National Multicenter Study of Predictors and Outcomes of Bacteremia upon Hospital Admission Caused by *Enterobacteriaceae* Producing Extended-Spectrum β -Lactamases[∇]

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Extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae* are pathogens that may lead to a spectrum of clinical syndromes. We aimed to identify predictors and outcomes of ESBL bacteremia upon hospital admission (UHA) in a nationwide prospective study. Thus, a multicenter prospective study was conducted in 10 Israeli hospitals. Adult patients with bacteremia due to *Enterobacteriaceae* diagnosed within 72 h of hospitalization were included. Patients with ESBL producers (cases) were compared to those with non-ESBL producers (controls), and a 1:1 ratio was attempted in each center. A case-control study to identify predictors and a cohort study to identify outcomes were conducted. Bivariate and multivariate logistic regressions were used for analyses. Overall, 447 patients with bacteremia due to *Enterobacteriaceae* were recruited: 205 cases and 242 controls. Independent predictors of ESBL were increased age, multiple comorbid conditions, poor functional status, recent contact with health care settings, invasive procedures, and prior receipt of antimicrobial therapy. In addition, patients presenting with septic shock and/or multiorgan failure were more likely to have ESBL infections. Patients with ESBL producers suffered more frequently from a delay in appropriate antimicrobial therapy (odds ratio [OR], 4.7; P , <0.001) and had a higher mortality rate (OR, 3.5; P , <0.001). After controlling for confounding variables, both ESBL production (OR, 2.3; P , 9.1) and a delay in adequate therapy (OR, 0.05; P , 0.001) were significant predictors for mortality and other adverse outcomes. We conclude that among patients with bacteremia due to *Enterobacteriaceae* UHA, those with ESBL producers tend to be older and chronically ill and to have a delay in effective therapy and severe adverse outcomes. Efforts should be directed to improving the detection of patients with ESBL bacteremia UHA and to providing immediate appropriate therapy.

Enterobacteriaceae producing extended-spectrum β -lactamases (ESBL) pose a major worldwide threat (27). These pathogens are resistant to all penicillins and cephalosporins and often are coresistant to multiple other classes of antibiotics (2). Thus, therapeutic options to treat infections with these pathogens are limited (27). The Infectious Diseases Society of America has listed ESBL-producing *Enterobacteriaceae* as pathogens necessitating the urgent development of new and novel therapeutics (37). While infections caused by ESBL-producing strains have been acquired primarily in hospitals and health care institutions, recent reports from multiple parts of the world show that these pathogens now have a role in community-acquired infections as well (2, 3, 5, 6, 8, 9, 12, 15,

19, 27, 29, 30, 32, 38). The burden of these infections is enormous, and compared to bacteremia caused by non-ESBL-producing *Enterobacteriaceae*, infections caused by ESBL producers are associated with a significantly higher mortality rate, 6 additional days of hospitalization, and approximately \$10,000 in additional costs per case (35, 36).

There are no official guidelines to direct the management of these infections, and comparative clinical trials are scarce (27). Since patients with serious infections upon hospital admission are frequently treated empirically with antibiotic agents to which ESBL-producing strains are resistant (e.g., cephalosporins, penicillins, and frequently quinolones), patients with ESBL bacteremia upon hospital admission may suffer from a delay in appropriate therapy, a modifiable factor significantly associated with mortality (20). Therefore, early identification of this group of patients by stratifying predictors may improve empirical treatment and, in turn, reduce mortality and morbidity. Predictors of ESBL carriage or infection in nonhospita-

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talized patients have been evaluated in several studies, whose results were recently summarized in a metanalysis (1). Risk factors and outcomes of ESBL bacteremia have also been examined previously (2, 3, 7, 13–15, 17, 18, 24–26, 28, 31, 32, 35, 36). However, the clinically important questions—which factors can predict ESBL bacteremia upon hospital admission, and what the outcomes of these infections are—have not yet been specifically addressed.

The changing epidemiology of Gram-negative bacteremia upon hospital admission, due to the worldwide spread of ESBLs in nonhospitalized patients (27, 32), may have a significant impact on clinical practice. We therefore conducted a nationwide prospective multicenter investigation in Israel to define the predictors and outcomes of ESBL bacteremia among patients with bacteremia due to *Enterobacteriaceae* upon hospital admission.

MATERIALS AND METHODS

Ethics and study settings. All 11 Infectious Disease units in Israel operating in large (>500-bed) hospitals were invited to participate in the study, and 10 acceded. The study was approved by the Institutional Review Board of each of the 10 participating centers. All patients were coded and deidentified locally, and data were then forwarded to be analyzed centrally. Patients were recruited from 1 November 2006 through 29 February 2008.

Study design. A prospective multicenter study was conducted, comparing two patient groups with bacteremia due to *Enterobacteriaceae* upon hospital admission: patients with ESBL-producing strains and patients with non-ESBL-producing strains. We included only adults (>18 years old) hospitalized for less than 72 h from the time when the blood culture that yielded the target organism was obtained. The Division of Epidemiology at Tel-Aviv Sourasky Medical Center served as the study coordinating center, where questionnaires were developed and data were gathered, processed, and analyzed. Participating centers were instructed to recruit patients with bacteremia due to *Enterobacteriaceae* upon hospital admission, aiming to recruit patients to each group at a 1:1 ratio. To avoid selection bias, centers were asked to recruit patients consecutively. Data were collected at each study site by using a preprepared data collection tool and included demographics (age, sex), microbiological parameters (name of organism, antimicrobial susceptibility profile, ESBL phenotypic test result), functional status before admission (based on Katz criteria [16]), comorbid conditions (Charlson's index [10] and McCabe score [4]), chronic medications, parameters for the severity of underlying infectious illness, the suspected organ source of the bacteremia, exposure to immunosuppressants (21) or conditions of immunosuppression (21), recent antibiotic usage, invasive devices or procedures, time to initiation of appropriate antimicrobial therapy, and various outcome parameters (length of hospitalization, functional deterioration following the infection, discharge disposition, in-hospital mortality, and infection-related mortality [defined as mortality where the symptoms and signs of infection had not resolved at the time of death and there was no other obvious cause of death]). Antimicrobial therapy was defined as appropriate or adequate if an agent with an *in vitro* activity for a specific isolate was administered to the patient, not including penicillins, cephalosporins, or monobactams, or aminoglycosides if given alone for a non-urinary-tract infection. We collected data on whether patients were hospitalized in the previous month or were referred from a health care institution, in order to define their infections as health care associated versus community acquired. The completed questionnaires were sent to the coordinating center for further analysis.

Microbiology. All the bacteriology laboratories participating in the study routinely follow the international guidelines published annually by the Clinical and Laboratory Standards Institute (CLSI) (11). Bacteria were isolated from blood cultures according to local routines in each medical center. All participating hospitals use automated blood culture incubators.

Organisms were identified to the species level according to CLSI criteria in each center (11). *Escherichia coli*, *Klebsiella* spp., and *Proteus mirabilis* were tested for ESBL production phenotypically by assessing susceptibility to ceftazidime, ceftioxone, or cefotaxime, with and without clavulanate, according to one of the CLSI-recommended methodologies (disk diffusion or a broth-based method) (11). Those bacteria for which CLSI has defined criteria for determining ESBL production—*E. coli*, *Klebsiella* spp., and *P. mirabilis*—were included

(11). In 31 cases in which ESBL production was not reported, we used resistance to ceftioxone as a marker for ESBL production, since in a previous pilot study in Israel, among 100 isolates of the bacterial species listed above, this marker proved to have $\geq 95\%$ sensitivity and specificity for ESBL production (D. Marchaim et al., unpublished data).

Statistical analysis. Several analyses were performed, in line with the study aims. The analysis performed to define predictors of having an ESBL-producing strain as the causative pathogen, among patients with bacteremia due to *Enterobacteriaceae*, examined variables that may be known to the clinician at the time of admission. This analysis was done not in an attempt to suggest causality but rather to identify markers that may help the clinician to predict ESBL production. Conversely, the analyses performed to examine the outcomes of the infection, e.g., mortality, deterioration of functional status, and need to discharge the patient to a long-term care facility (LTCF), were designed to examine both the role of ESBL production and the role of adequate empirical therapy in determining outcomes. These terms were therefore “forced” into each of the multivariate outcome models, both together and separately.

SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL) was used for all analyses. Continuous variables were compared between groups using an unpaired *t* test, while a paired *t* test was employed for comparisons within groups. Categorical parameters were compared using the Pearson χ^2 test. *P* values of ≤ 0.05 were considered indicators of a significant difference between groups. Logistic regression models were constructed in order to conduct the multivariate analyses. All variables that were found to have a statistically significant association with the dependent variable in the bivariate analysis were introduced into the multivariate model. Variables were selected to remain in the model by using a stepwise selection process.

RESULTS

Overall, 447 patients with *E. coli*, *Klebsiella* spp., or *Proteus mirabilis* bacteremia were recruited from 10 hospitals distributed throughout Israel: 205 patients with ESBL-producing strains and 242 patients with non-ESBL-producing strains. The overall median age of patients was 78 years (range, 20 to 101 years); 52% were females; 29% were admitted from institutions; and 58% were dependent in daily activities. A comparison of the two groups is presented in Table 1. Patients with ESBL-producing strains were significantly older, and a larger proportion were debilitated and institutionalized, with multiple comorbidities. In addition, they had more frequently been exposed to recent medical procedures and health care-associated devices and environments, were more likely to have been exposed to health care settings recently, presented with parameters indicating greater severity of infectious illness, and were more frequently exposed to antibiotics prior to hospitalization. Parameters that were not associated with ESBL infection included immunosuppressive states or exposure to immunosuppressants, present or past malignancy, the organ source of the bacteremia, a surgical versus a medical main admission diagnosis, and chronic medications.

The multivariate analysis of predictors of ESBL bacteremia upon hospital admission is shown in Table 2. Independent predictors were increased age, multiple comorbid conditions, poor functional status, recent contact with health care settings, invasive procedures, and receipt of antimicrobial treatment. In addition, patients presenting with septic shock and/or multiorgan dysfunction were more likely to have ESBL infections.

We examined whether exposure to a specific class of antibiotics prior to the present infection may be associated with the development of an infection due to an ESBL-producing strain. This was done by replacing the covariate “admitted on antibiotics,” in the model presented in Table 2, with the antibiotic under evaluation. Exposure to β -lactam agents (odds ratio [OR], 2.7; *P*, <0.001) and to fluoroquinolones (OR, 2.6; *P*,

TABLE 1. Bivariate analysis of predictors and outcomes of ESBL-producing *Enterobacteriaceae*

Parameter ^a	Value ^b for patients with:		Odds ratio (95% confidence interval)	P
	ESBL producers	Non-ESBL producers		
Demographic parameters				
Adult mean age (yr)	78.1 ± 13.8	71 ± 17		<0.001
Male sex	109 (53)	103 (43)	1.5 (1.1–2.2)	0.02
Pathogen				
<i>Escherichia coli</i>	128 (62)	177 (73)		
<i>Klebsiella</i> spp.	50 (24)	47 (20)		
<i>Proteus mirabilis</i>	26 (13)	19 (8)		
Background parameters				
Independent functional status	37 (18)	145 (59.9)	6.6 (4.3–10.3)	<0.001
Long-term-care facility residency	99 (48)	32 (13)	6.13 (3.9–9.7)	<0.001
Health care-associated acquisition of pathogen	144 (70)	77 (32)	5.1 (3.4–7.6)	<0.001
Chronic skin ulcers	42 (21)	16 (7)	3.6 (1.97–6.67)	<0.001
McCabe score at admission ^c	2 ± 0.8	2.4 ± 0.8		0.003
Myocardial infarction	46 (22)	34 (14)	1.77 (1.1–2.9)	0.02
Congestive heart failure	46 (22)	33 (14)	1.8 (1.12–3)	0.015
Peripheral vascular disease	21 (10)	11 (4.5)	2.4 (1.13–5.1)	0.02
Chronic renal disease	68 (33)	49 (20)	1.96 (1.28–3)	0.002
Chronic neurological disease	77 (38)	47 (19)	2.5 (1.6–3.8)	<0.001
Hemiplegia	31 (15)	14 (5.8)	2.9 (1.5–5.6)	0.001
Dementia	94 (46)	38 (16)	4.5 (2.9–7)	<0.001
Overall no. of comorbidities (mean)	3 ± 1.8	2 ± 1.5		<0.001
Hospitalization in past 3 mo	128 (63)	76 (32)	3.6 (2.4–5.3)	<0.001
LOS in preceding yr (mean days)	10.3 ± 12.3	6.4 ± 5.5		<0.001
Invasive procedure ^d or surgery in the past yr	84 (44)	54 (24)	2.5 (1.7–3.9)	0.001
Chronic/permanent invasive devices ^e	68 (33)	32 (13)	3.3 (2–5.2)	<0.001
Present illness parameters				
Reduced consciousness at admission	97 (49)	56 (23)	3.2 (2.1–4.8)	<0.001
Shock or MOF at ER	59 (29)	27 (11)	3.2 (1.9–5.3)	<0.001
Antimicrobial parameters				
Admitted on antibiotics	63 (31)	37 (15)	2.5 (1.6–3.9)	<0.001
Received antibiotics in the past 3 mo	125 (64)	60 (26)	4.9 (3.2–7.4)	<0.001
β-Lactams	82 (40)	34 (14)	4.1 (2.6–6.5)	<0.001
Fluoroquinolones	49 (24)	19 (8)	3.7 (2.1–6.4)	<0.001
Other ^f antibiotic	39 (19)	7 (3)	7.8 (3.4–18)	<0.001
Outcome parameters				
Hours to appropriate therapy (mean)	37 ± 40	12.8 ± 28		<0.001
Appropriate therapy administered in <48 h	71 (44)	95 (79)	4.7 (2.8–8)	<0.001
Length of hospitalization (days)	25 ± 156.4	13.25 ± 48.67		0.27
Discharged to long-term care facilities ^g	60 (47)	29 (15)	5 (3–8.4)	<0.001
Deteriorated functional status v. status on admission	100 (78)	75 (40)	5.4 (3.3–9)	<0.001
Mortality	55 (30)	23 (11)	3.5 (2.1–6.1)	<0.001

^a LOS, length of the hospital stay if the patient was hospitalized in the preceding year; MOF, multiorgan failure; ER, emergency room.

^b Unless otherwise indicated, values are numbers (percentages) of patients with the parameter. For all parameters except outcome parameters, data were collected from 205 patients with ESBL producers and 242 patients with non-ESBL producers. For outcome parameters, data were collected from 185 patients with ESBL producers and 216 patients with non-ESBL producers.

^c See reference 4. A higher score indicates a better prognosis.

^d Endoscopies, urinary catheterization, any percutaneous procedure (central venous catheter insertion, external biliary drainage, thoracocentesis, etc.), tracheotomy, and more.

^e Central venous catheter, tracheotomy, urinary catheter, gastrostomy, or external fixator.

^f Any class of antibiotic other than β-lactams, fluoroquinolones, trimethoprim-sulfamethoxazole, or macrolides.

^g Only among those discharged alive, who were not residents of long-term care facilities before the current admission.

0.006) remained significant predictors in the multivariate model.

Outcomes were recorded for 401 patients with bacteremia. In the bivariate analysis, as depicted in Table 1, patients with ESBL producers were prone to suffer from a delay in appropriate antimicrobial therapy, and their infections were associated with worse outcomes as measured by multiple parameters.

Overall, 102 patients in the ESBL group had delays of more than 72 h in the initiation of appropriate therapy, versus 56 patients in the non-ESBL group (50% versus 33%; P , <0.001 for the difference between groups). Both in-hospital mortality and infection-related mortality were higher among the ESBL group than among the non-ESBL group (30% versus 11% [P , <0.001] and 18% versus 7% [P , <0.001], respectively). We

TABLE 2. Multivariate analysis of predictors for ESBL bacteremia upon hospital admission^a

Variable ^b	Odds ratio	P	95% Confidence interval
Older age	1.8	0.03	1.1–3.1
>2 comorbidities	1.5	0.001	1.2–1.8
Dependent functional status	2.04	<0.001	1.43–2.94
Long-term care facility residency	3	0.001	1.6–5.6
Hospitalization in past 3 mo	1.5	<0.001	1.3–1.8
Admitted on antibiotics	2.4	0.003	1.4–4.4
Invasive procedure or surgery ^c in past yr	1.4	<0.001	1.2–1.6
Shock or MOF at ER	3.1	<0.001	1.6–5.7

^a Data for 447 patients were collected.^b MOF, multiorgan failure; ER, emergency room.^c Any surgery or invasive procedure in the past year, such as endoscopy, any percutaneous procedure (central line insertion, external biliary drainage, or thoracentesis, etc.), tracheotomy, and others.

constructed multivariate models for overall mortality, deteriorated functional status, and discharge to an LTCF (Tables 3, 4, and 5). The ESBL phenotype remained a significant independent predictor associated with each one of these adverse outcomes. Since ESBL leads to inadequate therapy, we examined the effect of ESBL with and without including inadequate therapy in the models. outcomes, The ESBL phenotype remained significantly associated with each of these outcomes, indicating that the adverse effect of ESBL on outcomes is not explained merely by their resulting in inadequate therapy.

DISCUSSION

Enterobacteriaceae cause more than 90% of Gram-negative bacteremia cases upon hospital admission (34). Among patients admitted to Israeli hospitals with sepsis, *Enterobacteriaceae* constitute the most common pathogens (22). A high proportion of ESBL producers have been reported among Israeli isolates of *E. coli*, *Klebsiella* spp., and *Proteus mirabilis*, reaching 14%, 45%, and 33%, respectively (23). These ESBL-producing strains are almost invariably multidrug resistant, with extremely high rates of coresistance to trimethoprim-sulfamethoxazole, fluoroquinolones, aminoglycosides, and beta-lactam/

TABLE 4. Multivariate analysis of deteriorated functional status following bacteremia due to *Enterobacteriaceae*^a

Variable ^b	Odds ratio	P	95% Confidence interval
ESBL production ^c	2.5	0.02	1.11–5
Inappropriate Rx for ≥ 48 h ^c	0.99	0.1	0.98–1.002
Low McCabe score ^d	2.7	<0.001	1.8–4.1
Reduced consciousness at ER	4	0.001	1.8–9.1
Severe sepsis criteria at ER	2.5	0.05	1.1–6.4
Older age (yr)	1.08	<0.001	1.05–1.1

^a Data for 401 patients were collected.^b Rx, therapy; ER, emergency room.^c The OR of ESBL production changed to 1.7 ($P = 0.04$) when inappropriate therapy was excluded from the model, and the OR of inappropriate therapy changed to 1.03 ($P = 0.06$) when ESBL production was excluded from the model.^d See reference 4. A lower score indicates a worse prognosis.

beta-lactamase inhibitors (12, 36). While ESBL producers have been considered primarily hospital pathogens (6), over the past decade they have become common in other health care settings as well (2, 32). Reports from various parts of the world over the past 5 years demonstrate the spread of ESBL-producing strains into community settings, not infrequently leading to community-acquired infections (2, 28), affecting ambulatory and previously healthy adults (27, 29). In a recent metasynthesis of studies evaluating risk factors for ESBL infections in nonhospitalized patients, 30% of these infections were found to occur in patients without recent contact with the health care setting, or without recent antibiotic exposure (1).

This national multicenter prospective investigation focused on bacteremia upon hospital admission. We chose to study this clinical syndrome for several reasons. (i) It is a relatively frequent event, and it may be the consequence of infections at various sites. (ii) It has severe outcomes if treated with inappropriate empirical therapy; thus, it is of great importance to identify accurately patients at risk for infections with resistant organisms in order to prescribe adequate empirical therapy. (iii) Because bacteremic patients are always infected, there is no need to distinguish between colonized and infected patients in the study cohort.

The scientific literature still lacks a report focused on these infections in this particular population. While a metasynthesis analyzing risk factors for ESBL infections in nonhospitalized

TABLE 3. Multivariate analysis of mortality^a

Variable ^b	Odds ratio	P	95% Confidence interval
ESBL production ^c	2.3	0.048	1.07–4.8
Inappropriate Rx for ≥ 48 h ^c	9.1	0.001	2.44–33.3
Low McCabe score ^d	2.5	<0.001	1.67–5
Dependent functional status	2.9	0.04	1.1–8.3
LTCF residency	2.5	0.05	1.05–5
Reduced consciousness at ER	3.1	0.004	1.5–6.8
Shock or MOF at ER	2.5	0.03	1.1–5.6

^a Data for 401 patients were collected.^b Rx, therapy; LTCF, long-term care facility; ER, emergency room; MOF, multiorgan failure.^c Since ESBL is an important predictor of inappropriate therapy, we examined their effects independently of each other: The OR of ESBL production changed to 2.76 ($P = 0.008$) when inappropriate therapy was excluded from the model, and the OR of inappropriate therapy changed to 11.4 ($P < 0.001$) when ESBL production was excluded from the model.^d See reference 4. A lower score indicates a worse prognosis.TABLE 5. Multivariate analysis of discharge to a long-term care facility following an episode of bacteremia due to *Enterobacteriaceae*^a

Variable	Odds ratio	P	95% Confidence interval
ESBL production ^b	2.34	0.035	1.1–5.2
Inappropriate Rx for ≥ 48 h ^b	2.04	0.05	1.01–4.2
Low McCabe score ^c	1.69	0.047	1.1–2.83
Dependent functional status	8.13	<0.001	2.6–25.6

^a Data for 401 patients were collected. These included only those discharged alive who were not residents of long-term care facilities before the current admission.^b Rx, therapy. The OR of ESBL production changed to 2.86 ($P = 0.01$) when inappropriate therapy was excluded from the model, and the OR of inappropriate therapy changed to 2.6 ($P = 0.006$) when ESBL production was excluded from the model.^c See reference 4. A lower score indicates a worse prognosis.

patients identified a total of 383 patients with ESBL producers isolated from any site (1), our study alone included 205 patients with bacteremia, studied prospectively. Moreover, it provides data relating specifically to bloodstream infections upon hospital admission (i.e., in nonhospitalized patients).

Our findings on predictors of ESBL among patients with bacteremia due to *Enterobacteriaceae* identified factors from 4 different domains: (i) factors related to the patient, i.e., old age and multiple comorbid conditions; (ii) factors related to contact with the health care setting, i.e., recent hospitalization, or admission from an LTCF; (iii) factors related to treatment, i.e., a recent surgery or invasive procedure, and recent antibiotic therapy; and (iv) factors related to the severity of infection upon admission, i.e., severe sepsis or multiorgan failure on admission to the emergency room. While the first three domains have been identified before in smaller retrospective studies, and were also confirmed by the metasynthesis (1), the fourth domain, severity of infection at admission, has not been identified previously as a predictor of ESBL bacteremia. The finding that patients with ESBL bacteremia presented more often with higher severity-of-infection indices may reflect differences in host characteristics as well as a failure of outpatient treatment prior to admission, but in our opinion, it more likely reflects the high virulence of ESBL-producing strains (33). This observation is important to the admitting clinician, in that it suggests that empirical antimicrobial therapy should include coverage of ESBL producers in patients with severe sepsis or multiorgan failure.

Delay of appropriate therapy was found to be tightly linked with ESBL status and is also associated with severe adverse outcomes. Thus, it is important to identify patients at high risk for ESBL bacteremia early and to direct empirical therapy according to risk stratification. The time to initiation of appropriate therapy as analyzed is probably underestimated, since patients were admitted from outpatient settings, so that the actual time from the initiation of infection to the detection of an organism in culture might be prolonged for some.

We chose to examine all patients with bacteremia upon hospital admission as a single group and to analyze exposures to health care settings as possible predictors for ESBL bacteremia upon hospital admission, rather than to compare health care-associated with community-acquired infections, since we believe the former analysis is more relevant to the clinician. However, we performed subgroup analyses based on this classification (results not shown) and found that for community-acquired cases (i.e., excluding patients hospitalized in the previous month or those referred from health care institutions), results were similar, indicating that the same variables predict both community-acquired infections and those acquired in the hospital or in other health care settings.

Our study emphasizes the severe adverse outcomes associated with ESBL bacteremia. We identify severe sepsis on admission as an independent predictor (not a unique predictor) for ESBL status, which should be considered in choosing empirical therapy. Predictors of ESBL status should be used to target empirical therapy on an individual-patient basis.

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