Extended spectrum Beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia

Risk factors and outcome in the Eastern Region of Saudi Arabia

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ABSTRACT

الأهداف: دراسة عوامل الخطورة لوجود بكتريا الإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) الواسع المجال في الدم وما ينتج عنها.

الطريقة: دراسة حالات مقارنة تم إجرائها في مستشفى الملك عبد العزيز للحرس الوطني– الأحساء – المملكة العربية السعودية، خلال الفترة ما بين يناير 2006م وحتى ديسمبر 2007م. شملت الدراسة جميع المرضى البالغين الذين كانت نتائج مزرعة الدم لديهم موجبة لبكتريا الإي كولاى والكلبسيلا. تمت مقارنة 29 مريض من أصحاب مزارع الدم الإيجابية للإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) الواسع لدى 80 مريض من أصحاب مزارع الدم الموجبة للإي كولاى والكلبسيل الغيرالمفرزة لإنزيم اللاكتاماز (ESBL) (مجموعة التحكم). نقطة النهاية للدراسة كانت الوفاة داخل المستشفى. كما تم عمل متغير أحادى وأخر متعدد لوجيستيكى متراجع لتحليل عوامل الخطورة والوفاة خلال ثلاثون يوما لوجود للإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) في الدم.

النتائج: اشتملت الدراسة على 109 مريض لديهم بكتريا بالدم و قد انقسموا إلى 29 مريض بـللإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) و80 في مجموعة التحكم. تسع وأربعون بالمائة من المرضى كانوا من الذكور، متوسط أعمارهم 60.2±21.1 عام. كانت العدوى المكتسبة من المستشفى هي عامل الخطورة الوحيد المعتمد على الذات لوجود للإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) بالدم (OR 3.40, 95% CI 1.14-8.44, p=0.02). كانت نسبة الوفاة خلال 30 يوما 22% في كلا المجموعتين. كانت عوامل الخطورة المعتمدة على الذات الوحيدة في الوفاة خلال 30 يوما هي العدوى المكتسبة من المستشفى (OR 3.20, 95% CI 1.48-6.94, p=0.01)، الصدمة التعفنية (OR 48.88, 95% CI 6.01-397.32, p=0.004) ودخول العناية المركزة (OR 7.40, 95% CI 1.94-28.34, p=0.001).

خاتمة: بكتريا الإي كولاى والكلبسيلا المفرزة لإنزيم اللاكتاماز (ESBL) الواسع في دم المرضى تعتبر عالية، وتعتبر العدوى المكتسبة من المستشفيات عامل خطورة رئيسي لوجودها بالدم وللوفاة.

Objectives: To study the risk factors for bacteremia caused by *Escherichia coli* (*E.coli*) or *Klebsiella pneumoniae* (*K.pneumoniae*) producing extended-spectrum beta-lactamase (ESBL) and their outcome.

Methods: A case-control study was conducted in King Abdul-Aziz National Guard Hospital, Al-Ahsa, Kingdom of Saudi Arabia from January 2006 through December 2007. All adult patients for whom culture results were positive for *E. coli* or *K. pneumoniae* were eligible. Twenty-nine patients with ESBL producing bacteremia (cases) were compared with 80 patients with non-ESBL producing bacteremia (controls). Hospital mortality was the primary end point. Univariable and multivariable logistic regression were performed to analyze risk factors for ESBL bacteremia and its 30-day mortality.

Results: A total of 109 patients with bacteremia were enrolled that included 29 cases and 80 controls. Forty-nine percent of the patients were male. The mean age was 60.2±21.1 years. Nosocomial infection was the only independent risk factor for bacteremia due to ESBL-producing pathogens (odds ratio [OR] 3.40, 95% confidence interval [CI] 1.14-8.44, p=0.02). Overall 30-day mortality was 22%, and was similar in both groups. The nosocomial infection (OR 3.20, 95% CI 1.48-6.94, p=0.01), presentation with septic shock (OR 48.88, 95% CI 6.01-397.32, p=0.004), and intensive care unit care (OR 7.40, 95% CI 1.94 - 28.34, p=0.001) were the independent risk factors for 30-day mortality.

Conclusions: The ESBL rate is high in our study among the bacteremic patients. Nosocomial infection is identified both as a risk factor for ESBL bacteremia and mortality.

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Extended-spectrum beta-lactamase (ESBL) producing organisms were first identified in1983.[1] These organisms lead to resistance to penicillins, cephalosporins, and aztreonam and often they are resistant to fluoroquinolones, aminoglycosides, and trimethprim-sulphmethoxazole. Globally, broad-spectrum cephalosporins, including oxymino-β-lactam antibiotics have been used frequently during the last 2 decades. It is observed that antibiotic resistant-strains of gram-negative organisms producing ESBL are emerging, predominantly *Eschericia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*).[2,3] *Klebsiella* causes nosocomial infections in most cases, however approximately one-half of infections caused by *E. coli* are community acquired.[4,5] Of the patients with ESBL producing *E. coli* infections, 12-16% are bacteremic.[6,7] The ESBL bacteremia can be acquired in a community as well as in a hospital setting.[8,9] It has been demonstrated that ESBL production by infecting organisms adversely affects the clinical outcome,[10-12] while the inadequate initial antibiotic therapy in ESBL bacteremia is associated with increased risk of mortality.[13-15] Prevalence of ESBL producing organisms has been studied in Saudi Arabia.[16,17] Risk factors and the clinical outcome secondary to ESBL producing community and hospital acquired *E. coli* as well as community acquired *Klebsiella* bacteremia are not studied in Saudi Arabia. Only one study looked at the risk factors and clinical outcome in ESBL producing hospital acquired *Klebsiella* pneumoniae bacteremia in the Saudi Arabia.[18] The objective of this study was to identify the risk factors for acquiring the ESBL bacteremia and their outcome in the Eastern province of Saudi Arabia. We selected a case-control design to achieve our objectives.

Methods. This study was conducted at the King Abdul-Aziz Hospital, a 300-bed tertiary care center in the eastern region of Saudi Arabia. A case-control design was selected to assess the risk factors for infection due to ESBL-producing *E. coli* or *K. pneumoniae*. All case and control patients were identified through records of the Microbiology Laboratory that processes all the cultures at our institution. All patients for whom culture results were positive for *E. coli* or *K. pneumoniae* from January 2006 through 31 December 2007 were eligible for inclusion in the study. The case and control patients were grouped on the basis of ESBL production.[12] The study design did not require informed consent and was approved by the Regional Research Committee, which addresses all the ethical issues as well. Each patient was included as a case patient only once. The first episode of ESBL producing *E. coli* or *K. pneumoniae* bacteremia was included, if more than one blood culture were positive from the same patient.[19] Potential controls were identified among hospitalized patients who were infected with non-ESBL-producing *E. coli* or *K. pneumoniae* during the same period. Only patients who met the Centers for Disease Control and Prevention's criteria for infection were included. Potential risk factors for ESBL-producing *E. coli* or *K. pneumoniae* infection were ascertained by means of a review of medical records. The variables obtained included age, gender, hospital location, and number of hospital days prior to infection. The presence of a central venous catheter, urinary catheter, or mechanical ventilation were also assessed. All antibiotics used by the patients 30-days prior to the admission were recorded. The presence of the following co-morbid conditions were documented: malignancy, diabetes mellitus, renal insufficiency, indicated by a creatinine level of >1.5 mg/dl or the requirement of dialysis, neutropenia (white blood cell count less than 500/mm^3), corticosteroid use, prior organ transplantation, use of an immunosuppressive agent in the 30 days prior to admission to the hospital, and surgical procedure or trauma in the 30 days prior to admission. To evaluate the effect of ESBL-producing *E. coli* or *K. pneumoniae* infection on clinical outcome, the following outcomes were assessed: clinical outcome, 30-day mortality attributable to infection, and duration of hospital stay after infection.

Definitions. Bacteremia was defined as the finding of organisms in a blood culture specimen. Community-onset bacteremia was defined as a positive blood culture taken on or within 48 hours of admission. Nosocomial acquisition of infection was defined as follows: infection that occurred >48 hours after admission to the hospital; infection that occurred <48 hours after admission to the hospital for patients who had been hospitalized within the 2 weeks prior to admission; and infection that occurred <48 hours after admission to the hospital for patients transferred from an outside hospital. Blood cultures were obtained primarily via peripheral venipuncture using a standard sterile technique. Blood cultures were obtained from the central venous catheters only if they were freshly inserted.[19] A body site was considered to be a source of bacteremia on the basis of evidence of inflammation and isolation from local sites of the same organism as found in the blood. When no cultural confirmation of local sites of origin could be obtained, or when more than one site fulfilled these criteria, or when death occurred too rapidly to document the primary infection focus, it was classified as an "unknown" source.

Statistical analysis. Values are presented as the mean ± SD for the continuous variables or as a percentage for the categorical variables. Continuous variables were compared with the use of Student's t-test. The chi-square test or Fisher's exact test was used

to compare categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A backward stepwise logistic regression analysis was used to control for the effects of confounding variables to identify the risk factors associated with development of ESBL-producing bacteremia. Multivariable analysis was used for the variables with a *p*-value of <0.10 in the univariable analysis. The Statistical Package for Social Sciences version 16.0 software (SPSS Inc., Chicago, IL., USA) was used for analysis.

Results. A total of 109 patients with bacteremia due to *E. coli* or *K. pneumoniae* were enrolled (**Table 1**). Forty-nine percent of the patients were male. The mean age was 60.2±21.1 years. Blood cultures yielded 74 *E. coli* isolates, and 35 *K. pneumoniae* isolates. Among these, 29 (27%) were found to produce ESBL, including 23 *E. coli* isolates and 6 *K. pneumoniae* isolates (p=0.12). The primary sites of infection are shown in **Table 2**. Case patients were more likely to have nosocomial infection, to have had longer hospitalizations prior to infection, and to have a central venous catheter or urinary catheter in place than were controls (**Table 2**). No significant differences were noted when hospital locations of case patients and control patients were compared. The median duration of hospital stay for case patients was 1.5 times greater than that for control patients; however, it was not statistically significant (p=0.45). When the comorbid conditions of the 2 groups were compared, we found no statistically significant difference, as seen in **Table 2**. However, case patients had significantly greater prior antibiotic exposure than control patients (**Table 2**).

Risk factors for ESBL-producing bacteremia. According to univariate analysis, nosocomial infection, previous treatment with third-generation cephalosporins and non-cephalosporins, placement of urinary catheter, and urinary tract infection were associated with isolation of ESBL-producing organisms in the blood (**Table 2**). Multivariate logistic regression analysis identified nosocomial infections as the only independent risk factor for bacteremia due to ESBL-producing pathogens (OR 3.40, 95% CI 1.14-8.44, p=0.02).

Mortality and its risk factors. Overall 30-day mortality due to *E. coli* or *K. pneumoniae* bacteremia was 24/109 (22%), and is similar in both groups (**Table 2**). The mortality rate for ESBL patients was 20.7% (6 of 29), was 33.3% (2 of 6) for patients with *K. pneumoniae* bacteremia, and 17.4% (4 of 23) for patients with *E. coli* bacteremia. Of the 6 patients that died, 3 had the lower respiratory tract infection, 2 had the urinary tract infection, and one had line sepsis. From univariate analysis, we found that nosocomial infection, neutropenia, presentation with septic shock, care in an intensive care unit, Foley's catheterization, and hospital stay >14 days were significantly associated with mortality. Multivariate analysis revealed that the nosocomial infection (OR 3.20, 95% CI 1.48-6.94, p<0.01), presentation with septic shock (OR 48.88, 95% CI 6.01-397.32, p=0.004), and care in the ICU

Table 1 - Characteristics and medical conditions of patients with *E. coli* or *K. pneumoniae* bacteremia.

Variable	Total (n=109)	(%)
Male gender	53	(48.6)
Age	60.2±21.1	
Hospital acquired	42	(38.5)
Clinical manifestations		
Fever (temp ≥37.5°C)	108	(99)
Shock	47	(43.1)
Underlying disease		
Malignancy	8	(7.3)
Diabetes mellitus	63	(57.4)
Immunosuppressives		
Corticosteroids	10	(9.1)
Other immunosuppressive	4	(3.6)
Laboratory findings		
Creatinine >1.5 mg/dl	7	(6.4)
Neutropenia	16	(14.6)
Invasive procedures		
Urinary catheter	43	(39.4)
Surgery	22	(20.1)
Organisms		
E. coli	74	(67.8)
K. pneumoniae	35	(32.1)
Primary infection focus		
Abdomen	5	(4.5)
Urinary tract	48	(44)
Lower respiratory tract	12	(11)
Central venous catheter	8	(7.3)
Surgical site	3	(2.7)
Other	8	(7.3)
Unknown	25	(22.9)
Antibiotics in last 30 days of admission		
None	65	(59.6)
Received antibiotics	44	(40.4)
Cephalosporins	11	(10.1)
Non-cephalosporins	12	(11.0)
Both groups	21	(19.3)
Outcome variables		
30-day mortality	24	(22)
Admission to ICU	58	(53.2)
Hospital stay		
Mean	24.3±30.9	
Median	15.0	

ICU - intensive care unit

Table 2 - Comparison of characteristics and medical conditions of patients with *E. coli* or *K. pneumoniae* bacteremia.

Variable	Case patients n=29	(%)	Control patients n=80	(%)	*P*-value
Male gender	13	(44.8)	40	(50)	0.60
Age	62.2±16.9		59.5±22.5		0.43
Hospital acquired	11	(37.9)	31	(38.7)	0.82
Clinical manifestations					
Fever (temp ≥37.5 °C)	28	(96.5)	80	(100)	0.91
Shock	14	(48.2)	33	(41.2)	
Underlying disease					
Malignancy	2	(6.8)	6	(7.5)	0.58
Diabetes mellitus	16	(55.1)	47	(58.7)	0.73
Immunosuppressives					
Corticosteroids	4	(13.7)	6	(7.5)	0.33
Other immunosuppressive	1	(3.4)	3	(3.7)	0.62
Laboratory findings					
Creatinine >1.5 mg/dl	3	(10.3)	4	(5.0)	0.72
Neutropenia	5	(17.2)	11	(13.7)	0.76
Invasive procedures					
Urinary catheter	16	(55.1)	27	(33.7)	0.001
Surgery	5	(17.2)	17	(21.2)	
Organisms					
E. coli	23	(79.3)	51	(63.7)	0.001
K. pneumoniae	6	(20.6)	29	(36.2)	0.001
Primary infection focus					
Abdomen	2	(6.8)	3	(3.7)	
Urinary tract	16	(55.1)	32	(40)	0.01
Lower respiratory tract	3	(10.3)	9	(11.2)	0.42
Central venous catheter	3	(10.3)	5	(6.2)	0.22
Surgical site	1	(3.4)	2	(2.5)	0.56
Other	4	(13.7)	4	(5.0)	
Unknown	0		25	(31.2)	0.001
Antibiotics in last 30 days of admission					
Cephalosporins	5	(17.2)	6	(7.5)	0.04
Non-cephalosporins	6	(20.6)	6	(7.5)	0.02
Both groups	3	(10.3)	18	(22.5)	0.04
Outcome Variables					
30-day Mortality	6	(20.6)	18	(22.5)	0.84
Admission to ICU	18	(62)	40	(50)	0.15
Hospital stay					
Mean	31.8±35.7		21.5±28.6		0.45
Median	18.0		12.0		

ESBL - extended-spectrum beta lactamase, ICU - intensive care unit

(OR 7.40, 95% CI 1.94-28.34, p=0.001) were the independent risk factors for mortality (**Table 3**).

Discussion. Our study showed the prevalence of ESBL bacteremia to be 27%. In a study carried out at the tertiary centers in Riyadh the capital city of Saudi Arabia,[16] the ESBL bacteremia rate was 15.8%, which is low compared to our study. Another study from Saudi Arabia reported the overall prevalence of ESBLs from the different body sites as 11%, while blood ESBLs constituted only 7%, which is quite low compared to our study.[17] The high prevalence of ESBL bacteremia in our study can be explained by considering our hospital as a tertiary referral center in a 200 kilometer radius,

Table 3 - Factors influencing mortality in bloodstream infections due to ESBL-producing *K. pneumoniae* and *E. coli*.

Parameter	No. of deaths/No. episodes (% mortality)	OR (95% CI)	*P*-value
Age (year)			
< 65	1/12 (8.3)	1.65 (0.44-4.78)	0.34
>65	5/17 (29.4)		
Gender			
Male	2/13 (15.4)	1.30 (0.64-2.54)	0.52
Female	4/16 (25)		
Organism			
E. coli	4/23 (17.4)	1.91 (0.45-8.10)	0.39
K. pneumoniae	2/6 (33.3)		
Origin of infection			
Community	1/18 (5.6)	3.20 (1.48-6.94)	0.01
Hospital	5/11 (45.4)		
Neutropenia			
No	4/24 (16.7)	3.59 (0.91-13.65)	0.06
Yes	2/5 (40.0)		
Presentation with septic shock			
No	0/15 (0.0)	48.88 (6.01-397.32)	0.004
Yes	6/14 (42.9)		
Care in intensive care unit			
No	0/10 (0)	7.40 (1.94-28.34)	0.001
Yes	6/19 (31.6)		

ESBL - extended-spectrum beta lactamase , OR - odds ratio, CI - confidence interval

where not only the sicker patients seek medical care, but also a significant number of patients are referred from various hospitals of the city. In a study carried out in Hafouf Al-Ahsa, Eastern Saudi Arabia,[18] 10 out of 26 patients (38%) had ESBL bacteremia, which is more than our study, however, the objective of this study was to only look at the bacteremia caused by hospital acquired *K. pneumoniae* and the number of patients enrolled in the study were small. It is interesting to note that this preceding study and our study, although the patient enrollment was different, both were conducted in the Eastern region and showed the high prevalence of ESBL bacteremia compared to other parts of Saudi Arabia, which may worth further investigation.

In our study, we found that indwelling urinary catheters, urinary tract infections, prior use of antibiotics, and nosocomial infections were the significant risk factors to acquire ESBL bacteremia. Prior use of antibiotics has been identified as a risk factor to acquire ESBL bacteremia.[19-21] One of these studies also showed an association of urinary catheterization with increased risk of acquiring ESBL bacteremia.[20] A case-control study reported that severe underlying diseases, nosocomial, and urinary origins of the bacteremia were independent risk factors for ESBL bacteremia.[22] All these studies strengthen our results that patients with urinary tract infections due to indwelling urinary catheters with past exposure to antibiotics are prone to develop nosocomial infections, which is a significant risk to develop ESBL bacteremia.

Our study also shows that ESBL bacteremic patients had higher length of stay compared to non-ESBL bacteremic controls, but it did not reach the statistically significant level. It has been shown that infections due to ESBL producing organisms were associated with significantly longer length of stay and higher hospital charges.[12] Our study did not show a statistically significant difference in septic shock and mortality between the case and control groups, and the overall 30-day mortality was 22%. Among the cases, the factors associated with increased risk of mortality were hospital-acquired infections, care in the intensive care, and patients with septic shock. The 21-day mortality associated with ESBL bactericidal was reported to be 38% in one study, while another study reported a 30-day mortality of 25.6%.[9] A recent study reported a mortality of 43% in patients with bloodstream infections due to ceftazidime-resistant *K. pneumoniae*.[15]

There were some limitations to our study. First, we did not look at the appropriateness of initial empiric antibiotics used in the management of the patients in both the case and control groups, which might have

affected the outcome. Secondly, the sample size might have influenced the results, for example, the mortality, and length of stay were not statistically different in the 2 groups, but a larger sample size might have suggested differently. The overall lower mortality rate, non significant difference in the septic shock, mortality, and length of stay between case and control groups in our study might be attributed to the appropriate empiric antibiotic started early in the course of disease in our study.

Our results, with the support of the literature suggest that patients with suspected nosocomial infections and prior use of antibiotics in the preceding 30 days should be identified early and empirically treated with appropriate antibiotics according to the hospitals antibiograms or carbapenems until culture and sensitivity are available to reduce the risk of poor outcome. This may also decrease the length of stay in the hospital and might be more cost-effective. Identification of the risk factors associated with higher risk of mortality also helps in ascertaining the prognosis of the patients with ESBL bacteremia.

In conclusion, the ESBL rate is high in our study amongst bacteremic patients. The nosocomial infection is identified as an independent risk factor for infection with ESBL producing organisms and its mortality.

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