (36.2)	≤0.001
Ceftazidime (MIC ≥16 mg/L)	13 (0.9)	5 (0.4)	17 (1.3)	21 (1.5)	14 (0.9)	13 (0.8)	20 (1.2)	0.38
Ceftriaxone (MIC ≥4 mg/L)	15 (1.1)	4 (0.3)	16 (1.2)	23 (1.6)	14 (0.9)	21 (1.3)	26 (1.2)	0.07

MIC Minimum inhibitory concentration; TMP-SMX Trimethoprim-sulfamethoxazole

cephalosporins remained uncommon. Not a single strain was resistant to imipenem or meropenem. Among all *E coli* urine isolates recovered between 2001 and 2007, 29% (132 of 449) of ciprofloxacin-resistant isolates and 1% (103 of 9739) of ciprofloxacin-susceptible isolates were resistant to gentamicin. Only 10 isolates (0.1%) were ESBL-producing.

Ninety-three CiGREC cases satisfied the inclusion criteria: six in the year 2000, four in 2001, three in 2002, seven in 2003, seven in 2004, 12 in 2005, 22 in 2006 and 32 in 2007. The control group included 186 subjects, four of which were infected with an *E coli* that was resistant to ciprofloxacin but susceptible to gentamicin, and one with a strain resistant to gentamicin but susceptible to ciprofloxacin. Table 2 compares the frequency of resistance to antibiotics between cases and controls. CiGREC strains were often resistant to TMP-SMX, ampicillin and cefazolin, but rarely resistant to third-generation cephalosporins. In only one case (and no control), the *E coli* isolate was an ESBL producer. Only three (3%) CiGREC isolates were susceptible to tobramycin, but only three (3%) were resistant to amikacin. Of fifty-nine CiGREC isolates tested against nitrofurantoin, 55 (93%) were susceptible.

Compared with controls, cases were older, more likely to be male, to reside outside Sherbrooke, to live in a nursing home, have a high Charlson score, present a urological risk factor, have acquired their infection in a health care setting, or have received a FQ, an aminoglycoside or metronidazole during the past month (Table 3). Cases and controls did not differ for the frequency of a past UTI within the previous month or year (data not shown). For antibiotics received one to 12 months before diagnosis, only FQ were received more frequently by cases. Cases and controls did not differ for recent (30 days) or distant (one to 12 months) exposure to TMP-SMX, ampicillin, beta-lactam/beta-lactamase inhibitors, cephalosporins, carbapenems, vancomycin, clindamycin or macrolides (data not shown). Among the 59 CIGREC cases given a FQ in the previous year, the most common indications had been another UTI (51%), pulmonary infection (19%), UTI or surgical prophylaxis (11%).

In multivariate analysis (Table 4), independent risk factors for CiGREC infection were older age, male sex, domicile outside Sherbrooke, living in a nursing home, urological risk factor, recent or distant intake of a FQ and recent intake of an aminoglycoside. Charlson score, hospital-acquisition and exposure to other antibiotics became nonsignificant. The association between CiGREC infection and recent intake of an aminoglycoside was seen essentially among patients unexposed to a FQ during the same period (data not shown).

TABLE 2
Resistance to other antimicrobials in cases of ciprofloxacin-gentamicin-resistant *Escherichia coli* and in control isolates of *E coli*

Resistance, n (%)	Cases (n=93)	Controls (n=186)	P
Trimethoprim-sulfamethoxazole	66 (71)	17 (9)	<0.001
Ampicillin	90 (97)	63 (34)	<0.001
Cefazolin	89 (96)	61 (33)	<0.001
Ceftriaxone	5 (5)	3 (2)	NS
Ceftazidime	2 (2)	3 (2)	NS
Imipenem	0 (0)	0 (0)	NS
Tobramycin	90 (97)	1 (1)	<0.001

NS Not significant

Symptomatic UTI, *E coli* bacteremia, septic shock or death within 30 days was more common among cases (Table 5). However, these associations became nonsignificant after adjustment for age and/or Charlson score (for the association between being a case and mortality, crude OR 5.23; 95% CI 1.00 to 27.47, P=0.05; after adjustment for age and Charlson score, AOR 1.97; 95% CI 0.33 to 11.64, P=0.46). Among patients with cystitis or pyelonephritis, the treatment as outpatients was not documented in nine cases and 18 controls. Among patients for whom a treatment was recorded, cases were less likely to receive an effective empirical antibiotic treatment within 48 h of diagnosis and, more surprisingly, less likely to receive an effective antibiotic at all. Cases were more likely than controls to relapse within two months, an association that remained highly significant after adjusting for age, Charlson score and receipt of an effective antimicrobial (AOR 6.56; 95% CI 1.98 to 21.73, P=0.002). Unexpectedly, cases who received an ineffective treatment were not more likely to relapse (four of 17 [24%]) than those given an active drug (10 of 53 [19%], P=0.73), but power to detect a difference was limited by the small number of patients in the former group. The frequency of relapse was the same among cases with cystitis (seven of 37 [19%]) and those with pyelonephritis (seven of 33 [21%]) (P=0.95).

TABLE 3
Characteristics of cases with ciprofloxacin-gentamicin-resistant *Escherichia coli* urinary tract infections and controls infected with other strains of *E coli*

	Cases (n=93)	Controls (n=186)	Crude odds ratio (95% CI)
Age, years, n (%)			
<18	3 (3)	46 (25)	0.20 (0.06–0.69)*
18–64	28 (30)	85 (46)	1
≥65	62 (67)	55 (30)	3.42 (1.95–5.99)†
Sex, n (%)			
Female	54 (58)	136 (73)	1
Male	39 (42)	50 (27)	1.96 (1.16–3.32)*
Residence, n (%)			
Sherbrooke	26 (28)	102 (55)	1
Estrie	55 (59)	59 (32)	3.66 (2.08–6.44)†
Other	12 (13)	25 (13)	1.88 (0.84–4.24)
Living in nursing home, n (%)			
No	67 (72)	177 (95)	1
Yes	26 (28)	9 (5)	7.63 (3.40–17.13)†
Charlson score, n (%)			
0	25 (27)	100 (54)	1
1–3	35 (38)	52 (28)	2.69 (1.46–4.97)*
≥4	33 (35)	34 (18)	3.88 (2.03–7.43)†
Urological risk factor, n (%)			
No	21 (23)	90 (48)	1
Yes	72 (77)	96 (52)	3.21 (1.83–5.65)†
Site of acquisition, n (%)			
Community-acquired	20 (22)	86 (46)	1
Health care-associated	35 (38)	45 (24)	3.34 (1.73–6.45)†
Nosocomial	38 (41)	55 (30)	2.97 (1.57–5.63)†
Antibiotics received in previous month, n (%)			
Fluoroquinolones			
No	56 (60)	178 (96)	1
Yes	37 (40)	8 (4)	14.70 (6.47–33.41)†
Aminoglycosides			
No	84 (90)	183 (98)	1
Yes	9 (10)	3 (2)	6.54 (1.73–24.76)*
Metronidazole			
No	86 (92)	185 (99.5)	1
Yes	7 (8)	1 (0.5)	15.06 (1.82–124.3)*
Antibiotics received in previous year, excluding previous month, n (%)			
Fluoroquinolones			
No	53 (59)	165 (89)	1
Yes	37 (41)	20 (11)	5.76 (3.08–10.77)†
Aminoglycosides			
No	83 (92)	173 (94)	1
Yes	7 (8)	12 (6)	1.22 (0.46–3.20)
Metronidazole			
No	86 (96)	183 (99)	1
Yes	4 (4)	2 (1)	4.25 (0.76–23.69)

**P<0.05; †P<0.001*

TABLE 4
Risk factors for infection with ciprofloxacin-gentamicin-resistant *Escherichia coli* in multivariate analysis

	Adjusted odds ratio (95% CI)
Age, per year	1.02 (1.01–1.04)*
Male sex	3.19 (1.46–6.98)*
Residence outside Sherbrooke	3.77 (1.73–8.23)*
Living in nursing home	11.73 (3.70–37.15)†
Urological risk factor	2.58 (1.13–5.88)*
Fluoroquinolones, previous month	15.24 (5.42–42.83)†
Aminoglycosides, previous month	6.59 (1.22–35.61)*
Fluoroquinolones, previous year excluding previous month	2.45 (1.06–5.62)*

**P<0.05; †P<0.001*

TABLE 5
Clinical characteristics, treatment and outcomes of cases with ciprofloxacin-gentamicin-resistant *Esherichia coli* urinary tract infections and controls infected with other strains of *E coli*

	Cases (n=93)	Controls (n=186)	P
Type of infection, n (%)			
Asymptomatic bacteriuria	6 (6)	34 (18)	
Cystitis	49 (53)	81 (44)	0.03
Pyelonephritis	38 (41)	71 (38)	
E coli bacteremia, n (%)			
No	83 (89)	181 (97)	0.01
Yes	10 (11)	5 (3)	
Intensive care unit admission*, n (%)			
No	81 (87)	176 (95)	0.05
Yes	12 (13)	10 (5)	
Septic shock*, n (%)			
No	88 (95)	185 (99)	0.02
Yes	5 (5)	1 (0.5)	
All-cause mortality within 30 days of diagnosis, n (%)			
No	88 (95)	185 (99)	0.04
Yes	5 (5)	2 (1)	
Appropriate treatment within 48 h of initial culture†, n (%)			
No	49 (63)	5 (4)	<0.001
Yes	29 (37)	129 (96)	
Appropriate treatment >48 h after initial culture†, n (%)			
No	19 (24)	0 (0)	<0.001
Yes	59 (76)	134 (100)	
Relapses†‡, n (%)			
No	56 (80)	126 (95)	0.002
Yes	14 (20)	7 (5)	

**Within 48 h of positive urine culture; †Only for patients with cystitis or pyelonephritis and evidence that their initial episode was treated; ‡Positive culture (>10^7 colony forming units/L) with same organism and same susceptibilities within two months of the end of the antibiotic treatment*

DISCUSSION

We documented an increase in the frequency of UTI caused by *E coli* resistant to ciprofloxacin and gentamicin. Empirical antibiotic treatment proved adequate in only one-third of CiGREC-infected patients. Unexpectedly, one-quarter of CiGREC cases did not receive an effective treatment even after results of susceptibility testing became available, presumably because the attending physician remained unaware of these results, a problem compounded in our centre by the use, until recently, of time-consuming agar dilution techniques. Twenty per cent of cases experienced at least one relapse. CiGREC cases were more likely to need intensive care unit admission than controls, and experienced higher 30-day mortality. This may reflect their inadequate initial treatment but also their age and burden of comorbidities, and the association

between CiGREC and mortality lost significance after adjustment. However, in patients with sepsis caused by *E coli*, the case-fatality ratio increases in parallel with the number of antibiotics to which the organism is resistant (29).

We demonstrated a strong association between CiGREC UTI and exposure to FQ or aminoglycosides. While receiving a FQ within the previous month or year was associated with CiGREC, the precipitating role of aminoglycosides seemed limited to their use within the previous month in patients unexposed to FQ. Presumably, these antimicrobials provided a selective advantage to CiGREC over antibiotic-susceptible *E coli* strains within the gastrointestinal tract, from where it ascended into the urinary tract, a process facilitated by the presence of a urological risk factor. A similar association between FQ intake and quinolone-resistant *E coli* was documented in Spanish patients with bacteremia (20). At the aggregate level, associations between increasing use of FQ and ciprofloxacin-resistant *E coli* have been reported (8,10).

Living in a nursing home was an independent risk factor for CiGREC infection, whether the patients resided in Sherbrooke, outside Sherbrooke or outside our region, indicating horizontal transmission of CiGREC in a variety of settings. The Quebec registry of nursing homes (used to define this variable) includes long-term care facilities with heavy nursing support, and private nursing homes, small or large, with variable degrees of support and contacts among residents. The association between CiGREC and residence outside Sherbrooke might reflect residual confounding (exposure to FQ or aminoglycosides might have been underestimated in such patients) or a selection bias (out-of-town patients with CiGREC being more likely to be seen at CHUS than those with antibiotic-susceptible infections). The association with male sex could reflect the lower propensity of men to develop UTIs such that antimicrobial resistance becomes more relevant in the pathogenesis, while in women CiGREC is diluted by the many other *E coli* strains that easily cause UTIs.

Resistance of *E coli* to FQ and gentamicin are often correlated (13,30). In Europe, 29% of ciprofloxacin-resistant isolates were gentamicin-resistant, compared with 0.3% for the ciprofloxacin-susceptible (14). Similarly, in our hospital, among all *E coli* urine isolates recovered between 2001 and 2007, 29% of ciprofloxacin-resistant isolates were resistant to gentamicin, versus 1% of ciprofloxacin-susceptible isolates, a correlation higher than what would be expected from the commonality of risk factors (exposure to both antibiotics). Robicsek et al (31) reported reduced susceptibility to ciprofloxacin conferred by a variant of the gene encoding aminoglycoside acetyltransferase AAC(6′)-Ib, a single-function resistance enzyme that crossed class boundaries. Whether coresistance to ciprofloxacin and gentamicin among our isolates was caused by this mutation seems unlikely given that it is associated with low-level resistance to ciprofloxacin, in contrast with our strains. Thus, the coincidence of other determinants of resistance seems more plausible (30,32). Given that most CiGREC strains were sensitive to amikacin, it is likely that the aminoglycoside resistance is plasmidic and related to an inactivating enzyme. Although probably underestimated by the use of a phenotypic detection method, ESBL-producing *E coli* remained very uncommon among our consecutive urine isolates as in an earlier pan-Canadian study of unselected isolates (33).

The emergence of CiGREC has implications for the empirical management of patients with UTIs in our centre. Patients with severe sepsis or shock, with urinary tract obstruction or comorbidities that could be adversely impacted by the infectious process (for instance, ischemic heart disease) need to receive at least one drug active against CiGREC (a carbapenem, piperacillin-tazobactam or ceftazidime), pending susceptibility data. For less severe cases, one of these drugs may be used for patients with confirmed exposure to FQ (past year) or aminoglycosides (past month) and those living in a nursing home, among which the probability of being infected with CiGREC is higher. After initial intravenous treatment, cefixime is often the only microbiologically adequate oral treatment for patients with confirmed CiGREC pyelonephritis, while nitrofurantoin can also be considered for those with cystitis. The effectiveness of this approach will need to be verified in clinical trials. The high urine concentrations of other antimicrobial agents may to some extent compensate for their in vitro resistance.

Our study had several limitations. The measure of past exposure to antibiotics was incomplete when ordered outside our hospital. Its retrospective nature made it sometimes difficult to ascertain the presence of symptoms. The low mortality precluded a meaningful multivariate analysis in which the effect of antibiotic resistance and inadequate treatment could be disentangled from confounding factors such as age and comorbidities. The study was limited to a single hospital, and whether our findings can be extrapolated to other centres remains to be determined because for many pathogens, including *E coli*, there are substantial geographic variations in prevalence of resistance to antimicrobial agents.

Given the progressive increase in the proportion of UTIs caused by CiGREC, and the higher frequency of adverse outcomes and relapses among such patients, it may be necessary in the future to avoid selecting as empirical therapy an antibiotic to which the patient has been recently exposed, as recently proposed for patients with community-acquired pneumonia (34).

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CONFLICTS OF INTEREST: Jacques Pépin has served on the speakers' bureau of Wyeth and Merck, and on advisory boards for Wyeth, Bayer, Pfizer, Novartis and Janssen Ortho. All other authors: nothing to declare.

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