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Clinical and Economic Impact of Bacteremia with Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*

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We studied outcomes of extended-spectrum β-lactamase (ESBL) production in *Enterobacteriaceae* bacteremia. Inpatients with bacteremia caused by ESBL-producing *Escherichia coli*, *Klebsiella* spp., or *Proteus* spp. (cases) were compared with patients with bacteremia caused by non-ESBL producers (controls). Outcomes included mortality, mortality due to infection, length of stay (LOS), delay in appropriate therapy (DAT), discharge to a chronic care facility, and hospital cost. Ninety-nine cases and 99 controls were enrolled. Thirty-five percent of cases died, versus 18% of controls (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.3 to 4.7; $P = 0.01$). Thirty percent of cases died due to infection, versus 16% of controls (OR, 2.3; 95% CI, 1.1 to 4.5; $P = 0.03$). The median LOS after bacteremia for cases was 11 days (interquartile range, 5 to 21), versus 5 days for controls (interquartile range, 3 to 9) ($P < 0.001$). DAT occurred in 66% of cases, versus 7% of controls (OR, 25.1; 95% CI, 10.5 to 60.2; $P < 0.001$). Cases were more likely than controls to be discharged to chronic care (52% versus 21%; OR, 4.0; 95% CI, 1.9 to 8.3; $P < 0.001$). The average hospital cost for cases was 65,509 Israeli shekels, versus 23,538 shekels for controls ($P < 0.001$). After adjusting for differences between groups by using multivariable analysis, ESBL production remained a significant predictor of mortality (OR, 3.6; 95% CI, 1.4 to 9.5; $P = 0.008$), increased LOS (1.56-fold; $P = 0.001$), DAT (OR, 25.1; 95% CI, 10.5 to 60.2; $P < 0.001$), and increased cost (1.57-fold; $P = 0.003$). The mean increase in equivalent cost attributable to ESBL production was $9,620. ESBL production was associated with severe adverse outcomes, including higher overall and infection-related mortality, increased LOS, DAT, discharge to chronic care, and higher costs.

Extended-spectrum β-lactamases (ESBLs), which were first reported as transferable in 1983 (15), have emerged as a major source of antimicrobial resistance in gram-negative pathogens. Generally encoded by plasmid-borne genes, these enzymes confer resistance to penicillins, cephalosporins, and aztreonam (6). In addition, their presence in bacteria has been associated with resistance to other classes of nonpenicillin antibiotics, including fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and β-lactam/β-lactamase inhibitor combinations (22). Thus, ESBL-producing organisms often possess a multidrug resistance phenotype.

While broad-spectrum β-lactamase resistance among certain gram-negative bacteria has been associated with increased mortality, length of hospitalization, and hospital costs (7), few studies have directly examined the specific impact of ESBL production on patient outcomes (8, 9, 10, 16, 18, 19). ESBLs have become increasingly widespread in recent years (2, 3, 20), their detection by the clinical microbiology laboratory remains labor-intensive and costly, and susceptibility results from cultures are often delayed. Moreover, control of ESBL spread may require extensive efforts and abundant resources. Finally, treatment options for ESBL infections are limited and often are withheld from empirical use. Quantifying the effect of ESBL production is therefore important to clinicians, laboratory personnel, and hospital administrators alike in making decisions regarding resource utilization.

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We examined the health and economic outcomes for 99 patients with bacteremia caused by ESBL-producing isolates of *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp., comparing them with those for 99 control patients with bacteremia caused by non-ESBL-producing pathogens of the same genera.

MATERIALS AND METHODS

Study design. We performed a retrospective cohort study of adult inpatients at Tel Aviv Sourasky Medical Center, a 1,200-bed tertiary care academic facility, from January 2000 through December 2003. Study patients had blood cultures positive for *Escherichia coli*, *Klebsiella* spp., or *Proteus* spp. Patients with bacteremia caused by ESBL-producing bacteria were compared with patients with bacteremia caused by non-ESBL-producing bacteria. Frequency matching was performed; i.e., an identical number of patients in each group was chosen for each pathogen. Study subjects could be included only once. Although this was not a case-control study, for ease of reference we use the terms "cases" to describe patients in the ESBL bacteremia group (exposed) and "controls" to describe patients in the non-ESBL bacteremia group (unexposed).

Organism identification and susceptibility testing. Growth in blood cultures was identified using the BacT/ALERT system (bioMérieux, Inc., Durham, NC). Organism identification and antimicrobial susceptibility testing were performed using the Vitek 2 system (bioMérieux). Pathogens identified by Vitek as ESBL producers were subjected to disk diffusion testing for confirmation of the ESBL phenotype, using 30-μg cefotaxime- and ceftazidime-impregnated disks with and without 10 μg clavulanic acid (Oxoid, Basingstoke, Hampshire, England). No specific tests for AmpC production were performed. *E. coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as negative and positive controls for ESBL production, respectively. All tests were performed according to CLSI (formerly NCCLS) guidelines (6).

Data collection. Data were extracted from patients' medical records and from hospital computerized databases according to a preprepared questionnaire. Cases and controls were compared regarding demographics (age and sex), comorbid conditions (diabetes mellitus, cardiovascular disease, pulmonary disease, renal disease, hepatic disease, central nervous system disease, malignancy, prior

TABLE 1. Baseline characteristics of the cohort and univariate analysis

Characteristic	Bacteremia type			Death during hospitalization			Length of stay (days)			Delay in appropriate therapy			Cost (shekels)		
	ESBL (%) (n = 99)	Non-ESBL (%) (n = 99)	P	Deaths (%) (n = 53)	OR (95% CI)	P	Median (IQR)	ME	P	No. (%) (n = 72)	OR (95% CI)	P	Median (IQR) (n = 168)[a]	ME	P
Demographics															
Median age, yr (IQR)	76 (67–83)	78 (68–85)	0.51	79 (71–83)		0.10			0.34	76 (68–83)		0.88			0.10
Male sex	64 (65)	47 (47)	0.02	28 (53)	NS[b]	0.63	8 (4–15)	NS	0.36	44 (61)	NS	0.30	19,272 (8,030–44,805)	NS	0.35
Comorbid conditions															
Diabetes mellitus	27 (27)	33 (33)	0.44	17 (32)	NS	0.73	7 (4–15)	NS	0.91	20 (28)	NS	0.63	14,454 (8,030–26,753)	NS	0.36
Cardiovascular disease	68 (69)	75 (76)	0.34	40 (75)	NS	0.59	7 (4–14)	NS	0.08	50 (69)	NS	0.51	15,954 (8,030–30,514)	NS	0.10
Pulmonary disease	13 (13)	13 (13)	1.00	9 (17)	NS	0.35	8 (4–28)	NS	0.22	12 (17)	NS	0.28	16,060 (9,636–28,908)	NS	0.72
Renal disease	30 (30)	22 (22)	0.26	13 (25)	NS	0.86	8 (4–13)	NS	0.30	19 (26)	NS	1.00	15,954 (8,030–28,908)	NS	0.30
Hepatic disease	14 (14)	10 (10)	0.51	6 (11)	NS	1.00	7 (3–10)	NS	0.25	9 (13)	NS	1.00	24,040 (7,227–64,662)	NS	0.22
Central nervous system disease	14 (14)	12 (12)	0.83	21 (40)	18.4 (6.4–52.4)	<0.001	6 (1–14)	NS	0.18	8 (11)	NS	0.66	28,908 (17,666–61,028)	NS	0.17
Malignancy	37 (37)	32 (32)	0.55	22 (42)	NS	0.24	8 (4–16)	NS	0.45	23 (32)	NS	0.54	17,666 (8,030–38,544)	NS	0.57
Transplant	3 (3)	2 (2)	1.00	0 (0)	NS		7 (6–10)	NS	0.83	2 (3)	NS	1.00	372,360 (16,308–720,163)	5.72	0.003
>2 comorbid conditions	37 (37)	33 (33)	0.66	26 (49)	2.2 (1.2–4.2)	0.02	7 (3–14)	NS	0.26	23 (32)	NS	0.54	19,616 (8,030–38,503)	NS	0.85
Treatment and procedures before bacteremia															
Immuno suppressive therapy	18 (18)	16 (16)	0.85	10 (19)	NS	0.68	7 (3–16)	NS	0.89	13 (18)	NS	0.85	16,060 (8,030–43,362)	NS	0.40
Central venous catheter	45 (45)	20 (20)	<0.001	31 (59)	4.6 (2.4–9.0)	<0.001	14 (5–27)	1.90	<0.001	27 (38)	NS	0.35	50,803 (19,883–107,686)	3.03	<0.001
Urinary catheter	80 (81)	59 (60)	0.002	48 (91)	5.7 (2.1–15.2)	<0.001	9 (4–18)	1.54	0.008	60 (83)	3.0 (1.5–6.1)	0.002	20,878 (8,142–53,427)	1.81	0.003
Intensive care unit stay	22 (22)	8 (8)	0.009	11 (21)	NS	0.19	19 (9–40)	2.29	<0.001	13 (18)	NS	0.41	59,422 (20,908–140,262)	4.67	<0.001
Dialysis	13 (13)	4 (4)	0.04	10 (19)	4.6 (1.7–12.8)	0.004	6 (2–11)	NS	0.21	7 (10)	NS	0.79	24,090 (11,242–72,270)	NS	0.60
Instrumentation	54 (55)	26 (26)	<0.001	20 (38)	NS	0.74	10 (6–21)	1.79	<0.001	36 (50)	1.9 (1.0–3.4)	0.05	25,981 (16,060–61,028)	2.55	<0.001
Surgery	31 (31)	11 (11)	<0.001	7 (13)	NS	0.12	18 (9–32)	2.77	<0.001	20 (28)	NS	0.10	55,662 (24,344–144,810)	4.01	<0.001
Mechanical ventilation	30 (30)	11 (11)	0.001	25 (47)	7.2 (3.4–15.2)	<0.001	14 (6–32)	1.73	0.003	21 (29)	2.2 (1.1–4.4)	0.03	49,116 (22,484–117,238)	3.15	<0.001
Other															
ESBL				35 (66)	2.46 (1.3–4.7)	0.01	11 (5–21)	1.88	<0.001	65 (90)	25.1 (10.5–60.2)	<0.001	26,873 (16,060–59,463)	2.49	<0.001
Admitted from an institution	27 (27)	14 (14)	0.03	11 (21)	NS	1.00	10 (4–18)	NS	0.23	21 (29)	2.2 (1.1–4.4)	0.03	16,060 (6,424–44,805)	NS	0.39
Hospitalized in previous 3 mo	51 (52)	41 (41)	0.20	25 (47)	NS	1.00	7 (4–14)	NS	0.85	32 (44)	NS	0.77	14,454 (8,030–28,908)	NS	0.19
Nosocomial bacteremia	61 (62)	27 (27)	<0.001	35 (66)	3.4 (1.7–7.0)	<0.001	11 (6–22)	1.15	<0.001	42 (58)	2.4 (1.3–4.4)	0.005	38,646 (20,878–89,092)	3.77	<0.001
Median length of stay before bacteremia, days (IQR)	8 (1–24)	1 (1–3)	<0.001			<0.001		1.01	0.004			0.004		1.03	<0.001
Poor functional status[c]	65 (66)	46 (47)	0.01	43 (81)	4.9 (2.3–10.4)	<0.001	7 (3–17)	NS	0.92	48 (67)	2.0 (1.1–3.7)	0.03	20,878 (8,030–53,427)	NS	0.15

Recent receipt of antibiotics[d]	65 (66)	17 (17)	<0.001	32 (60)	2.9 (1.5–5.5)	0.002	11 (5–21)	1.54	0.005	43 (60)	3.3 (1.8–6.0)	<0.001	38,461 (16,060–86,724)	2.82	<0.001
High-risk source of bacteremia[e]	41 (41)	39 (39)	0.88	34 (64)	3.9 (2.0–7.5)	<0.001	6 (4–14)	NS	0.87	33 (46)	NS	0.29	20,878 (8,030–53,427)	NS	0.53
McCabe score on admission[f] (mean ± SD)	2.13 ± 0.55	1.83 ± 0.70	0.001												
High dichotomized McCabe score[g]				31 (58)	24.1 (9.8–59.3)	<0.001	7 (1–17)	NS	0.81	15 (21)	NS	0.85	27,481 (11,242–51,392)	NS	0.31

[a] Cost data were not available for all periods of patient enrollment.
[b] NS, not significant.
[c] Requiring assistance in activities of daily living.
[d] Receipt of antibiotics at time of admission or between admission and bacteremia.
[e] Lung or primary bacteremia.
[f] 1, expected to live >2 years; 2, expected to die within 2 years; 3, expected to die within 1 month.
[g] McCabe score of 3 versus McCabe score of 1 or 2.

receipt of an organ transplantation, and overall number of comorbid conditions), length of stay, treatments and procedures prior to bacteremia (immunosuppressive therapy, placement of a central venous or a urinary catheter, stay in an intensive care unit, dialysis, instrumentation [including endoscopy, laparoscopic procedures, and tracheostomy], surgery, and mechanical ventilation), and additional characteristics (admission from an institution, hospitalization in the previous 3 months, nosocomial bacteremia [acquired 3 or more days after admission], source of bacteremia [dichotomized based on our data as follows: lung or primary source classified as high risk, and all others classified as non-high risk], functional status on admission [requiring assistance in activities of daily living or not], recent receipt of antibiotics [receiving on admission and/or after admission before bacteremia], and severity of illness). A modified McCabe score was used to rank severity of illness (17). A score of 1 indicated that the patient was expected to live more than 2 more years, 2 indicated that death was expected within 2 years, and 3 indicated that death was likely within 1 month. A dichotomized McCabe score, in which scores of 1 and 2 were combined, was also used, as the relationship with the studied outcomes was nonlinear.

Outcomes studied. Cases were compared with controls for all outcomes evaluated. The primary end point studied was in-hospital mortality. In addition, we examined mortality due to infection, which was defined as active infection at the time of death and a lack of an apparent alternative cause of death. Additional outcomes evaluated were length of stay from date of blood culture to discharge or death, delay in appropriate therapy (defined as the absence of treatment with an antibiotic possessing in vitro activity against the isolated pathogen within 48 h of the blood culture draw), discharge disposition (home versus an institution) for those who survived, and cost of hospitalization. Per CLSI guidelines, treatment with penicillins and cephalosporins was considered inappropriate for all ESBL producers (6), while all other treatments (including inhibitor combinations) were evaluated individually based on the in vitro susceptibility test results for each isolate.

Statistical analysis. Normally distributed continuous variables were compared via Student's *t* test, and nonnormally distributed continuous variables were compared via the Wilcoxon rank sum test or via Student's *t* test following natural log transformation. Categorical variables were compared via Fisher's exact test.

Multivariable regression models were constructed using a stepwise procedure, incorporating variables found to be significant on univariate testing, with the exception of ESBL production, to determine additional risk factors for in-hospital mortality and delay in appropriate treatment (logistic regression) and for increased length of hospital stay and increased cost (linear regression on natural log-transformed length of stay and cost). For the multivariable models, an invasive device score was utilized, in lieu of the individual covariates of mechanical ventilation, central line, and urinary catheter. Patients requiring either mechanical ventilation or both a central line and a urinary catheter prior to bacteremia were assigned a score of 1, while all others had a score of 0.

Significant covariates identified by the selection procedure were incorporated into new regression models that included the ESBL covariate, and covariates that remained significant were included in the final regression model for each outcome. The effect estimates for length of stay and cost were reported as the multiplicative effect (ME) (the antilog of the β coefficient) (4). For ease of comparison between adjusted and unadjusted effects, odds ratios (ORs) rather than relative risks were reported in the univariate analyses of mortality and delay. For all statistical analyses, a P value of ≤ 0.05 was considered significant.

Cost analysis. The cost of the hospital stay was obtained from bills sent to the third-party payer. Therefore, this study takes the third-party payer's perspective. Costs were censored at discharge (i.e., postdischarge expenses are not included). Israeli health care is dispensed via a national system in which universal coverage is provided by several health maintenance organizations, and cost of hospitalization is determined primarily by governmental regulations through negotiations with health maintenance organizations and hospitals (http://www.health.gov.il). Thus, the bills sent to the third-party payer are in accordance with directives of the government, which estimates the cost of hospitalization related to specific procedures and length of hospital stay, without profit to the medical institution. The cost, therefore, although based on the third-party payer's perspective, is also closely reflective of the provider's, i.e., the hospital's, cost.

Generalization of findings in cost analysis requires accounting for intercountry differences in currency and health spending per capita. Therefore, comparisons of health care expenditures among cases and controls were conducted after converting costs to the equivalent U.S. health care spending (EUSHS), i.e., the amount in U.S. dollars which would comprise an equivalent portion of health care expenditure per capita in the United States. The following formula was used: the sum in Israeli shekels was divided by the average dollar exchange rate over the 4-year study period (obtained by calculating the average among the annual exchange rate averages posted by the Bank of Israel); this quotient was

then multiplied by the conversion factor for health care expenditures between Israel and the United States, which was obtained by dividing the amount of money (in dollars) spent per capita in the United States by the corresponding dollar amount in Israel (data are available from the Organisation for Economic Co-operation and Development [http://www.oecd.org] and the Israel Central Bureau of Statistics [http://www.cbs.gov.il]). For the study period, one Israeli shekel was worth EUSHS $0.717.

The attributable cost of ESBL production was assessed by subtracting the mean cost of hospitalization among the controls from the sum obtained by multiplying the mean cost among the controls by the multiplicative effect of ESBL production on cost as determined in the adjusted model. We compared the efficiency of health care spending on lives saved among cases and controls by using the following formula: the quotient of the mean cost of hospitalization among cases divided by the proportion of cases surviving (i.e., the amount spent in order to save one life in the case group), divided by the quotient of the mean cost of hospitalization among controls divided by proportion of controls surviving (i.e., the amount spent in order to save one life in the control group).

TABLE 2. Outcomes of ESBL production in multivariable analysis

Outcome	OR (95% CI) or ME	*P*
Mortality[a]	3.6 (1.4–9.5)	0.008
Length of stay[b]	1.56	0.001
Delay in appropriate therapy[c]	25.1 (10.5–60.2)	<0.001
Cost of hospitalization[d]	1.57	0.003

[a] Also significant in multivariable mortality model: >2 comorbidities (OR, 4.0; 95% CI, 1.6–10.1; $P = 0.004$), central nervous system disease (OR, 5.4; 95% CI, 1.5–19.9; $P = 0.01$), high dichotomized McCabe score (OR, 23.9; 95% CI, 7.9–72.3; $P < 0.001$), and high-risk source of bacteremia (OR, 4.3; 95% CI, 1.7–11.3; $P = 0.003$).

[b] Also significant in length-of-stay model: surgery (ME, 2.42; $P < 0.001$).

[c] No other significant factors in multivariable model.

[d] Also significant in cost model: length of stay prior to bacteremia (ME, 1.02; $P < 0.001$), surgery (ME, 2.20; $P < 0.001$), and transplant (ME, 4.5; $P = 0.001$).

RESULTS

One hundred ninety-eight patients (99 cases and 99 controls) were enrolled. Fifty-six percent of the subjects were men, and 44% were women. The average age was 74 ± 14 years. The average number of comorbid conditions was two, and the most common were cardiovascular disease (73% of patients), malignancy (34%), and diabetes mellitus (30%). The pathogen distribution was identical for cases and controls: 23% *E. coli*, 63% *Klebsiella* spp., and 14% *Proteus* spp. The sources of bacteremia were as follows: urinary tract (37%), primary bacteremia (25%), pneumonia (16%), intra-abdominal infection (15%), and line and wound infections (4% each). No differences in source of bacteremia were found between groups.

Baseline characteristics of the cohort and univariate analysis. Table 1 summarizes the baseline characteristics of the cases and controls, as well as the univariate analyses performed for each of the four outcomes evaluated by regression modeling. Cases and controls differed in sex distribution (cases, 65% male; controls, 47% male; $P = 0.02$). There were no differences in the frequency of comorbid conditions between the groups. Prior to culture more cases than controls had a central venous catheter (45% versus 20%; $P < 0.001$), a urinary catheter (81% versus 60%; $P = 0.002$), an intensive care unit stay (22% versus 8%; $P = 0.009$), dialysis (13% versus 4%; $P = 0.04$), instrumentation (55% versus 26%; $P < 0.001$), surgery (31% versus 11%; $P < 0.001$), and mechanical ventilation (30% versus 11%; $P = 0.001$).

More cases than controls were admitted from an institution rather than from home (27% versus 14%; $P = 0.03$). More had nosocomial bacteremia (62% versus 27%; $P < 0.001$). The median length of stay prior to bacteremia was greater for cases than for controls (8 days versus 1 day; $P < 0.001$). More cases than controls had poor functional status (66% versus 47%; $P = 0.01$), and more had recently received antibiotics (66% versus 17%; $P < 0.001$). Cases were sicker than controls on average (mean McCabe severity of illness score on admission for cases was 2.13, versus 1.83 for controls; $P = 0.001$), although the groups had similar proportions with a high McCabe score (22% versus 17%; $P = 0.48$).

Outcomes associated with ESBL production. Since the study groups differed substantially, control for confounding in estimating the outcomes associated with ESBL production was a critical step. Thus, for each outcome studied a multivariable model predicting the outcome was constructed, and the effect of ESBL production in these models was examined.

(i) Mortality. Fifty-three patients (35 cases and 18 controls) died during hospitalization. For 46 (30 cases and 16 controls), death was associated with the infection. In univariate analysis, bacteremia with an ESBL-producing pathogen was predictive of mortality (OR, 2.5; 95% confidence interval [CI], 1.3 to 4.7; $P = 0.01$) as well as infection-associated mortality (OR, 2.3; 95% CI, 1.1 to 4.5; $P = 0.03$). The following factors were also found to predict mortality in univariate analysis: central nervous system disease (OR, 18.4; 95% CI, 6.4 to 52.4; $P < 0.001$), more than two comorbid conditions (OR, 2.2; 95% CI, 1.2 to 4.2; $P = 0.02$), a central venous catheter (OR, 4.6; 95% CI, 2.4 to 9.0; $P < 0.001$), a urinary catheter (OR, 5.7; 95% CI, 2.1 to 15.2; $P < 0.001$), dialysis (OR, 4.6; 95% CI, 1.7 to 12.8; $P = 0.004$), mechanical ventilation (OR, 7.2; 95% CI, 3.4 to 15.2; $P < 0.001$), nosocomial bacteremia (OR, 3.4; 95% CI, 1.7 to 7.0; $P < 0.001$), length of stay before bacteremia ($P < 0.001$), poor functional status (OR, 4.9; 95% CI, 2.3 to 10.4; $P < 0.001$), recent receipt of antibiotics (OR, 2.9; 95% CI, 1.5 to 5.5; $P = 0.002$), a high-risk source of bacteremia (OR, 3.9; 95% CI, 2.0 to 7.5; $P < 0.001$), and a high McCabe score (OR, 24.1; 95% CI, 9.8 to 59.3; $P < 0.001$).

In multivariable analysis, after adjusting for confounding variables, ESBL production remained a significant predictor of mortality (OR, 3.6; 95% CI, 1.4 to 9.5; $P = 0.008$) (Table 2).

(ii) Length of stay. The median length of stay after culture was 7 days (interquartile range [IQR] 4 to 14). In univariate analysis, ESBL production was associated with increased length of stay (median, 11 days; IQR, 5 to 21; ME, 1.88; $P < 0.001$). Other univariate predictors of increased length of stay were central venous catheter (median, 14 days; IQR, 5 to 27; ME, 1.90; $P < 0.001$), urinary catheter (median, 9 days; IQR, 4 to 18; ME, 1.54; $P = 0.008$), intensive care unit stay (median, 19 days; IQR, 9 to 40; ME, 2.29; $P < 0.001$), instrumentation (median, 10 days; IQR, 6 to 21; ME, 1.79; $P < 0.001$), surgery (median, 18 days; IQR, 9 to 32; ME, 2.77; $P < 0.001$), mechanical ventilation (median, 14 days; IQR, 6 to 32; ME, 1.73; $P = 0.003$), nosocomial bacteremia (median, 11 days; IQR, 6 to 22; ME, 1.15; $P < 0.001$), length of stay before bacteremia (ME, 1.01; $P = 0.004$), and recent receipt of antibiotics (median, 11 days; IQR, 5 to 21; ME, 1.54; $P = 0.005$).

In multivariable analysis, after adjusting for confounding

variables, ESBL production remained a significant predictor of increased length of stay (ME, 1.56, $P = 0.001$) (Table 2).

(iii) Delay in appropriate therapy. A delay in appropriate therapy occurred for 72 patients (65 cases and 7 controls). In univariate analysis, ESBL production significantly predicted delay in appropriate therapy (OR, 25.1; 95% CI, 10.5 to 60.2; $P < 0.001$). Other univariate predictors of delay in appropriate therapy included urinary catheter (OR, 3.0; 95% CI, 1.5 to 6.1; $P = 0.002$), instrumentation (OR, 1.9; 95% CI, 1.0 to 3.4; $P = 0.05$), mechanical ventilation (OR, 2.2; 95% CI, 1.1 to 4.4; $P = 0.03$), admission from an institution (OR, 2.2; 95% CI, 1.1 to 4.4; $P = 0.03$), nosocomial bacteremia (OR, 2.4; 95% CI, 1.3 to 4.4; $P = 0.005$), length of stay before bacteremia ($P = 0.004$), poor functional status (OR, 2.0; 95% CI, 1.1 to 3.7; $P = 0.03$), and recent receipt of antibiotics (OR, 3.3; 95% CI, 1.8 to 6.0; $P < 0.001$).

In multivariable analysis, after adjusting for confounding variables, ESBL production remained a significant predictor of delay in appropriate therapy (OR, 25.1; 95% CI, 10.5 to 60.2; $P < 0.001$) (Table 2).

(iv) Discharge to a chronic care facility. Of the 145 patients who survived their bacteremia, 50 (34%) were discharged to a chronic care facility (33 cases and 17 controls). Bacteremia with an ESBL-producing pathogen was significantly associated with discharge to chronic care (OR, 4.0; 95% CI, 1.9 to 8.3; $P < 0.001$).

(v) Cost of hospitalization. Cost data were not available for all portions of the study period; as a result, the cost analysis included 72 cases and 96 controls. The average cost of hospitalization for the cohort was 41,526 shekels (EUSHS $29,774). The median cost for one day of hospitalization was 1,600 shekels (EUSHS $1,147). The average cost for cases was 65,509 shekels (EUSHS $46,970), and that for controls was 23,538 shekels (EUSHS $16,877). In univariate analysis, ESBL production was significantly associated with increased cost of hospitalization (ME, 2.49; $P < 0.001$). Other univariate predictors of increased cost were prior transplant receipt (ME, 5.72; $P < 0.001$), central venous catheter (ME, 3.03; $P < 0.001$), urinary catheter (ME, 1.81; $P = 0.003$), intensive care unit stay (ME, 4.67; $P < 0.001$), instrumentation (ME, 2.55; $P < 0.001$), surgery (ME, 4.01; $P < 0.001$), mechanical ventilation (ME, 3.15; $P < 0.001$), nosocomial bacteremia (ME, 3.77; $P < 0.001$), length of stay before bacteremia (ME, 1.03; $P < 0.001$), and recent receipt of antibiotics (ME, 2.82; $P < 0.001$).

In multivariable analysis, after adjusting for confounding variables, ESBL production remained a significant predictor of cost of hospitalization (ME, 1.57; $P = 0.003$) (Table 2).

The average increase in cost of hospitalization attributable to ESBL production was 13,417 shekels (EUSHS $9,620). The average cost per life saved among cases was 56,853 shekels (EUSHS $40,764), versus 28,705 shekels (EUSHS $20,581) among controls (ratio, 2:1).

DISCUSSION

The implementation of measures to combat resistance and the development of treatment strategies to overcome the adverse consequences of resistance, i.e., early and accurate identification of patients at risk of resistance and effective antibiotic therapy, may require substantial resources. Hence, there is a need to quantify the effect of ESBL production on clinical and economic outcomes. In doing so, our main challenge was that patients with bacteremia caused by ESBL-producing *Enterobacteriaceae* were substantially different from the comparison group, patients with non-ESBL-associated bacteremia. While a comparison between these groups is required in order to determine the attributable adverse effects of ESBL production, without eliminating the effects of intergroup differences on patient outcomes, the purported effect of ESBL production on patient outcomes may be incorrect.

When facing such a challenge, an investigator has several options. The first is to restrict the analysis to a comparison between the study group and a control group with very similar characteristics (e.g., only those who acquired the infection in an intensive care unit). Another option is matching, an intuitively appealing method by which the investigator compares groups of "twin" patients who are very similar to each other (e.g., having the same age and same length of stay) but differ regarding the variable of interest. Both of these options may result in substantially limited sample sizes, however.

We chose a third method, adjusting for differences between groups by using multivariable analysis. This method uses computerized algorithms to perform multiple stratified analyses and combine the results of these analyses into one model that adjusts for the effects of the differences between groups. This method is very efficient yet is not intuitively understood, and it may leave the reader questioning whether the measures taken were sufficient to overcome the intergroup differences.

In designing our analysis we made an extensive effort to overcome these differences. Since our study question involved the specific contribution of ESBLs to outcomes of bacteremic infections in hospitalized adults, the proper choice of controls was hospitalized adults with non-ESBL bacteremia (13). We collected detailed data on prebacteremia patient characteristics, procedures, and exposures. We then performed multivariable analyses, and only after generating models that accounted for the independent risk factors for the outcomes studied did we measure in these models the effect of ESBL production. While residual confounding is always a theoretical possibility, we believe that we have made the best possible effort to control for it and that given the number of study participants, our approach addresses the questions raised in the most comprehensive and bias-free manner possible.

After controlling for confounding, we have demonstrated that ESBL production in *Enterobacteriaceae* bacteremia is associated with severe adverse clinical and economic outcomes. Compared to *Enterobacteriaceae* bacteremia involving ESBL nonproducers, ESBL production was associated with an adjusted 3.6-fold-increased risk of in-hospital mortality, an unadjusted 2.3-fold-increased risk of infection-related mortality, an adjusted 1.6-fold increase in length of stay, an adjusted 25-fold-increased risk of delay in appropriate therapy, and an unadjusted 4-fold-increased likelihood of discharge to a chronic care facility for those who survived.

The effect of ESBL production on cost of care was considerable: ESBL production was associated with an adjusted 1.6-fold increase in cost of hospitalization, with an average additional cost of 13,417 shekels, equivalent to U.S. health care spending of almost $10,000 per patient, attributable to ESBL production alone. The amount of money spent per life saved

among patients with ESBL-associated bacteremia was twice that among patients with non-ESBL-associated bacteremia. Thus, strategies currently used to treat patients with ESBL bacteremia are inefficient and need to be revised. New strategies should include facilitating diagnosis and reporting of ESBL production, revising empirical therapy choices, and improving definitive treatment.

The literature regarding outcomes of infection with ESBL-producing organisms is conflicting and incomplete. Although some studies have identified no deleterious effect of ESBL production on patients' ultimate outcomes (5, 11), most studies to date have provided evidence linking serious infection caused by ESBL-producing organisms with adverse sequelae, including death, increased length of stay, and increased hospital charges, in part due to the association between ESBL production and delays in appropriate therapy. However, small sample sizes and the mixing of various clinical syndromes have limited the ability of prior investigators to examine a range of outcomes while controlling for confounding variables, and the economic impact of ESBL infection has scarcely been evaluated (1, 8, 9, 10, 12, 14, 16, 18, 19, 21).

Our study comprises the largest controlled analysis of ESBL-associated bacteremia outcomes performed to date. The relatively large size of our cohort permitted control for confounding variables through multivariable analysis, as well as the assessment of multiple clinical and economic outcomes. We have shown that ESBL production in *Enterobacteriaceae* bacteremia is independently associated with a variety of adverse clinical outcomes and with a substantially increased cost of care.

Our study is among the first to estimate the economic impact of resistance outside the United States. We were confronted with the problem of reporting an estimate of cost that could be compared to the existing literature from the United States. To do so we used the equivalent U.S. health care spending (EUSHS). We recommend using this conversion formula in future studies examining the economic impact of resistance in non-U.S. populations, to allow for intercountry comparisons.

Our study has a few limitations. As we had data regarding the hospitalization period only, we were able to analyze in-hospital mortality only. Future studies analyzing mortality after discharge as well are warranted. Also, due to sample size limitations, we combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in our analysis. We believe it is reasonable to assume that these organisms behave similarly in bacteremic patients. Future studies with larger sample sizes might enable analysis at the level of the individual organism or the individual ESBL type.

Our findings reinforce the urgency of efforts to prevent the spread of ESBL-producing bacteria. Interventions geared towards improving methods for early identification of ESBL-producing bacteria, identifying patient populations at high risk for infection with ESBL producers, and, finally, improving treatment strategies and expanding therapeutic options are greatly needed.

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REFERENCES

1. **Ariffin, H., P. Navaratnam, M. Mohamed, A. Arasu, W. A. Abdullah, C. L. Lee, and L. H. Peng.** 2000. Ceftazidime-resistant Klebsiella pneumoniae bloodstream infection in children with febrile neutropenia. Int. J. Infect. Dis. **4:**21–25.
2. **Bradford, P. A.** 2001. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin. Microbiol. Rev. **14:**933–951, table of contents.
3. **Bush, K.** 2001. New beta-lactamases in gram-negative bacteria: diversity and impact on the selection of antimicrobial therapy. Clin. Infect. Dis. **32:**1085–1089.
4. **Carmeli, Y., N. Troillet, A. W. Karchmer, and M. H. Samore.** 1999. Health and economic outcomes of antibiotic resistance in Pseudomonas aeruginosa. Arch. Intern. Med. **159:**1127–1132.
5. **Carretto, E., V. Emmi, D. Barbarini, F. Capra Marzani, A. Bolongaro, A. Braschi, and P. Marone.** 2004. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in an Italian intensive care unit: clinical and therapeutical remarks. J. Chemother. **16:**145–150.
6. **Clinical and Laboratory Standards Institute.** 2005. Performance standards for antimicrobial susceptibility testing; fifteenth informational supplement. M100S15. Clinical and Laboratory Standards Institute, Wayne, Pa.
7. **Cosgrove, S. E., and Y. Carmeli.** 2003. The impact of antimicrobial resistance on health and economic outcomes. Clin. Infect. Dis. **36:**1433–1437.
8. **Du, B., Y. Long, H. Liu, D. Chen, D. Liu, Y. Xu, and X. Xie.** 2002. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. Intensive Care Med. **28:**1718–1723.
9. **Endimiani, A., F. Luzzaro, G. Brigante, M. Perilli, G. Lombardi, G. Amicosante, G. M. Rossolini, and A. Toniolo.** 2005. *Proteus mirabilis* bloodstream infections: risk factors and treatment outcome related to the expression of extended-spectrum beta-lactamases. Antimicrob. Agents Chemother. **49:**2598–2605.
10. **Ho, P. L., W. M. Chan, K. W. Tsang, S. S. Wong, and K. Young.** 2002. Bacteremia caused by Escherichia coli producing extended-spectrum beta-lactamase: a case-control study of risk factors and outcomes. Scand. J. Infect. Dis. **34:**567–573.
11. **Kang, C. I., S. H. Kim, D. M. Kim, W. B. Park, K. D. Lee, H. B. Kim, M. D. Oh, E. C. Kim, and K. W. Choe.** 2004. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. Infect. Control Hosp. Epidemiol. **25:**860–867.
12. **Kang, C. I., S. H. Kim, W. B. Park, K. D. Lee, H. B. Kim, M. D. Oh, E. C. Kim, H. S. Lee, and K. W. Choe.** 2004. Clinical outcome of bacteremic spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Korean J. Intern. Med. **19:**160–164.
13. **Kaye, K. S., J. J. Engemann, E. Mozaffari, and Y. Carmeli.** 2004. Reference group choice and antibiotic resistance outcomes. Emerg. Infect. Dis. **10:**1125–1128.
14. **Kim, Y. K., H. Pai, H. J. Lee, S. E. Park, E. H. Choi, J. Kim, J. H. Kim, and E. C. Kim.** 2002. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. Antimicrob. Agents Chemother. **46:**1481–1491.
15. **Knothe, H., P. Shah, V. Krcmery, M. Antal, and S. Mitsuhashi.** 1983. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of Klebsiella pneumoniae and Serratia marcescens. Infection **11:**315–317.
16. **Lautenbach, E., J. B. Patel, W. B. Bilker, P. H. Edelstein, and N. O. Fishman.** 2001. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. Clin. Infect. Dis. **32:**1162–1171.
17. **McCabe, W., and G. Jackson.** 1962. Gram-negative bacteremia. Arch. Intern. Med. **110:**847–855.
18. **Panhotra, B. R., A. K. Saxena, and A. M. Al-Ghamdi.** 2004. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia. Risk factors and clinical outcome. Saudi Med. J. **25:**1871–1876.
19. **Park, Y. H., H. C. Lee, H. G. Song, S. Jung, S. H. Ryu, J. W. Shin, Y. H. Chung, Y. S. Lee, and D. J. Suh.** 2003. Recent increase in antibiotic-resistant microorganisms in patients with spontaneous bacterial peritonitis adversely affects the clinical outcome in Korea. J. Gastroenterol. Hepatol. **18:**927–933.
20. **Paterson, D. L., W. C. Ko, A. Von Gottberg, S. Mohapatra, J. M. Casellas, H. Goossens, L. Mulazimoglu, G. Trenholme, K. P. Klugman, R. A. Bonomo, L. B. Rice, M. M. Wagener, J. G. McCormack, and V. L. Yu.** 2004. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann. Intern. Med. **140:**26–32.
21. **Schiappa, D. A., M. K. Hayden, M. G. Matushek, F. N. Hashemi, J. Sullivan, K. Y. Smith, D. Miyashiro, J. P. Quinn, R. A. Weinstein, and G. M. Trenholme.** 1996. Ceftazidime-resistant Klebsiella pneumoniae and Escherichia coli bloodstream infection: a case-control and molecular epidemiologic investigation. J. Infect. Dis. **174:**529–536.
22. **Schwaber, M. J., S. Navon-Venezia, D. Schwartz, and Y. Carmeli.** 2005. High levels of antimicrobial coresistance among extended-spectrum-beta-lactamase-producing *Enterobacteriaceae*. Antimicrob. Agents Chemother. **49:**2137–2139.