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# Dramatic Increase in the Prevalence of ESBL-Producing *Escherichia coli* (EC) in Canadian Hospitals Over a 5-Year Period

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## UPDATED ABSTRACT

**BACKGROUND:** The purpose of this study was to assess the prevalence, patterns of antibiotic resistance, and molecular characteristics of ESBL-, AmpC-, and KPC-producing EC and *Klebsiella pneumoniae* (KPN) isolated from Canadian hospitals between 2007 and 2011, inclusive.

**METHODS:** 5450 EC and 1659 KPN were collected from January 2007 to December 2011 as part of the ongoing CANWARD national surveillance study. Antimicrobial susceptibility testing was performed by CLSI broth microdilution. The presence of resistance genes in putative ESBL, AmpC, and KPC producers was examined by PCR and sequencing. All confirmed isolates were typed by PFGE and identification of EC O25b-ST131 was carried out by allele-specific PCR for the *pabB* gene.

**RESULTS:**

| Cohort | Prevalence (%)[a] | | | Resistance Profile (%R)[b] | | | | Genotypic Characterization | |
|---|---|---|---|---|---|---|---|---|---|
| | Overall | 2007 | 2011 | CIP | SXT | GEN | MDR | Family (% of cohort)[c] | Variant (% of family)[d] |
| ESBL-EC (n=231) | 4.2 | 3.4 | 7.1 p<0.001* | 88.3 | 70.1 | 48.5 | 78.8 | CTX-M-type (94.1) SHV-type (3.0) | $bla_{CTX-M-15}$ (69.0) $bla_{SHV-12}$ (57.1) |
| ESBL-KPN (n=48) | 2.9 | 1.5 | 4.0 p=0.047* | 62.5 | 68.8 | 47.9 | 68.8 p=NS | CTX-M-type (66.7) SHV-type (62.5) | $bla_{CTX-M-15}$ (50.0) $bla_{SHV-11}$ (43.3) |
| AmpC-EC (n=115) | 2.6 | 0.7 | 2.9 p=0.004* | 37.4 | 33.9 | 16.5 | 33.9 p<0.001* | Acquired (56.5) | $bla_{CMY-2}$ (98.5) |

[a] P-value comparing the rate of ESBL-EC, ESBL-KPN, and AmpC-EC from 2007-2011; * denotes statistical significance (p<0.05)

[b] %R: % resistant, CIP: ciprofloxacin, SXT: trimethoprim-sulfamethoxazole, GEN: gentamicin, MDR: multi-drug resistant (resistance to ≥3 ≠ antimicrobial classes); P-value comparing %MDR with ESBL-EC, NS: not significant

[c] SHV-type includes all non-$bla_{SHV-1}$ variants; AmpC-EC examined for the presence of acquired AmpC genes and for promoter/attenuator mutations within the chromosomal *ampC*

[d] The most common variant of each defined family has been listed

The majority of ESBL-EC (>95%), AmpC-EC (>98%), and ESBL-KPN (>89%) remained susceptible to colistin, amikacin, ertapenem, and meropenem. Isolates were generally unrelated by PFGE (<80% similarity), however ST131 was identified among 55.8% and 27.8% (p<0.001) of ESBL-EC and AmpC-EC, respectively. Significant predictors of ESBL-EC infections included patient age ≥65 years (OR: 1.37), inpatient status (OR: 1.90), and blood/urine source (OR: 1.49). KPC production was identified in 0.04% (n=2) of EC and 0.06% (n=1) of KPN, all of which contained $bla_{KPC-3}$.

**CONCLUSION:** The prevalence of ESBL-EC, ESBL-KPN, and AmpC-EC increased significantly across the study period, while the prevalence of KPC-producing EC and KPN remained low (<1%). As compared to AmpC-EC, ESBL-EC were significantly associated with MDR and the ST131 clone.

## BACKGROUND

The beta-lactams (penicillins, cephalosporins, carbapenems, and monobactams) comprise over 60% of the global antibiotic market [1]. Within this class, the oxyimino-cephalosporins and carbapenems represent extremely important agents for the treatment of serious community- and hospital-acquired infections [2]. Though bacterial susceptibility to beta-lactam agents can become compromised through a number of mechanisms, beta-lactamase production represents the single greatest source of beta-lactam resistance among Gram-negative organisms [3]. Members of the Enterobacteriaceae, including *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KPN), are among the top ranked pathogens causing bacterial disease in Canadian hospitals [4]. Within the Enterobacteriaceae, oxyimino-cephalosporin resistance is largely attributable to the production of extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases, able to hydrolyze a variety of beta-lactams including the extended-spectrum cephalosporins and monobactams. Furthermore, beta-lactamases with carbapenemase activity (e.g. $bla_{KPC}$) have emerged worldwide and now threaten the use of the carbapenems. Infections caused by these organisms hold serious implications for both public health and infection control practices. Such infections are often associated with delays in the administration of effective therapy, as beta-lactam resistance often undermines empiric therapy [2,5]. Furthermore, the frequent association of such organisms with multi-drug resistance severely limits available treatment options. As a result, patients are subject to increased length of hospital stay, increased hospital cost, as well as an elevated risk of infection-related mortality [2].

The purpose of this study was to assess the prevalence, patterns of antibiotic resistance, and molecular characteristics of ESBL-, AmpC-, and KPC-producing EC and KPN isolated from Canadian hospitals between 2007 and 2011, inclusive.

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## MATERIALS & METHODS

**Bacterial Isolates:** A total of 5450 EC and 1659 KPN were collected from January 2007 to December 2011, inclusive, as part of the ongoing CANWARD national surveillance study [4]. Tertiary-care medical centers submitted clinically relevant isolates from in- and outpatients attending hospital clinics, medical and surgical wards, emergency rooms, and intensive care units (ICUs) with blood, urine, wound, and respiratory tract infections.

**Antimicrobial Susceptibility Testing:** Antimicrobial susceptibility testing was performed using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI M07-A9, 2012). Minimum inhibitory concentration (MIC) interpretive standards were defined by CLSI M100-S22 breakpoints. Food and drug administration (FDA) breakpoints were used for colistin (S: ≤2, R: ≥4 µg/ml) and tigecycline (S: ≤2, I: 4, R: ≥8 µg/ml). Multi-drug resistance (MDR) is defined as resistance to ≥3 different antimicrobial classes and extreme-drug resistance (XDR) is defined as resistance to ≥5 different antimicrobial classes, as described by Magiorakos et al. [6]. Putative ESBL-producers were identified as any EC or KPN isolate with a ceftriaxone and/or ceftazidime MIC of ≥1 µg/ml and were phenotypically confirmed by CLSI disk diffusion methods. Putative AmpC-hyperproducers were identified as any EC with a cefoxitin MIC of ≥32 µg/ml.

**Molecular Characterization:** All phenotypically confirmed ESBL-producing isolates were further characterized by PCR and sequencing for the detection of $bla_{SHV}$, $bla_{TEM}$, $bla_{CTX-M}$, and $bla_{OXA}$ genes [7]. All putative AmpC-producing EC were screened for genes encoding the $bla_{ENT}$, $bla_{DHA}$, $bla_{FOX}$ and $bla_{CIT}$ groups of AmpC acquired enzymes using a previously described multiplex PCR [8]. Isolates negative for all acquired AmpC β-lactamases were analyzed for promoter/attenuator mutations within the chromosomal *ampC* gene [9]. Any EC or KPN with an ertapenem MIC of ≥0.12 µg/ml was screened for the production of $bla_{KPC}$ by PCR and sequencing [10]. Following genomic extraction and *XbaI* digestion, all isolates were typed by pulsed-field gel electrophoresis (PFGE) using a standardized protocol [7]. Sequence type (ST) 131 was identified with an allele specific PCR for the *pabB* gene as previously described by Clermont et al. [11].

**Statistical Analysis:** Statistical significance was calculated by the chi-squared test, binary logistic regression, or the Fisher exact test using the SPSS statistics (Version 20) program (IBM Corporation).

## CONCLUSIONS

1. A national increase in the prevalence of ESBL-EC, ESBL-KPN, and AmpC-EC was observed across the study period while the prevalence of KPC-producing isolates remained <1.0%.
   - The national rate of ESBL-EC and ESBL-KPN reached maximum incidence in 2011 with ESBL-EC demonstrating a significant increase as compared to 2010.
2. ESBL-EC are generally polyclonal by PFGE, however ST131 was identified in 55.8% of isolates.
   - The rate of ST131 increased significantly among ESBL-EC across the study period and ESBL-EC are significantly more likely to belong to the ST131 clone as compared to AmpC-EC.
3. ESBL-EC infections are distributed across all specimen sources. The frequency of ESBL-EC infections isolated from respiratory specimens was significantly higher as compared to blood and urine sources (p=0.022 and p=0.006, respectively), while all other comparisons were non-significant.
4. CTX-M-type ESBLs represent the dominant family in Canadian hospitals with CTX-M-15 being the most common variant.
   - 37.7% of ESBL-EC and 41.7% of ESBL-EKPN co-expressed TEM-1.
5. 56.6% of AmpC-EC produced an acquired AmpC beta-lactamase, of which 98.5% produced CMY-2 and 1.5% produced FOX-5.
6. ESBL-EC and ESBL-KPN are frequently MDR (78.8% and 68.8%, respectively) and are significantly more likely to be MDR as compared to AmpC-EC (33.9%), while ESBL-KPN (10.4%) are significantly more likely to be XDR as compared to ESBL-EC and AmpC-EC (2.6% and 0.0%, respectively).
7. The majority of ESBL-EC (>95%), AmpC-EC (>98%), and ESBL-KPN (>89%) remained susceptible to colistin, amikacin, ertapenem, and meropenem.

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## RESULTS

**TABLE 1.** Antimicrobial susceptibility testing of ESBL-*E. coli*, ESBL-*K. pneumoniae* and AmpC-*E. coli*.

| Cohort (n) / Antibiotic | MIC (µg/ml) $MIC_{50}$ | $MIC_{90}$ | Min. | Max. | MIC Interpretation[a] %S | %I | %R |
|---|---|---|---|---|---|---|---|
| ESBL-*E. coli* (231) | | | | | | | |
| AMC[b] | 8 | 16 | 1 | >32 | 62.3 | 33.8 | 3.9 |
| Cefazolin | >128 | >128 | 16 | >128 | | | 100.0 |
| Cefoxitin | 8 | 16 | 0.5 | >32 | 81.8 | 10.0 | 8.2 |
| Ceftriaxone | >64 | >64 | ≤0.25 | >64 | 1.3 | 1.7 | 97.0 |
| Ceftazidime | 16 | >32 | ≤0.5 | >32 | 36.5 | 7.3 | 56.2 |
| Cefepime | 8 | >32 | ≤1 | >32 | 53.2 | 24.9 | 21.9 |
| TZP[b] | 4 | 16 | ≤1 | 512 | 93.1 | 4.8 | 2.2 |
| Ertapenem | ≤0.06 | 0.25 | ≤0.06 | 4 | 97.4 | 1.3 | 1.3 |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 | 1 | 100.0 | | |
| Ciprofloxacin | >16 | >16 | ≤0.06 | >16 | 10.8 | 0.9 | 88.3 |
| Amikacin | 4 | 16 | ≤2 | >64 | 95.7 | 3.9 | 0.4 |
| Gentamicin | 4 | >32 | ≤0.5 | >32 | 51.1 | 0.4 | 48.5 |
| Tigecycline | 0.5 | 1 | 0.12 | 4 | 99.6 | 0.4 | |
| SXT[b] | >8 | >8 | ≤0.12 | >8 | 29.9 | | 70.1 |
| Colistin | 0.5 | 1 | ≤0.06 | 4 | 99.6 | | 0.4 |

| Cohort (n) / Antibiotic | MIC (µg/ml) $MIC_{50}$ | $MIC_{90}$ | Min. | Max. | MIC Interpretation[a] %S | %I | %R |
|---|---|---|---|---|---|---|---|
| ESBL-*K. pneumoniae* (48) | | | | | | | |
| AMC[b] | 16 | 32 | 2 | >32 | 47.7 | 34.1 | 18.2 |
| Cefazolin | >128 | >128 | 16 | >128 | | | 100.0 |
| Cefoxitin | 8 | >32 | 2 | >32 | 77.3 | 11.4 | 11.4 |
| Ceftriaxone | >64 | >64 | ≤0.25 | >64 | 14.6 | 8.3 | 77.1 |
| Ceftazidime | >32 | >32 | 1 | >32 | 29.3 | 2.4 | 68.3 |
| Cefepime | 8 | >32 | ≤1 | >32 | 57.9 | 7.9 | 34.2 |
| TZP[b] | 16 | 256 | 2 | >512 | 66.7 | 18.8 | 14.6 |
| Ertapenem | 0.06 | 0.5 | ≤0.06 | 1 | 97.7 | 2.3 | |
| Meropenem | ≤0.12 | ≤0.12 | ≤0.12 | 0.12 | 100.0 | | |
| Ciprofloxacin | 8 | >16 | ≤0.06 | >16 | 27.1 | 10.4 | 62.5 |
| Amikacin | ≤2 | 32 | ≤2 | >64 | 89.6 | 2.1 | 8.3 |
| Gentamicin | 2 | >32 | ≤0.5 | >32 | 52.1 | | 47.9 |
| Tigecycline | 1 | 4 | 0.5 | 16 | 83.3 | 8.3 | 8.3 |
| SXT[b] | >8 | >8 | ≤0.12 | >8 | 31.3 | | 68.8 |
| Colistin | 0.5 | 1 | 0.25 | >16 | 97.7 | | 2.3 |

| Cohort (n) / Antibiotic | MIC (µg/ml) $MIC_{50}$ | $MIC_{90}$ | Min. | Max. | MIC Interpretation[a] %S | %I | %R |
|---|---|---|---|---|---|---|---|
| AmpC-*E. coli* (115) | | | | | | | |
| AMC[b] | 16 | >32 | 1 | >32 | 27.8 | 22.6 | 49.6 |
| Cefazolin | >128 | >128 | 0.5 | >128 | 0.9 | 3.5 | 95.7 |
| Cefoxitin | >32 | >32 | 32 | >32 | | | 100.0 |
| Ceftriaxone | 8 | 32 | ≤0.25 | >64 | 40.0 | 2.6 | 57.4 |
| Ceftazidime | 16 | >32 | 1 | >32 | 43.2 | 5.4 | 51.4 |
| Cefepime | ≤0.25 | 1 | ≤0.25 | >32 | 96.6 | 1.1 | 2.3 |
| TZP[b] | 4 | 16 | ≤1 | 256 | 91.3 | 7.0 | 1.7 |
| Ertapenem | ≤0.06 | 0.25 | ≤0.06 | 1 | 97.4 | 2.6 | |
| Meropenem | ≤0.06 | ≤0.06 | ≤0.06 | 0.12 | 100.0 | | |
| Ciprofloxacin | ≤0.06 | >16 | ≤0.06 | >16 | 61.7 | 0.9 | 37.4 |
| Amikacin | 2 | 4 | ≤2 | >64 | 98.3 | | 1.7 |
| Gentamicin | ≤0.5 | 32 | ≤0.5 | >32 | 83.5 | | 16.5 |
| Tigecycline | 0.5 | 1 | 0.12 | 2 | 100.0 | | |
| SXT[b] | 0.25 | >8 | ≤0.12 | >8 | 66.1 | | 33.9 |
| Colistin | 0.25 | 0.5 | 0.12 | 1 | 100.0 | | |

[a]%S: % susceptible, %I: % intermediate, %R: % resistant; [b]AMC: amoxicillin/clavulanic acid; TZP: piperacillin/tazobactam; SXT: trimethoprim-sulfamethoxazole.

**TABLE 2.** Patient demographics associated with ESBL-*E. coli*, ESBL-*K. pneumoniae*, and AmpC-*E. coli* infections.

| Parameter / Value | Cohort: % (no. in cohort/total no. collected) ESBL-*E. coli* (n=231) | AmpC-*E. coli* (n=115) | ESBL-*K. pneumo.* (n=48) |
|---|---|---|---|
| Gender | | | |
| Male | 4.9 (104/2120) | 2.6 (46/1737) | 3.3 (30/906) |
| Female | 3.8 (127/3330) | 2.5 (69/2711) | 2.4 (18/753) |
| Age (years) | | | |
| ≤17 | 1.0 (6/576) | 2.2 (10/446) | 3.9 (6/155) |
| 18-64 | 4.3 (96/2244) | 2.6 (48/1821) | 4.0 (27/677) |
| ≥65 | 4.9 (129/2630) | 2.6 (57/2181) | 1.8 (15/827) |
| Hospital Location | | | |
| Clinic/Office | 3.3 (31/943) | 1.9 (14/755) | 2.1 (4/191) |
| Emergency Room | 3.0 (62/2081) | 2.0 (35/1716) | 1.2 (5/433) |
| Intensive Care Unit | 6.1 (31/506) | 3.8 (16/420) | 4.1 (13/318) |
| Medical Ward | 5.8 (89/1543) | 3.2 (40/1268) | 4.0 (22/547) |
| Surgical Ward | 4.8 (18/377) | 3.5 (10/289) | 2.4 (4/170) |
| Specimen Source | | | |
| Blood | 4.2 (116/2733) | 2.4 (59/2413) | 2.7 (24/890) |
| Urine | 3.8 (81/2141) | 2.5 (40/1579) | 3.5 (13/372) |
| Wound | 4.1 (8/197) | 3.7 (6/162) | 3.8 (3/80) |
| Respiratory | 6.9 (26/379) | 3.4 (10/294) | 2.5 (8/317) |
| Multi-Drug Resistance | | | |
| MDR | 78.8 (182/231) | 33.9 (39/115) | 68.8 (33/48) |
| XDR | 2.6 (6/231) | 0.0 (0/115) | 10.4 (5/48) |
| *E. coli* O25b ST131 | 55.8 (129/231) | 27.8 (32/115) | |

**TABLE 3.** Resistance profile and patient demographics associated with KPC-*E. coli* and KPC-*K. pneumoniae*.

| Parameter | KPC-*E. coli* (2) MIC (µg/ml) | Interpretation | KPC-*K. pneumoniae* (1) MIC (µg/ml) | Interpretation |
|---|---|---|---|---|
| Susceptbility | | | | |
| AMC | >32, >32 | R, R | >32 | R |
| Cefazolin | >128, >128 | R, R | >128 | R |
| Cefoxitin | 16, 16 | I, I | >32 | R |
| Ceftriaxone | 32, 64 | R, R | >64 | R |
| Ceftazidime | >32, >32 | R, R | >32 | R |
| TZP | 128, 256 | R, R | 512 | R |
| Ertapenem | 2, 8 | R, R | 16 | R |
| Meropenem | 1, 1 | S, S | 4 | R |
| Ciprofloxacin | >16, >16 | R, R | >16 | R |
| Amikacin | 32, 8 | I, S | 32 | I |
| Gentamicin | >32, 2 | R, S | 8 | S |
| Tigecycline | 0.5, 0.25 | S, S | 2 | S |
| SXT | >8, >8 | R, R | >8 | R |
| Colistin | 0.5, 0.25 | S, S | 0.25 | S |
| Demographics | | | | |
| Year | 2010, 2011 | | 2009 | |
| Region | Quebec, Quebec | | Ontario | |
| Gender | Male, Male | | Female | |
| Age | 77, 74 | | 67 | |
| Source | Resp., Resp. | | Blood | |
| Location | ICU, ICU | | Medical Ward | |
| *E. Coli* ST131 | POS, POS | | Not Applicable | |

**TABLE 4.** Genotypic characterization of ESBL-*E. coli*, ESBL-*K. pneumoniae,* and AmpC-*E. coli*.

| Cohort (n) | Genotype | No. (%) |
|---|---|---|
| ESBL-*E. coli* (231) | CTX-M-3 | 2 (0.9) |
| | CTX-M-14 | 45 (19.5) |
| | CTX-M-15 | 153 (66.2) |
| | CTX-M-24 | 2 (0.9) |
| | CTX-M-27 | 15 (6.5) |
| | CTX-M-65 | 1 (0.4) |
| | SHV-2a | 3 (1.3) |
| | SHV-12 | 4 (1.7) |
| | TEM-12 | 1 (0.4) |
| | TEM-1[a] | 87 (37.7) |
| | Unknown | 5 (2.2) |
| ESBL-*K. pneumo.* (48) | CTX-M-2 | 1 (2.1) |
| | CTX-M-3 | 1 (2.1) |
| | CTX-M-14 | 5 (10.4) |
| | CTX-M-15 | 24 (50) |
| | CTX-M-27 | 1 (2.1) |
| | SHV-2 | 1 (2.1) |
| | SHV-2a | 4 (8.3) |
| | SHV-5 | 1 (2.1) |
| | SHV-11 | 13 (27.1) |
| | SHV-12 | 7 (14.6) |
| | SHV-28 | 1 (2.1) |
| | SHV-31 | 1 (2.1) |
| | SHV-108 | 1 (2.1) |
| | SHV-1[a] | 17 (35.4) |
| | TEM-1[a] | 20 (41.7) |
| | Unknown | 4 (8.3) |
| AmpC-*E. coli* (115) | Chromosomal AmpC hyperproduction | 50 (43.5) |
| | CMY-2 | 64 (55.7) |
| | FOX-5 | 1 (0.9) |

[a]$bla_{TEM-1}$ and $bla_{OXA-1}$ are not ESBLs, however they have been included due to frequent co-expression.

**TABLE 5.** The national prevalence of ESBL-*E. coli*, ESBL-*K. pneumoniae* and AmpC-*E. coli from* 2007-2011.

| Cohort (n) | CANWARD Study Year: % (no. in cohort/total no. of species collected) 2007 | 2008 | 2009 | 2010 | 2011 | 2007-2011 | P-value[b,c] |
|---|---|---|---|---|---|---|---|
| ESBL-*E. coli* (231) | 3.4 (53/1560) | 4.9 (55/1131) | 4.3 (47/1097) | 2.9 (30/1017) | 7.1 (46/645) | 4.2 (231/5450) | <0.001 |
| ESBL-*K. pneumoniae* (48) | 1.5 (7/455) | 3.2 (10/314) | 3.4 (12/356) | 3.3 (10/307) | 4.0 (9/227) | 2.9 (48/1659) | 0.047 |
| AmpC-*E. coli* (115) | 0.7 (4/558[a]) | 3.1 (35/1131) | 2.7 (30/1097) | 2.7 (27/1017) | 2.9 (19/645) | 2.6 (115/4448) | 0.004 |

[a]Cefoxitin was tested against 558 E. coli during CANWARD 2007; [b]P-value comparing the rate of ESBL-*E. coli*, ESBL-*K. pneumoniae*, and AmpC-*E. coli* from 2007-2011; [c]NS: not statistically significant (P > 0.05).