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# Bloodstream infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* at a tertiary care hospital in New Zealand: risk factors and outcomes

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SUMMARY

*Objectives:* To define local risk factors and outcomes for bacteremia with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) at a tertiary hospital in New Zealand.
*Methods:* Patients with ESBL-E bacteremia were compared to matched control patients with non-ESBL-producing *Enterobacteriaceae* bacteremia. Patients were matched by onset of bacteremia (community vs. hospital), site of blood culture collection (peripheral vs. via central line), and infecting organism species.
*Results:* Forty-four cases with matched controls were included. Eight- and 30-day mortality was higher in cases than controls (27% vs. 7%; $p = 0.011$ and 34% vs. 11%, $p = 0.011$). Twenty-one cases (48%) were community-onset. Community-onset cases were associated with urinary tract infection, whereas hospital-onset cases were associated with central line infection, intensive care admission, and *Enterobacter cloacae*. Independent risk factors for ESBL-E bacteremia were fluoroquinolone exposure (odds ratio (OR) 6.56, 95% confidence interval (CI) 1.79–24), first-generation cephalosporin exposure (OR 12.3, 95% CI 1.01–148), and previously-known colonization with ESBL-E (OR 46.2, 95% CI 3.45–619).
*Conclusions:* The association with fluoroquinolone exposure suggests that measures to reduce unnecessary use may be an effective preventative strategy. Known colonization with ESBL-E is a strong risk factor for ESBL-E bacteremia, and colonization status should be taken into consideration when choosing empirical therapy.


## 1. Introduction

The incidence of bloodstream infections due to ESBL-producing *Enterobacteriaceae* (ESBL-E) has increased worldwide during the last 10 years.[1] These infections have limited treatment options, and when treated with inappropriate empirical therapy are associated with increased mortality.[2] Identification of locally relevant risk factors for such infections is therefore essential, both to guide empirical therapy and to design rational preventative strategies. Although numerous risk factors have been described in a variety of geographic and epidemiological settings, few studies have evaluated specific risk factors in the setting of a tertiary hospital in Australasia. We performed a retrospective case–control study in order to identify risk factors and outcomes for bacteremia with ESBL-E in patients admitted to Middlemore Hospital in Auckland, New Zealand. The study protocol was approved by the local institutional ethics committee.

## 2. Methods

Middlemore Hospital (MMH) is a 720-bed university-affiliated tertiary hospital. With approval from the regional ethics committee, all patients admitted to MMH between May 1, 2003 and March 31, 2007 who had ESBL-E isolated from blood cultures were identified using the Microbiology Laboratory database. Identification of bacterial isolates was performed using the Vitek 2 system (BioMérieux). Confirmatory testing for ESBL was performed using the Clinical and Laboratory Standards Institute (CLSI) recommendations,[3] except for *Enterobacter cloacae*, which was confirmed using combination disk testing with cefepime and clavulanic acid.[4]

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**Table 1**
Comparison of patient characteristics between community-onset and hospital-onset cases

| | All ESBL-E bacteremia ($n=44$)[a] | Community-onset bacteremia ($n=21$)[a] | Hospital-onset bacteremia ($n=23$) | $p$-Value[b] |
|---|---|---|---|---|
| Male gender | 29 (66%) | 15 (71%) | 14 (61%) | 0.54 |
| Age | 63.6 (18.2) | 68.5 (17.3) | 59.1 (18.3) | 0.089 |
| Residential care | 6 (14%) | 4 (19%) | 2 (9%) | 0.40 |
| CVC | 22 (50%) | 4 (19%) | 18 (78%) | 0.0002 |
| Long term urinary catheter | 4 (9%) | 3 (14%) | 1 (4%) | 0.335 |
| Endotracheal tube | 18 (41%) | 1 (5%) | 17 (74%) | 0.0007 |
| Inpatient days | 51.0 (53.1) | 59.0 (55.5) | 43.7 (51.0) | 0.35 |
| Intensive care | 15 (34%) | 0 (0%) | 15 (65%) | <0.0001 |
| Medical ward | 26 (59%) | 17 (81%) | 9 (39%) | 0.0065 |
| General surgery ward | 20 (45%) | 9 (43%) | 11 (48%) | 0.77 |
| Inpatient antibiotic days | 29.4 (25.3) | 29.1 (26.0) | 29.7 (25.3) | 0.95 |
| Fluoroquinolone exposure | 22 (50%) | 9 (43%) | 13 (57%) | 0.55 |
| *Escherichia coli* | 16 (36%) | 11 (52%) | 5 (22%) | 0.059 |
| *Klebsiella pneumoniae* | 18 (41%) | 8 (38%) | 10 (43%) | 0.77 |
| *Enterobacter cloacae* | 9 (20%) | 1 (5%) | 8 (35%) | 0.023 |
| *Enterobacter aerogenes* | 1 (2%) | 1 (5%) | 0 (0%) | 0.48 |
| Urinary tract source | 15 (34%) | 12 (57%) | 3 (13%) | 0.0036 |
| CVC-related source | 13 (30%) | 1 (5%) | 12 (52%) | 0.0007 |

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; CVC, central venous catheter.
[a] Categorical variables presented as absolute numbers and percentages, continuous variables as mean (standard deviation).
[b] Statistically significant at $p < 0.05$.

The clinical records of each patient were reviewed. Patients whose blood culture isolate was considered a contaminant by the clinical team were excluded. Matched control patients with bacteremia due to non-ESBL-producing *Enterobacteriaceae* were also identified using the laboratory database. Control patients were matched one to one with cases for the following characteristics: (1) species of organism, (2) type of blood culture (peripheral culture or central venous catheter culture), and (3) timing of bacteremia relative to hospital admission ('community-onset' bacteremia was defined as bacteremia within 48 h of hospital admission, and 'hospital-onset' bacteremia was defined as bacteremia occurring >48 h after admission). Control patients were those whose bacteremia was temporally closest to their matched case and who had not been used as a control for another case. The following data were collected from the clinical records: demographic data (age, gender, and residential care facility residency), service providing care, comorbidity (diabetes, chronic renal failure, renal replacement therapy, and burn injury), clinical features (known colonization with ESBL-E and source of bacteremia as determined by managing team), healthcare exposures (timing, location, and duration of hospital admissions, inpatient antibiotic use during the 12 months prior to bacteremia, surgical procedures, and presence of invasive medical devices during the admission prior to the bacteremia), and all-cause mortality at 8 and 30 days.

The statistical analysis was performed using SAS v9.2 (SAS Institute Inc., Cary, NC, USA). Fisher's exact test was used for the analysis of $2 \times 2$ contingency tables and the Student's $t$-test for the comparison of means. Univariate and multivariate logistic regression (stepwise regression) analyses were used to compare matched cases and controls. With the exception of mortality, variables found to be significant on univariate analysis were included in the multivariate model. Statistically significant differences were defined as a $p$-value of $\leq 0.05$. All $p$- and $t$-values were two-tailed. Study size was not pre-specified due to the limited numbers of available cases and controls.

## 3. Results

A total of 45 patients had at least one positive blood culture with ESBL-E during the study period. One patient was excluded because their isolate was considered a contaminant, leaving 44 cases included. The characteristics of case patients are shown in Table 1. Cases and controls were not significantly different in gender and age. The ethnic composition of the case and control groups was also similar: 21 New Zealand Europeans in each group; nine vs. five Maori and 11 vs. 15 Pacific Islanders for cases and controls, respectively.

Nearly half of the cases (48%; 21/44) had community-onset bacteremia. Cases with community-onset bacteremia were not significantly different from hospital-onset cases with respect to gender, age, or domicile in a residential care facility (Table 1). However, community-onset cases were more likely to have a urinary source of infection (12/21 vs. 3/23; $p = 0.0036$), whereas hospital-onset cases were more likely to have *E. cloacae* bacteremia (1/21 vs. 8/23; $p = 0.023$) and to have a central venous catheter infection source (1/21 vs. 12/23; $p = 0.0007$). Hospital-onset ESBL-E bacteremia occurred a median of 10 days after admission (range 3–57 days).

Mortality outcomes are shown in Table 2. Mortality rates associated with ESBL-E bacteremia were 27% at 8 days (95% confidence interval (CI) 16–42%) and 34% at 30 days (95% CI 22–49%). These rates were significantly higher than rates in the control group at both 8 days (12/44 vs. 3/44; $p = 0.0112$) and 30 days (15/44 vs. 5/44; $p = 0.0114$). When stratified by species, no significant

**Table 2**
Mortality associated with bacteremia

| | 8-day mortality | | | 30-day mortality | | |
|---|---|---|---|---|---|---|
| Species | ESBL-E case | Non-ESBL-E control | $p$-Value[a] | ESBL-E case | Non-ESBL-E control | $p$-Value[a] |
| *Escherichia coli* | 50% (8/16) | 6% (1/16) | 0.0155 | 63% (10/16) | 13% (2/16) | 0.0091 |
| *Klebsiella pneumoniae* | 22% (4/18) | 6% (1/18) | 0.3377 | 28% (5/18) | 11% (2/18) | 0.40 |
| *Enterobacter spp* | 0% (0/10) | 10% (1/10) | 1.0000 | 0% (0/10) | 10% (1/10) | 1.00 |
| Total | 27% (12/44) | 7% (3/44) | 0.0112 | 34% (15/44) | 11% (5/44) | 0.011 |

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.
[a] Statistically significant at $p < 0.05$.

**Table 3**
Univariate analysis comparing cases and controls with respect to putative risk factors

| | ESBL-E bacteremia cases ($n = 44$)[a] | Non-ESBL-E bacteremia controls ($n = 44$)[a] | $p$-Value[b] |
|---|---|---|---|
| Male gender | 29 (66%) | 21 (48%) | 0.13 |
| Age | 64 (18) | 59 (19) | 0.25 |
| Residential care | 6 (14%) | 2 (5%) | 0.27 |
| Central line | 22 (50%) | 14 (32%) | 0.13 |
| Endotracheal tube | 18 (41%) | 13 (30%) | 0.37 |
| Long-term urinary catheter | 4 (9%) | 2 (5%) | 0.68 |
| Temporary urinary catheter | 20 (45%) | 19 (43%) | 1.0 |
| Known ESBL-E colonization | 16 (36%) | 1 (2%) | <0.0001 |
| Total inpatient days medical | 11.0 (13.4) | 4.3 (8.1) | 0.0053 |
| Total inpatient days surgical | 8.6 (16) | 9.9 (27) | 0.39 |
| Total inpatient days | 51.0 (53.1) | 20.1 (28.1) | 0.0011 |
| Hemodialysis | 9 (20%) | 2 (5%) | 0.0075 |
| Diabetes | 16 (36%) | 12 (27%) | 0.49 |
| Urinary tract infection | 13 (30%) | 3 (7%) | 0.066 |
| Quinolone exposure | 22 (50%) | 7 (16%) | 0.0007 |
| Metronidazole exposure | 16 (36%) | 5 (11%) | 0.0062 |
| First-generation cephalosporin | 10 (23%) | 1 (2%) | 0.014 |
| Second-generation cephalosporin | 28 (64%) | 10 (23%) | 0.0001 |
| Third-generation cephalosporin | 13 (30%) | 4 (9%) | 0.016 |
| Total antibiotic days | 29.4 (25.3) | 15.9 (28.8) | 0.022 |

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.
[a] Categorical variables presented as absolute numbers and percentages, continuous variables as mean (standard deviation).
[b] Statistically significant at $p < 0.05$.

differences in mortality were found between cases and controls for *Klebsiella pneumoniae* and *Enterobacter* species cases, whereas *Escherichia coli* bacteremia had a higher mortality rate in cases than in controls. Cases with *E. coli* bacteremia were also different from controls with respect to time in hospital during the preceding year (mean 68 bed-nights for cases vs. 12 bed-nights for controls $p = 0.0019$) and inpatient exposure to antibiotics (mean 30 days vs. 6 days; $p = 0.0060$).

In order to determine risk factors for ESBL-E bacteremia, cases were compared to controls with respect to a number of putative risk factors for ESBL-E bacteremia. On univariate analysis, cases were significantly more likely to be known to be colonized with ESBL-E prior to their bacteremia and had a significantly higher mean number of days as an inpatient during the preceding year. Cases also had greater exposure to antimicrobial agents in general and to a number of specific antimicrobial classes (including first-, second-, and third-generation cephalosporins, fluoroquinolones, and metronidazole) during the 12 months prior to their bacteremia (Table 3).

Multivariate analysis included all variables found to be statistically significant on the univariate analysis except mortality (Table 4). Known colonization with an ESBL-E (odds ratio (OR) 46.2), exposure to first-generation cephalosporins (OR 12.3), and exposure to fluoroquinolones (OR 6.56) were found to be independently associated with ESBL-E bacteremia, as was total inpatient days (OR 1.033 per admission day); admission under general surgery was found to be protective (OR 0.95 per inpatient day).

An additional multivariate analysis was also performed on the subgroup of 22 patients with 'hospital-onset' bacteremia. In this subgroup, fluoroquinolone use and known colonization remained significant with ORs of 7.0 (95% CI 1.4–34.6, $p = 0.014$) and 13.9 (95% CI 1.4–133.6, $p = 0.02$), respectively. For this subgroup of patients, 13 were exposed to fluoroquinolones during the preceding year, 4/13 (31%) during the same admission as their bacteremia, and 9/22 (41%) during admissions within the prior 6 months. Thirty of 44 (68%) ESBL isolates were resistant to ciprofloxacin using the CLSI interpretive criteria.

## 4. Discussion

In our study, cases of ESBL-E bacteremia were associated with higher all-cause mortality than non-ESBL-E controls at both 8 and 30 days. A number of factors may have contributed to this observation. It is likely that this finding is at least partially explained by intrinsic differences in comorbidity between cases and controls. Nonetheless, the high mortality that we observed highlights the frequently poor prognosis associated with ESBL-E bacteremia and the importance of defining clinical risk factors for such infections.

Notably, nearly half of all cases in our study presented to the hospital with their infection from the community. However, all but one of the community-onset cases had been admitted to hospital at some stage during the previous year; 52% (11/21) had invasive medical devices in situ and a further 10% (2/21) were receiving regular dialysis. These findings suggest that although these patients had community-onset infections, many of these patients may have acquired their ESBL-E during a previous hospital admission. Only one patient (a previously healthy 21-year-old Maori female who presented in 2005 with ESBL-E pyelonephritis) appeared to have no comorbidities or previous healthcare exposure. Importantly, the absence of healthcare exposure in this patient suggests that acquisition of uropathogenic strains of ESBL-producing *E. coli* is to some extent occurring in the community in New Zealand. Similar reports of community spread of ESBL-producing *E. coli* have been made in Spain, Canada, and the UK.[5–7]

In contrast to community-onset cases, hospital-onset cases were less likely to have a urinary tract infection, but more likely to have been previously admitted to the intensive care unit, to have bacteremia due to *E. cloacae*, and to have a central venous catheter source of infection. These differences are likely to reflect intrinsic differences in epidemiology between different species of ESBL-E. *E. coli* for example, has a particular propensity to cause urinary tract infections in non-hospitalized patients compared to *E. cloacae* and *K. pneumoniae*.[8]

Despite these differences within the case group, our study identified several overarching risk factors for ESBL-E bacteremia. ESBL-E bacteremia was highly associated with known colonization with ESBL-E (OR 46.2). Nine of 16 cases with known colonization had ESBL-E previously isolated from a clinical specimen and the

**Table 4**
Odds ratios for independent risk factors on multivariate analysis comparing cases of ESBL-E bacteremia with matched non-ESBL-E bacteremia controls

| Risk factor | OR (95% CI) | $p$-Value[a] |
|---|---|---|
| Known colonization with an ESBL-producing organism | 46.2 (3.45–619) | <0.0001 |
| Exposure to first-generation cephalosporins within preceding 12 months | 12.3 (1.01–148) | 0.049 |
| Exposure to quinolone antibiotics within preceding 12 months | 6.56 (1.79–24) | 0.0066 |
| Total inpatient days within preceding 12 months | 1.033 (1.001–1.066)[b] | 0.0017 |
| Days admitted under general surgery within preceding 12 months | 0.95 (0.9–0.99)[b] | 0.0019 |

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; OR, odds ratio; CI, confidence interval.
[a] Statistically significant at $p < 0.05$.
[b] Odds ratios for continuous variables are per unit of increment, i.e., per day of admission.

remaining seven had ESBL-E previously isolated as a consequence of the hospital's ESBL-E surveillance policy. Our findings therefore support the intuitive notion that previous colonization or infection with ESBL-E increases the probability of subsequent ESBL-E bacteremia. A similar finding was reported in a case–control study performed in Israel, where patients colonized with ESBL-E on admission were found to be 39 times more likely than controls to develop bacteremia during their hospital stay.[9] Awareness of a patient's colonization status may therefore be useful, not only for preventing hospital transmission of these organisms, but also for guiding empirical therapy at the individual patient level.

Fluoroquinolone and first-generation cephalosporin exposure were found to be independently associated with ESBL-E bacteremia. Series in other geographic settings have also described fluoroquinolone use as an independent risk factor for ESBL-E bacteremia.[10,11] Fluoroquinolone-resistant, urovirulent clones such as ST-131 *E. coli* have disseminated internationally in association with ESBL production.[12] In settings where fluoroquinolone-resistant ESBL-E are prevalent, fluoroquinolones will exert selective pressure on the gut flora that will favor ESBL-E proliferation and infection in susceptible patients.[13] Moreover, it is possible that fluoroquinolone use increases vulnerability for acquisition of fluoroquinolone-resistant organisms in non-colonized patients.[14] It seems likely therefore that measures to reduce unnecessary fluoroquinolone use could lead to decreased rates of ESBL-E bacteremia.

Although the cephalosporins as a class have been repeatedly associated with ESBL-E bacteremia in numerous studies, the particular association with first-generation cephalosporins that we observed is an unusual finding. This finding may be explained by the fact that in our hospital these agents are used in orthopedic wards as surgical prophylaxis, and the orthopedic wards were sites of documented ESBL-E cross-transmission during the study period. Nonetheless, the association between first-generation cephalosporins and ESBL-E bacteremia suggests that amongst cephalosporins it is not solely third-generation agents that exert selective pressure for ESBL-E.

This study has several limitations. Firstly, whilst the study had adequate power to detect large differences between cases and controls, the ability to detect small differences between the groups was limited. Secondly, the cases were heterogeneous with respect to timing of bacteremia onset. Also, our examination of antimicrobial use did not account for community use, or for concurrent use of multiple agents.

Despite these limitations, our study is to our knowledge, the first to describe risk factors and outcomes for ESBL-E bacteremia in the setting of a tertiary hospital in New Zealand. Moreover, we identified several risk factors that deserve further attention. The strong association between ESBL-E bacteremia and previous colonization suggests that systematic screening for ESBL-E colonization may provide useful information to guide empirical therapy in high-risk patient groups. This concept is important because inappropriate empirical therapy has been associated with increased mortality. Also, our findings suggest that reduction of unnecessary use of fluoroquinolones and cephalosporins may be a useful strategy to help reduce the incidence of ESBL-E bacteremia. Further prospective studies to evaluate ESBL-E screening and antimicrobial stewardship programs are warranted. The importance of such strategies will increase as the incidence of ESBL-E bacteremia continues to increase in New Zealand hospitals.

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