Clinical characteristics of bacteraemia caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae* in the era of CTX-M-type and KPC-type β-lactamases

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Abstract

A multicentre, case–control study was conducted to assess risk factors and patient outcomes of bacteraemia caused by *Enterobacteriaceae* producing extended-spectrum β-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs). One hundred and five and 20 patients with bacteraemia caused by ESBL-producing and KPC-producing organisms were matched to controls who had bacteraemia caused by non-ESBL/KPC-producing organisms, respectively. Independent risk factors for ESBL production included admission from a nursing home (OR 4.64; 95% CI 2.64–8.16), chronic renal failure (OR 2.09; 95% CI 1.11–3.92), the presence of a gastrostomy tube (OR 3.36; 95% CI 1.38–8.18), length of hospital stay before infection (OR 1.02; 95% CI 1.01–1.03), transplant receipt (OR 2.48; 95% CI 1.24–4.95), and receipt of antibiotics with Gram-negative activity in the preceding 30 days (OR 1.76; 95% CI 1.00–3.08). Twenty-eight-day crude mortality rates for patients infected with ESBL-producing or KPC-producing organisms and controls were 29.1% (34/117) and 19.5% (53/272), respectively (OR 1.70; 95% CI 1.04–2.80). On multivariate analysis, inadequate empirical therapy (OR 2.26; 95% CI 1.18–4.34), onset of bacteraemia while in the intensive-care unit (OR 2.74; 95% CI 1.47–5.11), Apache II score (OR 1.17; 95% CI 1.12–1.23) and malignancy (OR 2.66; 95% CI 1.31–5.41) were independent risk factors for mortality. CTX-M was the most common ESBL type in *Escherichia coli*, whereas SHV predominated in *Klebsiella* spp. and *Enterobacter* spp.

Keywords: bacteraemia, carbapenem, *Enterobacteriaceae*, extended-spectrum β-lactamase, *Klebsiella pneumoniae* carbapenemase
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Introduction

Extended-spectrum β-lactamases (ESBLs) are now well recognized as a major cause of cephalosporin resistance among *Enterobacteriaceae* [1,2]. Two important changes in the epidemiology of ESBLs have occurred in the last decade. One is the rapid global dissemination of *Escherichia coli* producing CTX-M-type ESBLs. CTX-M has now become the predominant ESBL type in Europe, Canada, South America, and Asia [3]. Several recent studies suggest that it is finally replacing classic TEM-type and SHV-type ESBLs in the USA as well [4–6]. The other change is the advent of *Klebsiella pneumoniae* carbapenemases (KPCs). Initially causing outbreaks in hospitals on the east coast of the USA, KPC-producing *K. pneumoniae* has now spread worldwide [7]. The aims of the present study were to investigate the risk factors, clinical outcome and predictors of mortality in a contemporary cohort of patients with bacteraemia caused by ESBL-producing and KPC-producing *Enterobacteriaceae* in the USA.

Patients and Methods

Study design and patients

This multicentre, retrospective case–control study was conducted at three medical centres in the northeastern USA (New York, Massachusetts, and Pennsylvania) between 2005 and 2008. Patients with blood cultures growing *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae* and *Enterobacter aerogenes* were included. The two case groups consisted of those caused by ESBL-producing and KPC-producing organisms. Controls were selected so that each study site and species occurred in similar proportions in both cases and controls, with a ratio of three controls per case. The entire control group was used for the ESBL analysis, whereas only cases caused by *K. pneumoniae* were included in the KPC analysis, as all KPC-producing organisms belonged to this species. Only the first episode of bacteraemia was included for each patient. The study was approved by the Institutional Review Board at each participating site.

Risk factor analyses

The variables reviewed for risk factor analyses included demographic data, admission from a nursing home, prior use of antibiotics with Gram-negative activity in the preceding 30 days, presence of tracheostomy tube, gastrostomy tube, intravenous line or urinary catheter at the time of infection, prior hospitalization, length of hospital stay before the onset of bacteraemia, intensive-care unit (ICU) admission, surgery, outpatient intravenous therapy or dialysis in the preceding 1 year, diabetes, the presence of chronic renal failure, liver disease, chronic obstructive pulmonary disease, cardiovascular disease, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, malignancy and history of organ transplant. The Apache II score was also collected and included in the univariate analysis, but was not included in the multivariate analysis because it could not be defined for >10% of the cases. Immunocompromised state was defined as the presence of diabetes mellitus, neutropenia, human immunodeficiency virus infection, or receipt of steroids or other immunosuppressive agents in the 30 days prior to infection.

Predictors of mortality

The primary outcome measure was death within 28 days from the onset of bacteraemia. Predictors of 28-day mortality were analysed for the whole study population, as well as within the ESBL or KPC cases and the controls separately. Patients for whom 28-day status was unknown were excluded from the mortality analyses ($n = 61$). The parameters reviewed in addition to those used for risk factor analyses were inadequate empirical therapy, defined as receipt of empirical antibiotics with no *in vitro* activity against the infecting organism, ICU stay at the time of infection, source of bacteraemia, and Apache II score.

Microbiological methods

All *E. coli* and *Klebsiella* isolates that were reported as ESBL producers were subjected to PCR analyses to identify the presence of TEM-type, SHV-type and CTX-M-type β-lactamase genes [8]. Positive PCR results were followed by sequencing of the amplified products. For *Enterobacter* spp., all piperacillin-resistant or ceftriaxone-non-susceptible *Enterobacter* isolates were subjected to PCR analyses for the ESBL genes and sequencing [9]. For all species, ceftriaxone-non-susceptible isolates (corresponding to MICs $\geq$16 mg/L) underwent PCR analysis for detection of the KPC gene [10].

Statistical analyses

Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA). For univariate analysis of risk factors and predictors of mortality, univariate logistic regression was performed. To identify independent risk factors and predictors of mortality, variables with a p-value $\leq$0.15 on univariate analysis were included in a stepwise conditional multivariate logistic regression model. All p-values were two-tailed, and a p-value $\leq$0.05 was considered to be statistically significant.

Results

Demographics of the cohorts

A total of 450 patients with bacteraemia caused by *Enterobacteriaceae* (*E. coli*, *Klebsiella* spp., and *Enterobacter* spp.) were included. One hundred and twenty-five bacteraemia cases were caused by ESBL-producing or KPC-producing organisms, including *E. coli* ($n = 32$), *Klebsiella* spp. ($n = 76$), and *Enterobacter* spp. ($n = 17$). Of these, 20 cases were caused by KPC-producing *K. pneumoniae*, all of which were from the study site in New York City. The remaining 105 cases constituted the ESBL group. A total of 325 control cases were selected for analysis of the ESBL group. For analysis of the KPC group, *K. pneumoniae* cases from this control group were assigned ($n = 176$). The characteristics of these patients relative to ESBL and KPC status are shown in Tables 1 and 2, respectively. In the analysis of the ESBL and control groups, there was no significant difference in the proportion of patients >60 years of age, sex or race between the cases and

TABLE 1. Demographics and risk factors of cases with extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*

	Univariate analysis							Multivariate analysis		
Demographics/risk factors	ESBL group	%	Control group	%	OR	95% CI	p-value	OR	95% CI	p-value
Apache II score	15.5[a]	0–49[b]	13[a]	1–45[b]	1.04	1.01–1.07	0.01	–	–	–
Male	54	51.43	167	51.38	1.00	0.65–1.56	0.99	–	–	–
Age >60 years	51	48.57	174	53.70	0.81	0.52–1.26	0.36	–	–	–
Immunocompromised	63	60.00	160	49.23	1.55	0.99–2.42	0.06	–	–	–
Caucasian	54	66.67	173	66.03	1.03	0.61–1.74	0.92	–	–	–
Hispanic	5	6.17	27	10.31	0.57	0.21–1.54	0.27	–	–	–
Admitted from nursing home	44	43.14	41	12.65	5.24	3.14–8.73	<0.0001	4.64	2.64–8.16	<0.0001
Number of days hospitalized before infection	5[a]	0–328[b]	1[a]	0–141[b]	1.02	1.01–1.03	<0.0001	1.02	1.01–1.03	0.0015
Any hospitalization in past year	84	80.00	242	74.46	1.37	0.80–2.35	0.25	–	–	–
Any ICU admission in past year	44	41.90	95	29.23	1.75	1.11–2.75	0.02	–	–	–
Any surgery in past year	47	44.76	113	34.77	1.52	0.97–2.38	0.07	–	–	–
Dialysis in past year	19	18.10	29	8.92	2.26	1.21–4.22	0.01	–	–	–
Outpatient intravenous therapy in past year	15	14.29	24	7.38	2.09	1.05–4.15	0.04	–	–	–
Prior surgery within 30 days	15	14.29	53	16.31	0.86	0.46–1.59	0.62	–	–	–
Antibiotics in 30 days prior to enrolment	48	47.06	76	23.38	2.91	1.83–4.64	<0.0001	1.76	1.00–3.08	0.0491
Carbapenem[c]	8	7.62	8	2.46	3.27	1.20–8.94	0.02	–	–	–
Ampicillin–sulbactam	6	5.71	15	4.62	1.25	0.47–3.32	0.65	–	–	–
Fluoroquinolone[d]	12	11.43	28	8.62	1.37	0.67–2.80	0.39	–	–	–
Cefepime	18	17.14	17	5.23	3.75	1.85–7.58	0.0002	–	–	–
Ceftriaxone	4	3.81	4	1.23	3.18	0.78–12.94	0.11	–	–	–
Piperacillin–tazobactam	8	7.62	17	5.23	1.49	0.63–3.57	0.37	–	–	–
Chronic renal failure	28	26.67	41	12.62	2.52	1.46–4.33	0.0008	2.09	1.11–3.92	0.0223
Diabetes	40	38.10	79	24.31	1.92	1.20–3.06	0.006	–	–	–
Chronic obstructive pulmonary disease	11	10.48	45	13.85	0.73	0.36–1.47	0.37	–	–	–
Cardiovascular disease	29	27.62	77	23.69	1.23	0.75–2.02	0.42	–	–	–
Peripheral vascular disease	4	3.81	8	2.46	1.57	0.46–5.32	0.47	–	–	–
Cerebrovascular disease	9	8.57	27	8.31	1.03	0.47–2.28	0.93	–	–	–
Peptic ulcer disease	3	2.86	13	4.00	0.71	0.20–2.53	0.59	–	–	–
Liver disease	17	16.19	35	10.77	1.60	0.86–3.00	0.14	–	–	–
Malignancy	14	13.33	61	18.77	0.67	0.36–1.25	0.20	–	–	–
Solid organ malignancy	10	9.52	53	16.31	0.54	0.26–1.10	0.09	–	–	–
Transplant	23	21.90	34	10.46	2.40	1.34–4.30	0.003	2.48	1.24–4.95	0.0103
Tracheostomy tube at enrolment	26	24.76	29	8.92	3.36	1.87–6.03	<0.0001	–	–	–
Gastrostomy tube at enrolment	17	16.19	12	3.69	5.04	2.32–10.95	<0.0001	3.36	1.38–8.18	0.0076
Indwelling urinary catheter at enrolment	26	24.76	51	15.69	1.77	1.04–3.02	0.04	–	–	–
Vascular catheter at enrolment	74	70.48	176	54.15	2.02	1.26–3.24	0.004	–	–	–

ICU, intensive-care unit.
[a]Median.
[b]Range.
[c]Ertapenem, imipenem, and meropenem.
[d]Ciprofloxacin, levofloxacin, and moxifloxacin.

controls (Table 1). In the analysis of the KPC and control groups, there were significantly fewer Caucasian patients in the KPC group, reflecting the predominance of African American patients at the study site in New York City, where all of the KPC cases were identified (Table 2).

Risk factors for ESBL production

Independent risk factors for bacteraemia caused by ESBL-producing organisms, after adjustment for potential confounding variables, included admission from a nursing home (OR 4.64; 95% CI 2.64–8.16, p <0.0001), chronic renal failure (OR 2.09; 95% CI 1.11–3.92, p 0.0223), the presence of a gastrostomy tube (OR 3.36; 95% CI 1.38–8.18, p 0.0076), length of hospital stay before infection (OR 1.02; 95% CI 1.01–1.03, p 0.0015), history of transplant (OR 2.48; 95% CI 1.24–4.95, p 0.0103), and receipt of antibiotics with Gram-negative activity in the preceding 30 days (OR 1.76; 95% CI 1.00–3.08, p 0.0491) (Table 1).

For further characterization of the association between prior antibiotic exposure and ESBL-producing organisms, the antibiotics were divided into classes and assessed for their association. We observed that prior use of cefepime and carbapenems was significantly associated with infection with an ESBL-producing organism in the univariate analysis, but the significance did not remain in the multivariate analysis (Table 1).

Risk factors for KPC production

Owing to the relatively small number of KPC cases, multivariate analysis was deferred for this comparison. In the univariate analysis, significant risk factors were largely consistent with those observed with the ESBL group, with the exception of surgery in the past year (Table 2). Regarding the individual antibiotic classes, receipt of carbapenems, cefepime or ceftriaxone in the prior 30 days was associated with infection with a KPC-producing organism.

TABLE 2. Demographics and risk factors of cases with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*

Demographics/risk factors	KPC group	%	Control group	%	OR	95% CI	p-value
Apache II score	21[a]	3–44[b]	14[a]	1–45[b]	1.11	1.05–1.17	0.0001
Male	8	40.00	92	52.27	0.61	0.24–1.56	0.30
Age >60 years	12	60.00	95	54.29	1.26	0.49–3.24	0.63
Immunocompromised	13	65.00	93	52.84	1.66	0.63–4.35	0.30
Caucasian	4	21.05	96	67.61	0.13	0.04–0.41	0.0005
Hispanic	3	15.79	13	9.15	1.86	0.48–7.24	0.37
Admitted from nursing home	6	30.00	28	16.00	2.25	0.80–6.35	0.13
Number of days hospitalized before infection	20[a]	0–323[b]	1[a]	0–141[b]	1.03	1.01–1.05	0.0006
Any hospitalization in past year	16	80.00	141	80.11	0.99	0.31–3.16	0.99
Any ICU admission in past year	9	45.00	54	30.68	1.85	0.72–4.72	0.20
Any surgery in past year	13	65.00	64	36.36	3.25	1.23–8.56	0.02
Dialysis in past year	1	5.00	8	4.55	1.11	0.13–9.32	0.93
Outpatient intravenous therapy in past year	3	15.00	16	9.09	1.76	0.47–6.68	0.40
Prior surgery within 30 days	3	15.00	26	14.77	1.02	0.28–3.72	0.98
Antibiotics in 30 days prior to enrolment	17	85.00	40	22.73	19.3	5.37–69.07	<0.0001
Carbapenem[c]	5	25.00	4	2.27	14.3	3.48–59.10	0.0002
Ampicillin–sulbactam	2	10.00	11	6.25	1.67	0.34–8.12	0.53
Fluoroquinolone[d]	2	10.00	13	7.39	1.39	0.29–6.67	0.68
Cefepime	9	45.00	8	4.55	17.2	5.54–53.23	<0.0001
Ceftriaxone	3	15.00	2	1.14	15.3	2.40–98.27	0.004
Piperacillin–tazobactam	0	0.00	7	3.98	0.90	0.00–6.33	0.93
Chronic renal failure	6	30.00	21	11.93	3.16	1.10–9.13	0.03
Diabetes	6	30.00	41	23.30	1.41	0.51–3.91	0.51
Chronic obstructive pulmonary disease	4	20.00	29	16.48	1.27	0.40–4.07	0.69
Cardiovascular disease	5	25.00	41	23.30	1.10	0.38–3.20	0.86
Peripheral vascular disease	1	5.00	3	1.70	3.04	0.30–30.65	0.35
Cerebrovascular disease	3	15.00	13	7.39	2.21	0.57–8.55	0.25
Peptic ulcer disease	0	0.00	9	5.11	0.68	0–4.60	0.74
Liver disease	2	10.00	17	9.66	1.04	0.22–4.87	0.96
Malignancy	8	40.00	41	23.30	2.20	0.84–5.74	0.11
Solid organ malignancy	7	35.00	36	20.45	2.09	0.78–5.63	0.14
Transplant	1	5.00	17	9.66	0.49	0.06–3.91	0.50
Tracheostomy tube at enrolment	8	40.00	17	9.66	6.24	2.24–17.38	0.0005
Gastrostomy tube at enrolment	9	45.00	7	3.98	19.8	6.19–63.06	<0.0001
Indwelling urinary catheter at enrolment	5	25.00	25	14.20	2.01	0.67–6.03	0.21
Vascular catheter at enrolment	15	75.00	101	57.39	2.23	0.78–6.40	0.14

ICU, intensive-care unit.
[a]Median.
[b]Range.
[c]Ertapenem, imipenem, and meropenem.
[d]Ciprofloxacin, levofloxacin, and moxifloxacin.

Empirical therapy

Of the 450 patients included in the study, 329 (73.1%) received appropriate empirical antibiotic therapy. Of the 125 cases with ESBL-producing or KPC-producing organisms, 44 (35.2%) received appropriate empirical therapy, whereas 285 of 325 (87.7%) patients received appropriate therapy in the control group. Patients with bacteraemia caused by an ESBL-producing or KPC-producing organism were significantly more likely to receive inappropriate empirical antibiotic therapy than the controls (OR 13.12; 95% CI 8.00–21.50; p <0.001).

Clinical outcome

For cases whose clinical outcome 28 days after enrolment was available (n = 389), 28-day crude mortality rates for patients infected with ESBL-producing or KPC-producing organisms and controls were 29.1% (34/117) and 19.5% (53/272), respectively (OR 1.70; 95% CI 1.03–2.79; p 0.04). When cases with KPC-producing and ESBL-producing *K. pneumoniae* were compared, the 28-day crude mortality rate was 47.4% (9/19) for cases with KPC-producing *K. pneumoniae* as opposed to 27.5% (14/51) for cases with ESBL-producing *K. pneumoniae* (OR 2.38; 95% CI 0.80–7.08; p 0.12).

Predictors of mortality

Predictors of mortality were first assessed for the whole study population. The results from univariate and multivariate analyses are shown in Table 3. Independent predictors included inadequate empirical therapy (OR 2.26; 95% CI 1.18–4.34; p 0.01), bacteraemia while in the ICU (OR 2.74; 95% CI 1.47–5.11; p 0.002), Apache II score (OR 1.17; 95% CI 1.12–1.23; p <0.001), and malignancy (OR 2.66; 95% CI 1.31–5.41; p 0.007) (Table 3). Production of ESBL or KPC was a significant predictor of mortality in the univariate analysis but was not a predictor after adjustment for other confounding variables in the multivariate analysis.

The predictors of mortality were then assessed for the ESBL group. Inadequate empirical therapy (OR 6.30; 95% CI 1.64–24.3; p 0.007) and Apache II score (OR 1.14;

TABLE 3. Predictors of mortality in all patients with bacteraemia caused by *Enterobacteriaceae*

	Univariate analysis		Multivariate analysis	
Predictors of mortality	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Apache II score	1.18 (1.14–1.23)	<0.0001	1.2 (1.12–1.23)	<0.0001
Male	1.0 (0.62–1.62)	0.99	–	–
Caucasian	0.85 (0.49–1.48)	0.57	–	–
Hispanic	2.0 (0.92–4.35)	0.08	–	–
Age >60 years	1.6 (0.98–2.60)	0.06	–	–
Immunocompromised	1.2 (0.74–1.93)	0.48	–	–
Onset of bacteraemia in ICU	3.7 (2.24–6.02)	<0.0001	2.7 (1.47–5.11)	0.002
Pneumonia as a source of bacteraemia	2.1 (1.05–4.29)	0.04	–	–
Length of hospital stay before bacteraemia	1.0 (1.00–1.01)	0.33	–	–
Admitted from nursing home	1.5 (0.87–2.68)	0.14	–	–
Inadequate empirical therapy	2.5 (1.52–4.15)	0.0003	2.3 (1.18–4.34)	0.01
Production of ESBL or KPC	1.7 (1.03–2.80)	0.04	–	–
Diabetes	1.0 (0.59–1.69)	0.99	–	–
Chronic renal failure	1.1 (0.57–2.03)	0.82	–	–
Dialysis	1.0 (0.47–2.09)	0.98	–	–
Chronic obstructive pulmonary disease	1.7 (0.90–3.28)	0.10	–	–
Cardiovascular disease	1.8 (1.08–3.12)	0.02	–	–
Peripheral vascular disease	0.8 (0.16–3.61)	0.74	–	–
Cerebrovascular disease	2.2 (1.08–4.65)	0.03	–	–
Peptic ulcer disease	1.3 (0.34–5.06)	0.69	–	–
Liver disease	2.2 (1.17–4.15)	0.01	–	–
Malignancy	1.9 (1.12–3.37)	0.02	2.7 (1.31–5.41)	0.007
Solid organ malignancy	1.7 (0.92–3.00)	0.09	–	–
Transplant	0.4 (0.15–0.88)	0.02	–	–
Hospitalization in the past year	1.7 (0.90–3.17)	0.10	–	–
ICU admission in the past year	1.3 (0.79–2.12)	0.30	–	–
Any surgery in past year	0.8 (0.47–1.29)	0.33	–	–
Outpatient intravenous therapy in past year	1.3 (0.59–2.73)	0.54	–	–
Any surgery in past 30 days	1.1 (0.58–2.17)	0.73	–	–
Antibiotics with Gram-negative activity in past 30 days	1.1 (0.65–1.76)	0.80	–	–
Presence of tracheostomy tube	0.9 (0.48–1.81)	0.83	–	–
Presence of gastrostomy tube	1.1 (0.51–2.49)	0.76	–	–
Presence of indwelling urinary catheter	1.8 (1.03–3.12)	0.04	–	–
Presence of vascular catheter	0.9 (0.58–1.54)	0.83	–	–

ESBL, extended-spectrum β-lactamase; ICU, intensive-care unit; KPC, *Klebsiella pneumoniae* carbapenemase.

95% CI 1.06–1.24; p 0.0009) were independent predictors of mortality. However, when the analysis was performed for the control group, inadequate empirical therapy, which 11% of the patients received, was no longer a predictor (p 0.34). Apache II score (OR 1.24; 95% CI 1.16–1.32; p <0.001), onset of bacteraemia while in the ICU (OR 3.97; 95% CI 1.77–8.92; p <0.001) and malignancy (OR 2.62; 95% CI 1.09–6.27; p 0.03) remained as independent predictors in the control group. Mortality analysis for the KPC group was deferred because of the small number of cases.

Types of ESBL and KPC

The types of ESBL, including KPC-type β-lactamases, are summarized in Table 4. Of 29 *E. coli* cases for which isolates were available, 21 (72.4%) had CTX-M-type ESBLs, of which 11 (52%) were CTX-M-15. Only seven (24.1%) had SHV-type or TEM-type ESBLs. For 74 *Klesbiella* spp. cases for which isolates were available, 20 (27.0%) were KPC producers (all *K. pneumoniae*). They were found to produce either KPC-2 (n = 8) or KPC-3 (n = 12). Of the remaining 54 ESBL-producing, non-KPC-producing *Klesbiella* spp., isolates 47 (87.0%) and 6 (11.1%) had SHV-type and CTX-M-type ESBLs, respectively. For *Enterobacter* spp., 14 of 17 (82.4%) ESBL cases produced SHV-type ESBLs, whereas three (17.6%) produced CTX-M-type ESBLs.

TABLE 4. Types of extended-spectrum β-lactamase (ESBL) and *Klebsiella pneumoniae* carbapenemase (KPC) produced by the study isolates

	Species (number of isolates)		
ESBL	***Escherichia coli***	***Klebsiella* spp.**	***Enterobacter* spp.**
CTX-M-1 group	13	2	–
CTX-M-2 group	2	3	–
CTX-M-9 group	6	1	3
SHV	6	47	14
TEM	1	–	–
KPC	–	20	–
Others	1[a]	1[b]	–
Unknown	3	2	–
Total	32	76	17

[a]CMY-33 β-lactamase.
[b]OXY-2 β-lactamase of *Klebsiella oxytoca*.

Discussion

The emergence and spread of CTX-M-type ESBLs and KPC-type carbapenemases are the two major developments

in β-lactam resistance that have taken place in the last decade. CTX-M-type ESBLs became the predominant ESBLs in *E. coli* in many parts of the world by the early 2000s [3]. Although they were initially considered to be rare, recent reports indicate that CTX-M-type ESBLs are becoming more common in the USA as well, especially in *E. coli* [4]. KPC-type carbapenemases rapidly spread among *K. pneumoniae* strains, which have caused nosocomial outbreaks in hospitals throughout the east coast of the USA [7]. Studies from the USA that have addressed the clinical characteristics of bacteraemia caused by ESBL-producing *Enterobacteriaceae* were conducted either before the advent of these newer β-lactamases or without molecular characterization [2,11]. The present study was thus undertaken to identify the clinical features of bacteraemia caused by ESBL-producing and KPC-producing *Enterobacteriaceae* in a contemporary cohort of patients from tertiary hospitals in the northeastern USA.

Our results indicate that CTX-M-type ESBLs are now common among bacteraemic isolates of *Enterobactericeae* in this geographical area. Among *E. coli*, the majority had this group of ESBLs. About half of them had CTX-M-15, which is increasingly recognized as the most common CTX-M-type ESBL in many parts of the world [12], but the CTX-M-2 and CTX-M-9 groups, which are known to predominate in South America and Spain, respectively, were also present [3]. SHV-type and TEM-type ESBLs constituted the rest, although they were much less common than CTX-M-type ESBLs. This trend was also reported in a recent study of ESBL-producing *E. coli* conducted in Philadelphia [13]. Taking these findings together, we may assume that CTX-M-type ESBLs are now prevalent in this species in the northeastern USA. In *Klebsiella* spp. and *Enterobacter* spp., SHV was still the most common ESBL type, but CTX-M-type ESBLs were also present in both organisms. All 20 KPC-producing organisms were from the study site in New York City, where they are known to be endemic [14].

The 28-day mortality rate of patients with bacteraemia caused by organisms producing ESBL or KPC was significantly higher, at 29.1%, than in the control group, at 19.5%. This is in line with the results of a recent meta-analysis that pooled data from 16 studies and showed a significantly increased mortality rate for ESBL-associated bacteraemia [1]. The subset of patients with KPC-producing *K. pneumoniae* in our study had an even higher mortality rate, at 47.4%, as opposed to 27.5% for those with ESBL-producing *K. pneumoniae*. Although the difference was not statistically significant, probably because of the relatively small number of patients, our data strengthen the previously reported association between KPC-producing *K. pneumoniae* bacteraemia and increased mortality [14].

The independent risk factors for ESBL-associated bacteraemia included recent antibiotic use, admission from a nursing home, length of hospital stay prior to infection, chronic renal failure, presence of a gastrostomy tube, and history of transplant. Recent antibiotic use has been pointed out as an independent risk factor in multiple studies that have investigated ESBL-associated bacteraemia [11,15–18]. Admission from a nursing home has also been identified as a risk factor for ESBL production in several studies investigating bacteraemia [19–21]. The presence of a gastrostomy tube has been associated with acquisition of ESBL-producing organisms among nursing home residents [22,23], whereas chronic renal failure has not been associated with acquisition of ESBL-producing organisms.

Independent risk factors for mortality in the ESBL group included higher Apache II score at the time of positive blood culture and inappropriate empirical therapy. The association of higher Apache II score with increased mortality is not surprising and this was an independent risk factor for mortality in control cases as well. Inappropriate empirical therapy, defined by the use of antibiotic(s) that lack *in vitro* activity against the causative organism, has been identified as independent risk factor for death in ESBL-associated bacteraemia in several studies [24,25]. We may therefore speculate that the significantly increased mortality with inappropriate empirical therapy, which occurred more frequently in the ESBL and KPC groups than in the control group, contributed to the excess mortality.

Our study has several limitations. First, we analysed ESBL-producing *Enterobacteriaceae* together, not by species. The selection of controls to be in the same proportions by species as the cases helped to address some of the potential bias arising from this. Second, our analysis of the KPC cases was limited, owing to the relatively small number of cases. Finally, we were not able to associate types of ESBL with clinical attributes, because of their heterogeneity.

In conclusion, mortality associated with bacteraemia caused by ESBL-producing or KPC-producing *Enterobacteriaceae* continues to be high, despite improved detection in the clinical laboratory. CTX-M-type ESBLs are now common in *E. coli* and are also present in other species in the northeastern USA. The frequent occurrence of delay in appropriate therapy probably contributes to the excess mortality. The use of antimicrobials with activity against ESBL-producing organisms, such as carbapenems, is generally accepted as appropriate in unwell patients with risk factors. However, the advent of *K. pneumoniae* producing KPC-type carbapenemase further complicates this issue.

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Transparency Declaration

D. L. Paterson has served on advisory boards for Novartis, AstraZeneca, Merck, Johnson & Johnson, Cubist, Leo Pharmaceuticals, and Pfizer. A. Y. Peleg has acted as an advisor to Abbott Molecular and Ortho-McNeil-Janssen. B. Polsky is a member of the speakers' bureau for Ortho-McNeil. Y. Doi has served on an advisory board for Pfizer and has received research support from Merck. The other authors report no potential conflict of interest.

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