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ORIGINAL ARTICLE

# Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years

**Liam Toner[1,6] · Nathan Papa[1] · Sani H. Aliyu[2] · Harveer Dev[3] · Nathan Lawrentschuk[1,4,5] · Samih Al-Hayek[3]**

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**Abstract**
*Purpose* Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are an increasing concern regarding antibiotic resistance and their potential to cause serious infections which are difficult to treat. The purpose of this surveillance programme was to assess the incidence of ESBL in adults amongst urinary isolates, identify risk factors, and detail the antibiotic susceptibility profile in order to guide empirical treatment.
*Methods* From 2006 to 2014, we reviewed 21,414 positive urine cultures for *E. coli* and *Klebsiella* sp. from a University hospital in the UK and found 1420 ESBL-positive specimens. Susceptibility testing was performed by British Society of Antimicrobial Chemotherapy disc diffusion testing. ESBL screening was performed on samples resistant to cefpodoxime and confirmed by double disc diffusion (Oxoid Ltd, Basingstoke, UK). Patient gender, age, inpatient status, and catheterisation were assessed as risk factors.
*Results* ESBL production amongst *E. coli* urine cultures increased 44 %, from 4.6 to 6.6 % of all *E. coli* isolates. ESBL-positive organisms were associated with increases in drug resistance, particularly amongst fluoroquinolones, trimethoprim, and cephalexin. Multidrug resistance was a feature with 75 % of ESBL+ *Klebsiella* sp.-resistant ≥6 antibiotic classes. ESBL producers remained largely susceptible to carbapenems. Male gender, urinary catheterisation, inpatient status, and increasing age were identified as risk factors for ESBL infection or colonisation.
*Conclusion* We demonstrate that the incidence of ESBL-producing *E. coli* in urine cultures is increasing and that such isolates are multidrug resistant. Carbapenems and nitrofurantoin for *E. coli* infections remain effective, which may guide empirical antibiotic therapy.

**Keywords** Urinary tract infections · Drug resistance, microbial · Enterobacteriaceae · Fluoroquinolones · Nitrofurantoin

✉ Liam Toner
liam.toner@yahoo.com

1 Urology Unit, Department of Surgery, University of Melbourne, Melbourne, VIC, Australia

2 Department of Microbiology, Addenbrookes' Hospital, Cambridge University, Cambridge, UK

3 Department of Urology, Addenbrookes' Hospital, Cambridge University, Cambridge, UK

4 Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia

5 Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

6 Urology Research Office, Level 8 Harold Stokes Building, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia

## Introduction and objective

Urinary tract infection (UTI) can occur in a diverse set of clinical circumstances, ranging from a relatively benign community-acquired UTI to life-threatening pyelonephritis or urosepsis [19]. The incidence of UTI requiring hospital admission is increasing [25]. Common causative organisms of UTI include *E. Coli*, *Klebsiella*, *Proteus*, and *Enterococcus* species [9]. Urine culture is the mainstay of UTI diagnosis, and antibiotic susceptibility results guide subsequent therapy [7]. Empirical treatment may be ineffective in many hospital UTIs caused by extended-spectrum

beta-lactamase (ESBL)-producing uropathogens [2, 6, 16]. Effective antibiotic therapy is important to treat symptoms and is life-saving in severe cases [19]. Earlier effective antibiotic treatment has been shown to improve outcomes and further illustrates the importance of local antibiograms to guide empirical treatment [10, 14, 19].

ESBLs are enzymes which confer extended resistance profiles by degrading beta-lactam antibiotics [3]. ESBL infections occur most frequently in the urinary tract, but can also cause severe life-threatening infections such as sepsis [3, 6, 8, 9]. Globally, ESBL prevalence is rising, thus increasing concerns regarding antibiotic resistance [8]. This increase is thought to be occurring via both clonal expansion and plasmid-mediated horizontal dissemination [3]. ESBL-producing urinary pathogens are associated with higher morbidity and mortality amongst hospitalised patients [11, 14, 15, 24].

ESBL is not solely confined to the hospital setting but is also of increasing importance in community health care. A 2004 UK-based study found 24 % of ESBL producers found in urine, blood, faecal, sputum, and wound cultures occurred in patients from the community, with minimal known hospital contact [23].

ESBL may be one of the mechanisms for increasing fluoroquinolone resistance in the setting of prostate biopsy [17], which is noted by rectal swab in one of every 4–5 cases [4] and is a risk factor for subsequent infective complications [12]. Adjusting antibiotic prophylaxis in this setting may improve patient outcomes [21, 22].

The study aims to detail the contemporary incidence of ESBL-producing uropathogens amongst positive urine cultures in a single centre and the changing antibiotic susceptibility profile over an almost 10-year period.

## Materials and methods

### Ethics approval

Our study was deemed surveillance by the Health Research Authority, and as such, formal ethical review or National Health Service (NHS) Research and Development (R&D) approval was waived.

### Population

The computerised laboratory results' database (MediTech) at Addenbrooke's Hospital, UK, was searched for urinary isolates of all ESBL-producing organisms for the period 1 Jan 2006 to 31 October 2014. The database included patient and sample identifiers, date of birth, gender, date and location of collection, specimen type, causative organism, and antibiotic susceptibility. Locations not classified as inpatient included the emergency and outpatient departments and the day surgery units. Urine samples received from outside our institution (including community isolates) were excluded from the analysis. In total, we found 981 ESBL-producing *E. coli* specimens and 439 ESBL-producing *Klebsiella* sp. specimens. Additionally, 60 ESBL-positive *Enterobacter* sp. and 10 ESBL-positive *Proteus* sp. were identified; however, the small number or these specimens precluded a meaningful analysis, and hence, these are not included in the study sample for this paper.

### Culture analysis

Urine was processed by calibrated loop sampling on to chromogenic clear media (Oxoid Ltd, Basingstoke, UK). A positive culture was defined as $\geq 10^5$ CFU/mL except for samples from children and pregnant women where a cut-off value of $>10^3$ CFU/mL was used. Susceptibility testing was performed by British Society of Antimicrobial Chemotherapy (BSAC) disc diffusion testing and reported for ampicillin, co-amoxiclav, piperacillin–tazobactam, carbapenems (ertapenem, meropenem), nitrofurantoin, pivmecillinam, trimethoprim, cephalexin, cefpodoxime, third-generation cephalosporins (ceftriaxone, ceftazidime), quinolones (norfloxacin or ciprofloxacin), and aminoglycosides (gentamicin, amikacin). Susceptibilities that were classified as "intermediate resistance" were re-designated as "sensitive". ESBL screening was performed on samples that were resistant to cefpodoxime and confirmed by double disc diffusion (Oxoid Ltd, Basingstoke, UK).

We excluded patients aged <16 years as paediatric populations have separate treatment guidelines to adult populations. Unusual specimen types such as a nephrostomy, ileal conduit, extraprostatic secretion, suprapubic aspirate, or a bag specimens were also excluded as they each represent distinct clinical scenarios. Samples ordered less than 30 days after a previous sample (unless a different organism was isolated) were excluded as they would skew our data by analysing the same infection multiple times.

We defined multidrug resistance (MDR) according to 2011 guidelines published by an international consensus panel where MDR is defined as resistance to $\geq 3$ classes and where resistance to a class is defined as $\geq 1$ resistant agent within that class [13]. Additionally, we considered nitrofurantoin and included trimethoprim alongside trimethoprim–sulphamethoxazole.

### Statistical analysis

To evaluate risk factors for being infected with an ESBL-producing organism versus an ESBL-negative organism, we fitted two multivariable logistic regression models for both *E. coli* and *Klebsiella* sp. All four predictor variables: gender,

catheter use, inpatient status, and age as a continuous variable were entered simultaneously. We tested for multicollinearity by observing variance inflation factors, for interactions by including these terms in the model and for linearity with respect to age by visual inspection of locally weighted scatterplot smoothing plots. None of these were found to be an issue. All tests were two-sided with significance set at <0.05. Data management and analysis was performed using Stata SE v.12.0SE (Statacorp, College Station, TX).

## Results

From 1 January 2006 to 31 October 2014, we identified 18,112 isolates of *E. coli* with 981 (5.4 %) ESBL producers and 3302 *Klebsiella* sp. with 439 (13.3 %) ESBL producers. The median patient age was 70 years with interquartile range 40–82 years.

For both bacteria, an ESBL-producing organism was more likely to occur in a male, in a catheterised patient, as an inpatient, and in older patients, Table 1. Over 20 % of *Klebsiella* sp. catheter specimens were ESBL positive, and an almost similar proportion of *Klebsiella* sp. inpatient specimens were also ESBL positive.

In the multivariable models, all of these four risk factors were independent predictors of ESBL positivity, Table 2. Being male conferred around a 50 % increase in the odds of having an ESBL-producing organism, a catheter increased the odds by over 30 %, and there was about a 10 % increase in odds for every 10-year increase in patient age. Being an inpatient with a *Klebsiella* sp., UTI was considerably more predictive (OR 2.54) of having an ESBL producer than not

**Table 1** Distribution of risk factors for ESBL-producing organisms

| | *E. coli* $N = 18{,}112$ (ESBL = 981) | | *Klebsiella* sp. $N = 3302$ (ESBL = 439) | |
|---|---|---|---|---|
| | ESBL positive | ESBL negative | ESBL positive | ESBL negative |
| Gender | | | | |
| Male | 287 (7.6 %) | 3505 (92.4 %) | 195 (17.2 %) | 937 (82.8 %) |
| Female | 694 (4.8 %) | 13,626 (95.2 %) | 244 (11.2 %) | 1926 (88.8 %) |
| Catheter | | | | |
| Yes | 227 (7.9 %) | 2632 (92.1 %) | 143 (21.0 %) | 538 (79.0 %) |
| No | 754 (4.9 %) | 14,499 (95.1 %) | 296 (11.3 %) | 2324 (88.7 %)* |
| Inpatient | | | | |
| Yes | 538 (6.6 %) | 7663 (93.4 %) | 324 (18.6 %) | 1414 (81.4 %) |
| No | 443 (4.5 %) | 9468 (95.5 %) | 115 (7.4 %) | 1449 (92.6 %) |
| Age (years) | | | | |
| ≥65 | 620 (6.0 %) | 9640 (94.0 %) | 311 (15.1 %) | 1747 (84.9 %) |
| <65 | 361 (4.6 %) | 7491 (95.4 %) | 128 (10.3 %) | 1116 (89.7 %) |

* One missing data

**Table 2** Multivariable logistic regression model used to predict ESBL + tests

| | *E. coli* | | | *Klebsiella* sp. | | |
|---|---|---|---|---|---|---|
| | OR | 95 % CI | *p* value | OR | 95 % CI | p-value |
| Gender | | | | | | |
| Male versus female | 1.46 | 1.26, 1.69 | <0.001 | 1.60 | 1.30, 1.97 | <0.001 |
| Catheter | | | | | | |
| Yes versus no | 1.30 | 1.10, 1.53 | 0.002 | 1.44 | 1.14, 1.82 | 0.002 |
| Inpatient | | | | | | |
| Yes versus no | 1.28 | 1.12, 1.47 | <0.001 | 2.54 | 2.01, 3.21 | <0.001 |
| Age | | | | | | |
| Per 10-year increase | 1.10 | 1.06, 1.13 | <0.001 | 1.12 | 1.05, 1.18 | <0.001 |

*OR* odds ratio, *CI* confidence interval

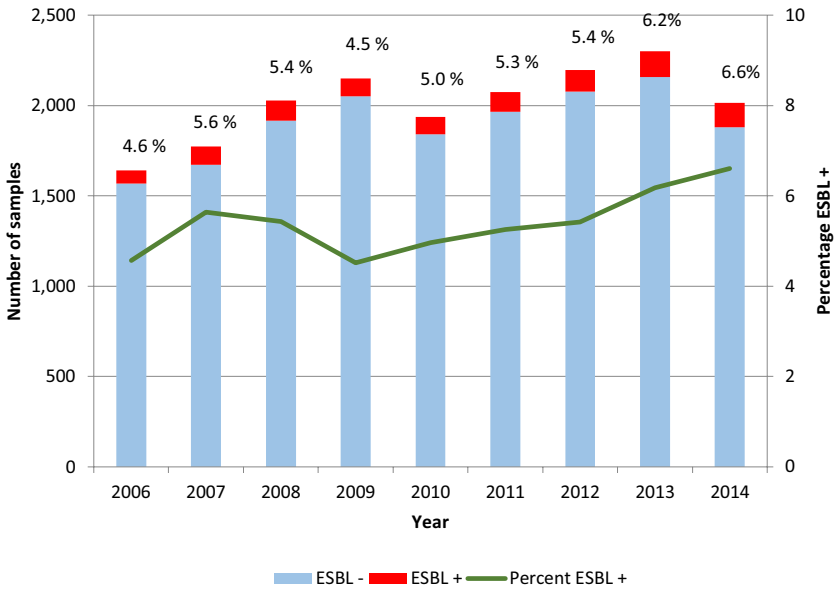


**Fig. 1** Number of isolates each year of *E. coli* coloured according to ESBL status. *Percentages above the columns* and the *green line* indicate the proportion of ESBL producers per year

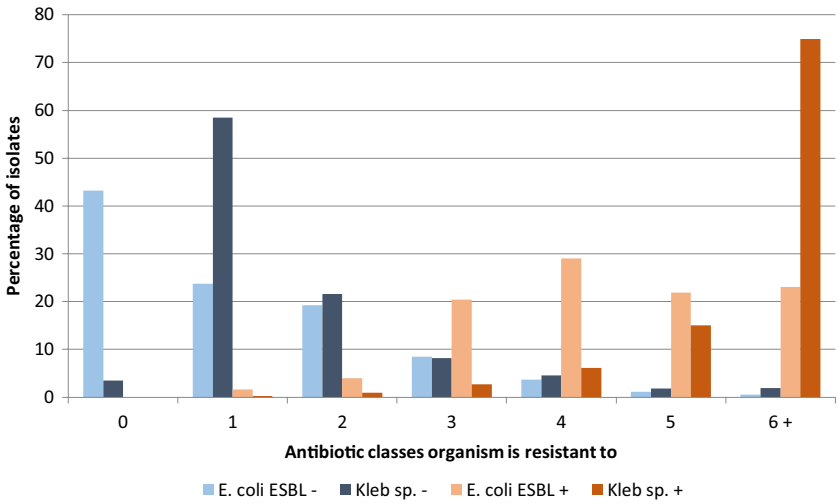


**Fig. 2** Percentage of isolates of *E. coli* and *Klebsiella* sp., subdivided according to ESBL status, and the number of antibiotic classes each group of isolates was resistant to

being an inpatient after adjustment for the other three risk factors.

The incidence of ESBL-producing *E. coli* increased 44 % from 2006 (4.6 % of total) to 2014 (6.6 % of total), Fig. 1. The absolute number of *E. coli* ESBL infections also increased in the same time period from 75 cases in 2006 to 133 in the first 10 months of 2014. The year-on-year proportion of ESBL *Klebsiella* sp. specimens was more fluctuant over the same period, and no trend was evident.

ESBL production was shown to be associated with MDR defined as resistance to three or more antibiotic classes, Fig. 2. For *E. coli*, 94 % of ESBL-positive isolates were MDR compared to 14 % of ESBL-negative isolates. For *Klebsiella* sp., the percentages were 99 versus 16 % with almost 75 % of ESBL-positive isolates resistant to six or more antibiotic classes.

We observed that ESBL production was associated with increased resistance to numerous antibiotic classes including fluoroquinolones, cephalexin, and trimethoprim, Table 3. However, ESBL-positive isolates of both bacteria remain clearly susceptible to carbapenems, and *E. coli*, but not *Klebsiella* sp., are overwhelmingly susceptible to nitrofurantoin (>90 %).

## Discussion

This study comprises the largest sample of ESBL-producing bacteria in urinary specimens. There are a number of publications considering the antibiotic susceptibility profile of ESBL-producing Enterobacteriaceae but relatively few of these specifically focus on urinary isolates.

**Table 3** Antibiotic susceptibility percentages of Enterobacteriaceae over the entire study

| | *E. coli* ESBL+ | *E. coli* ESBL− | *Klebsiella* sp. ESBL+ | *Klebsiella* sp. ESBL− |
|---|---|---|---|---|
| Amikacin | 99.1 | 99.7 | 98.4 | 99.8 |
| Amoxicillin | 0.13 | 48.8 | 0 | 2.05 |
| Augmentin | 66.3 | 93.6 | 57.9 | 94.7 |
| Cephalexin | 6.32 | 94.9 | 0.91 | 94.6 |
| Ertapenem | 99.6 | 99.9 | 97.1 | 99.6 |
| Gentamicin | 74.4 | 94.2 | 38.4 | 96.6 |
| Meropenem | 99.8 | 99.98 | 99.3 | 99.8 |
| Nitrofurantoin | 90.4 | 97.2 | 23.7 | 75.1 |
| Norfloxacin/ciprofloxacin | 18.7 | 85.9 | 11.8 | 92.1 |
| Piperacillin + tazobact | 85.5 | 95.5 | 47.0 | 87.8 |
| Trimethoprim | 16.6 | 70.6 | 13.0 | 79.1 |

The longitudinal nature of our data allows us to demonstrate a steady rise in the incidence of ESBL-producing *E. coli* from 4.6 % in 2006 to 6.6 % in 2014, Fig. 1.

Similar studies to our own in Spain and Switzerland observed significant increases in the proportion of ESBL producers amongst *E. coli* UTI [1, 5]. These older studies detail the emergence of the ESBL phenotype at their respective institutions, whereas our study describes the ongoing rise in more recent years. The numbers we report are comparable to more recent cross-sectional studies in North America, South America, and Europe which reflects the global nature of this issue [2, 9, 18].

This increase is likely driven by over use of antibiotic therapy and returned travellers from endemic areas [15]. We have demonstrated that ESBL-positive organisms are far more likely to be multidrug resistant, Fig. 2; hence, this rise will translate into a greater number of infections that are more difficult to treat empirically leading to delays in effective therapy being initiated.

Our results demonstrated that patients with an ESBL-positive urine culture were more likely to be male, catheterised, an inpatient, and of older age, Table 2, when compared to those with an ESBL-negative urine culture, and this broadly concurs with other studies [1, 5, 15]. These factors, particularly catheterisation and inpatient status, are related to complicated UTIs [19] that have in turn been shown to be associated with ESBL [20]. Whilst we do not have data recorded on whether the infections in our study occurred in complicated UTI, our identification of these four risk factors can be viewed as proxy measures for this. It also serves to remind the clinician that in the presence of a patient with these factors, ESBL infection is significantly more likely. However, recent antibiotic therapy, overseas travel, recurrent UTI, and residential care are other reported risk factors that were not recorded in our database [5, 15, 19].

We observed that ESBL production in *E. coli* is associated with slightly increased resistance to gentamicin, tazobactam–piperacillin, and nitrofurantoin as well as greatly increased resistance to amoxycillin, augmentin, cephalexin, fluoroquinolones, and trimethoprim, Table 3. Resistance to broad-spectrum agents such as carbapenems including meropenem and ertapenem was consistently below 2 % for *E. coli*, regardless of ESBL status. These observations are consistent with other studies from Europe and North America [1, 5, 9, 15, 18]. In addition, our study has quantified the MDR conferred by ESBL production, Fig. 2, demonstrating that 94 % of ESBL-producing *E. coli* may be considered multidrug resistant compared to 14 % of non-ESBL-producing *E. coli*. This clearly illustrates the difficulties in treating these infections.

Nitrofurantoin has a role as initial therapy against ESBL-producing *E. coli* UTI as resistance was typically below 10 % and may be decreasing. Nitrofurantoin should not be used for the treatment of systemic infection.

Across the 9-year course of our study, no obvious patterns emerged regarding the antibiotic susceptibility profile of ESBL-producing *Klebsiella* species. In line with previous European and North American studies [9, 18], our results indicate ESBL production amongst *Klebsiella* sp. is associated with MDR, Fig. 2, with nearly 75 % of ESBL producers resistant to six or more antibiotic classes. Specifically, we observed increased resistance to augmentin, cephalexin, gentamicin, nitrofurantoin, fluoroquinolones, piperacillin–tazobactam, and trimethoprim, Table 3.

The main limitation of the present study is the lack of clinical data to correlate with our pathology results. As our study included all positive urine cultures, it was not possible to distinguish colonisation and infection. A recent study of urine cultures positive for ESBL-producing uropathogens found 60 % of patients were asymptomatic so it is likely that the majority of our samples were from patients with asymptomatic bacteriuria [15]. Due to the large size of our study, we feel it is reasonable to assume the proportions of colonisation and infection remained constant and were not responsible for differences between years. However, even if we have included results representing colonisation, as infection may arise from earlier colonisation, the susceptibility profile we have reported is still relevant to management of symptomatic infection. Our institution is a tertiary referral hospital, and the results might not apply to other district general hospitals. However, none of these limitations diminish our study's ability to identify or confirm risk factors for ESBL-positive infections and to demonstrate increases in overall incidence as we have shown this longitudinally across time.

Clinical practice guidelines for uncomplicated UTI published by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases recommend nitrofurantoin, trimethoprim–sulphamethoxazole, fosfomycin, or pivmecillinam as first-line therapy for uncomplicated UTI and advise against fluoroquinolones and beta-lactams as initial therapy as they may be ineffective and their inappropriate use may contribute to increasing antibiotic resistance [7]. Whilst the guidelines do not have any specific recommendation for the treatment for ESBL-producing uropathogens, our results support the use of nitrofurantoin as a first-line agent for uncomplicated UTI caused by an ESBL-producing *E. coli* but not *Klebsiella* sp. Further, we report that carbapenem resistance is an extremely rare occurrence, and their use as a last-resort agent remains effective.

## Conclusion

This large, 9-year retrospective study identified that male gender, catheterisation, inpatient status, and increasing age are independent predictors of UTI with an ESBL-producing *E. coli* or *Klebsiella* sp. We observed that the incidence of ESBL-producing *E. coli* is increasing and that such organisms are multidrug resistant. We have demonstrated that ESBL-producing uropathogens remain susceptible to last-resort, broad-spectrum antimicrobials such as carbapenems and that nitrofurantoin remains useful as initial therapy in uncomplicated cases of ESBL-producing *E. coli* UTI.

**Authors contribution** L. Toner contributed to protocol/project development, data collection and management, data analysis, manuscript writing, and editing. N. Papa contributed to data management, analysis and manuscript writing. S.H. Aliyu contributed to protocol/project development, data collection and management, manuscript writing, and editing. H. Dev collected and managed the data. N. Lawrentschuk wrote and edited the manuscript. S. Al-Hayek contributed to protocol/project development, data collection and management, manuscript writing, and editing.

**Compliance with ethical standards**

**Conflict of interest** Dr. Aliyu has received sponsorship to attend international conferences from Merck Sharpe and Dohme and Gilead Pharmaceuticals.

**Ethical approval** Our study was deemed surveillance by the Health Research Authority, and as such, formal ethical review or NHS R&D approval was waived.

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