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Decreased Susceptibility to Noncarbapenem Antimicrobials in Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* Isolates in Toronto, Canada

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Retrospective review from 11 Canadian hospitals showed increasing incidence of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* from 0.12 per 1,000 inpatient days during 2005 to 0.47 per 1,000 inpatient days during 2009. By 2009, susceptibility rates of ESBL-positive *E. coli*/*K. pneumoniae* were as follows: ciprofloxacin, 12.8%/9.0%; TMP/SMX, 32.9%/12.2%; and nitrofurantoin, 83.8%/10.3%. Nosocomial and nonnosocomial ESBL-producing *E. coli* isolates had similar susceptibility profiles, while nonnosocomial ESBL-producing *K. pneumoniae* was associated with decreased ciprofloxacin ($P = 0.03$) and nitrofurantoin ($P < 0.001$) susceptibilities.

Multidrug-resistant *Enterobacteriaceae* strains have become a global concern. Increasing incidence of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) may be attributable, in part, to the successful clonal dissemination of the CTX-M-15 plasmid worldwide (2, 22). Carbapenem-resistant *Enterobacteriaceae* (CRE) are also emerging across the globe (3, 9, 15). Low prevalence rates (4.1%) of ESBL-producing *E. coli* have been described in Canada, predominantly due to CTX-M β-lactamases (23), and only sporadic cases of imported CRE have been reported (13, 23).

Infections due to ESBL-E are associated with increased morbidity, mortality, length of hospital stay, and cost (11). Therapeutic alternatives for ESBL-E are limited with increasing resistance to non-β-lactam antibiotics (6), resulting in a high likelihood of inappropriate initial empirical therapy (8). Carbapenems continue to be the treatment choice for severe infections due to ESBL-E (16), but resistance to these agents is also emerging (9, 15).

In light of these concerns regarding ESBL-E, a retrospective review of incidence rates and susceptibility profiles for ESBL-E was conducted in 11 large hospitals (five academic and six community) in Toronto, Canada, from 2005 to 2009. Participating hospital characteristics have been previously described (12). All ESBL-producing Ambler class A *Escherichia coli* and *Klebsiella pneumoniae* clinical isolates were included. Susceptibility testing was performed utilizing VITEK2 (bioMérieux, St. Laurent, Quebec, Canada) in 10 hospitals and Phoenix2 (Becton Dickenson, Mississauga, Ontario, Canada) in the remaining hospital. Isolates intermediate or resistant to an extended-spectrum cephalosporin (cefpodoxime, ceftriaxone, or ceftazidime) were confirmed as ESBL-E with double disk diffusion testing as per the 2009 CLSI standards (1). Mean incidence rates were calculated after each site was adjusted per 1,000 inpatient days. Only the first clinical isolate from any one patient was included. Isolates were defined as nosocomial if they were identified from cultures obtained 3 or more days after admission to the hospital in patients without a prior specimen yielding ESBL-E. Statistical analysis was performed utilizing the chi-squared test or the chi-squared test for trend, as well as a multivariate analysis (SAS 9.2; Cary, NC).

Overall incidence of ESBL-E per 1,000 inpatient days increased as follows: 0.12 in 2005, 0.28 in 2006, 0.29 in 2007, 0.35 in 2008, and 0.47 in 2009. Incidence rates stratified by organism are shown in Fig. 1. There were 1,994 ESBL-E isolates over the 5 years: 1,736 *E. coli* and 258 *K. pneumoniae*. Isolates were most commonly from a urinary source (74.1%) but were also recovered from blood (12.0%), respiratory tract (5.2%), wound (4.6%), abscess/fluid (2.7%), and other sources (1.4%). Figures 2 and 3 describe the susceptibility profile of *E. coli* and *K. pneumoniae* over time. Declining susceptibility to piperacillin-tazobactam in *E. coli* ($P < 0.001$) and *K. pneumoniae* ($P = 0.01$) was observed. With respect to *E. coli*, susceptibility to non-β-lactam agents was stable except for improved susceptibility to aminoglycosides (gentamicin and amikacin, $P < 0.001$; tobramycin, $P = 0.002$). For *K. pneumoniae*, susceptibility rates decreased for ciprofloxacin ($P < 0.001$) and nitrofurantoin ($P < 0.001$) over the course of the study. Both of these agents were also found to have reduced susceptibilities in nonnosocomial settings and community hospitals (Table 1). This study identified 3 carbapenem-resistant *E. coli* isolates: 1 in 2008 and 2 in 2009. Multivariate analysis adjusting for date of culture, nosocomial status, and hospital type did not differ from the univariate analysis. In addition, resistance to ≥3 non-β-lactam antimicrobial classes occurred in 30.2% of *E. coli* and 40.5% of *K. pneumoniae* isolates and did not change significantly over time.

We report a 4-fold increase in overall incidence and a 2-fold increase in nosocomial incidence of ESBL-E over a 5-year period in Toronto, Canada. Previous Canadian surveillance in 2000 identified 0.3% of *E. coli* and 0.7% of *K. pneumoniae* isolates as ESBL producers (14). Between 2007 to 2009, estimated national preva-

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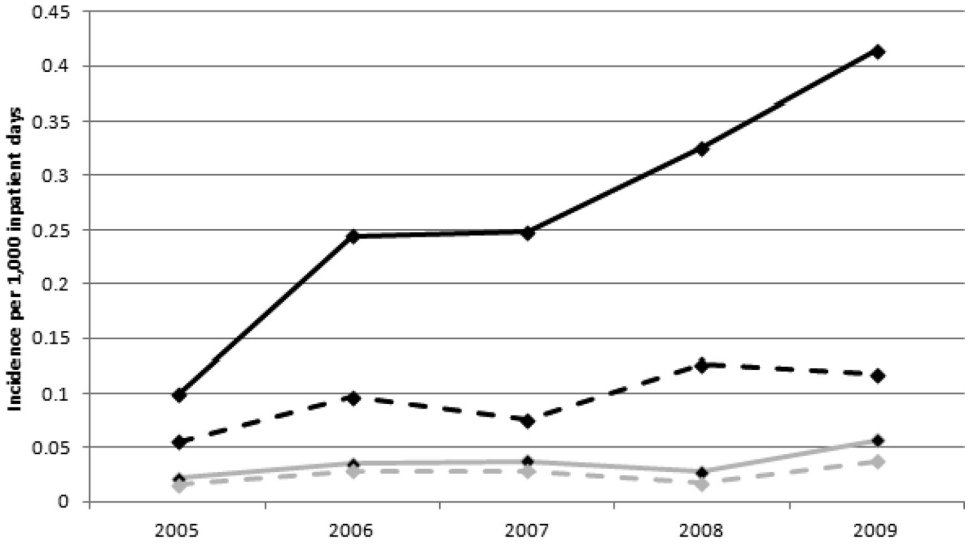

FIG 1 Overall (solid lines) and nosocomial (dashed lines) incidence of ESBL-E clinical isolates between 2005 and 2009. Black, *E. coli*; gray, *K. pneumoniae*.

lence of ESBL-producing *E. coli* was reported to be 4.1% and stable over the 3-year study period (23). Concurrently, studies in Calgary have described increasing rates of ESBL-producing *K. pneumoniae* (0.1% to 1.1%) and *E. coli* (0.3% to 14%) in the past decade (17, 19). This underscores the importance of understanding local epidemiology, particularly for antimicrobial susceptibility, as local geographic changes may not be apparent in larger surveillance studies.

ESBL-E is associated with a delay in administration of active antimicrobial agents (25), a risk factor for mortality due to ESBL-E infection (8). Over the 5-year study, the majority of agents had stable susceptibility profiles. Aminoglycoside susceptibility improved among *E. coli*, although about one-third of isolates remained resistant to gentamicin and tobramycin. Reduced ciprofloxacin susceptibility was observed in *E. coli* (12.8%), similar to rates reported in Canada and worldwide (5, 7, 23). However, *K. pneumoniae* susceptibility to ciprofloxacin (28 to 36%) (17, 26) was significantly higher in other Canadian centers than observed in this study in 2009 (9.0%). More concerning was the frequent occurrence of multiclass resistance among ESBL-E. Use of alternative agents, such as piperacillin-tazobactam, have been assessed (21), but *in vitro* susceptibility testing is required, as decreasing susceptibility was observed over the course of this study. In patients with severe sepsis where ESBL-E is considered the probable organism, empirical treatment with carbapenems is warranted. However, dependence on carbapenems will increase the selective pressure for carbapenem resistance. Resistance was rare in Toronto in 2009, but several recent case reports suggest that CRE incidence may be increasing (10, 24).

Although for *K. pneumoniae* there was a trend toward reduced

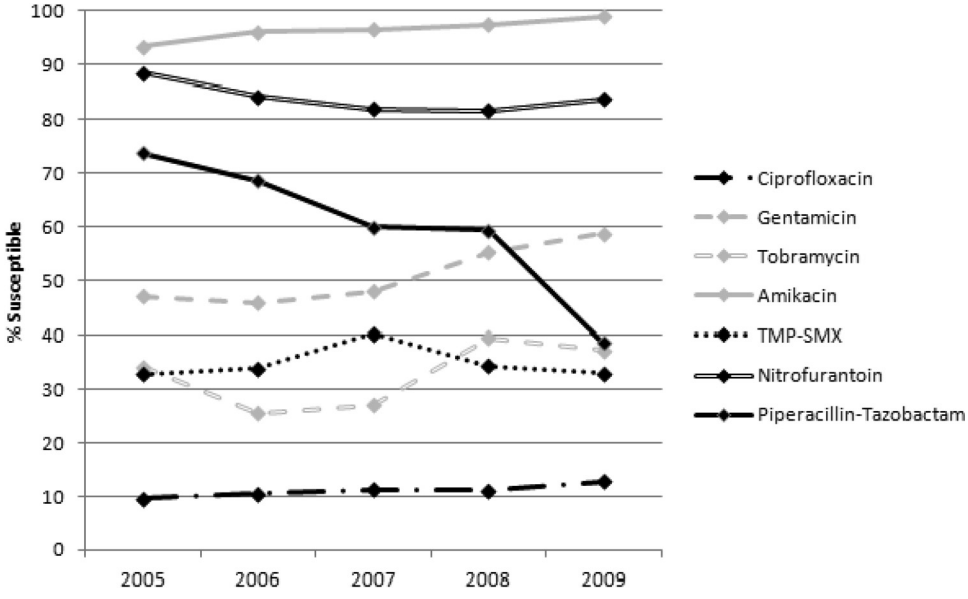

FIG 2 Susceptibility profile of ESBL-producing *E. coli* recovered over a 5-year period.

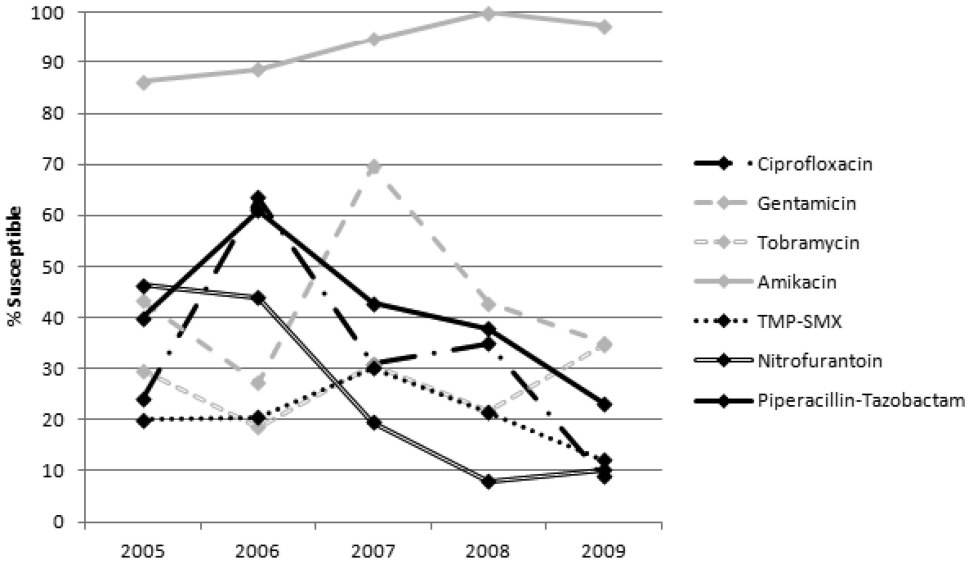

FIG 3 Susceptibility profile of ESBL-producing *K. pneumoniae* recovered over a 5-year period.

susceptibility among nonnosocomial isolates to ciprofloxacin, TMP-SMX, and nitrofurantoin, there was no difference in the susceptibility to these oral agents in nosocomial and nonnosocomial *E. coli* isolates. Susceptibility profiles within academic and community institutions were generally indistinguishable. This may be due to the community introduction and spread of CTX-M β-lactamase-producing *E. coli* in Canada (18–20). The lack of difference between nosocomial and nonnosocomial isolates poses challenges in treatment of severe community-acquired infections in which ESBL-E is a potential pathogen.

There are limitations to this study, as antimicrobial susceptibility testing was based on 2009 CLSI standards with higher cephalosporin breakpoints. Although both extended-spectrum cephalosporin-intermediate and cephalosporin-resistant isolates were confirmed with phenotypic testing in this study, ESBL-E with low-level ceftazidime resistance could have been missed (4). As a result, ESBL-E incidence rates may have been underestimated. Also, given the retrospective nature of the study, nosocomial and nonnosocomial isolates were stratified by a predetermined definition. Without correlation with the clinical history, these isolates are "probable" rather than "confirmed" nosocomial isolates.

Increasing rates of ESBL-E, especially in nonnosocomial patients, presents therapeutic challenges due to low susceptibility to non-β-lactam antimicrobials. In addition, nonnosocomial

TABLE 1 Comparison of susceptibility rates in *E. coli* and *K. pneumoniae* with respect to nosocomial status and hospital type

Organism and drug	Value[a]					
	Nosocomial	Nonnosocomial	*P* value	Academic	Community	*P* value
E. coli						
Ciprofloxacin	12.6 (76/601)	10.7 (106/995)	0.26	11.8 (109/927)	10.9 (73/669)	0.66
Gentamicin	49.1 (295/601)	54.7 (525/960)	0.04	52.5 (487/927)	52.5 (333/634)	0.96
Tobramycin	33.4 (189/566)	33.4 (292/874)	0.96	37.1 (343/925)	26.8 (138/515)	<0.001
Amikacin	95.8 (588/614)	98.0 (982/1002)	0.01	97.1 (898/925)	97.3 (672/691)	0.96
TMP-SMX	36.9 (222/601)	33.4 (319/955)	0.17	31.5 (292/925)	38.5 (243/631)	0.005
Nitrofurantoin	83.9 (468/558)	83.2 (754/906)	0.80	83.1 (765/921)	84.2 (457/543)	0.63
Piperacillin-tazobactam	60.4 (252/417)	58.2 (291/500)	0.53	60.4 (460/762)	61.9 (86/139)	0.81
Meropenem	99.6 (272/273)	100.0 (447/447)	0.80	99.8 (515/516)	100.0 (204/204)	0.63
Imipenem	99.5 (366/368)	100.0 (517/517)	0.34	99.8 (482/483)	99.8 (401/402)	0.56
K. pneumoniae						
Ciprofloxacin	34.3 (59/172)	19.5 (15/77)	0.03	33.0 (65/197)	17.3 (9/52)	0.04
Gentamicin	36.9 (62/168)	37.3 (28/75)	0.94	35.0 (69/197)	45.7 (21/46)	0.24
Tobramycin	28.6 (46/161)	27.1 (19/70)	0.75	25.0 (49/196)	45.7 (16/35)	0.02
Amikacin	92.9 (158/170)	97.4 (76/78)	0.95	94.9 (186/196)	92.3 (48/52)	0.70
TMP-SMX	22.0 (37/168)	16.0 (12/75)	0.36	21.3 (42/197)	15.2 (7/46)	0.47
Nitrofurantoin	29.1 (46/158)	7.4 (5/68)	<0.001	25.0 (49/196)	6.7 (2/30)	0.05
Piperacillin-tazobactam	42.3 (60/142)	38.0 (19/50)	0.72	39.6 (72/182)	70.0 (7/10)	0.12
Meropenem	100.0 (73/73)	100.0 (35/35)	0.99	100.0 (83/83)	100.0 (25/25)	0.99
Imipenem	100.0 (105/105)	100.0 (41/41)	0.99	100.0 (127/127)	100.0 (19/19)	0.99

[a] Values (except for *P* values) are the percentages (numbers) of isolates susceptible to each drug.

ESBL-E isolates were associated with lower susceptibility to the limited oral agents remaining for ESBL-E, particularly *K. pneumoniae*. Fluoroquinolones should be avoided in patients with suspicion for an ESBL-E infection due to the very low rates of susceptibility to ciprofloxacin observed in both *E. coli* and *K. pneumoniae*.

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