Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae hospital acquired bacteremia

Risk factors and clinical outcome

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ABSTRACT

Objectives: To study the risk factors and clinical outcome in patients having extended-spectrum beta-lactamase producing (ESBL) *Klebsiella pneumoniae* (*K. pneumoniae)* hospital acquired bacteremia.

Methods: The study was conducted at 500 bedded King Fahad Hospital and Tertiary Care Center, Al-Hofuf, Al-Hasa, Eastern Province of Saudi Arabia. Retrospectively infection control and microbiology records of patients having hospital acquired *K. pneumoniae* bacteremia during July 2001 to July 2003 were reviewed. Data on age, gender, location, onset of bacteremia, hospital stay after onset of bacteremia, prior antibiotic therapy, comorbid conditions and clinical outcome were recorded.

Results: During 2 years of study period 26 patients developed hospital acquired *K. pneumoniae* bacteremia, out of them 10 patients had bacteremia due to ESBL producing strains. Extended-spectrum beta-lactamase producing *K. pneumoniae* bacteremia was significantly higher among patients of >65 years of age (p=0.004). *Klebsiella pneumoniae* bacteremia was more common (12/26, 46.1%) among diabetic patients and 8/12 had ESBL *K. pneumoniae* bacteremia. (p=0.02). Invasive devices (urinary and vascular catheters) were more commonly observed among patients having ESBL *K.pneumoniae* bacteremia (p=0.004, 0.001). Significantly higher number (9/10) of patients with ESBL *K.pneumoniae* bacteremia received prior third generation cephalosporins (p=0.001). Extended-spectrum beta-lactamase *K. pneumoniae* hospital acquired bacteremia had significantly longer hospital stay and higher mortality (p=0.0001).

Conclusion: Elderly age, diabetes, invasive devices and prior third generation cephalosporin therapy are the major risk factors for hospital acquired ESBL *K.pneumoniae* bacteremia, leading to significantly higher mortality and prolonged hospitalization. Infection control measures should be aggressively followed to prevent such infections among these high risk patients.

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Multiple antimicrobial resistant *Klebsiella pneumoniae* (*K. pneumoniae*) are one of the major causes of hospital acquired infections.[1,2] Importance of these bacteria as causative agents of hospital acquired infections has further increased by appearance of extended-spectrum ß-lactamase

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(ESBL) enzymes which hydrolyze the amide bond of the ß-lactam ring of antibiotics including third generation cephalosporins and aztreonam.[3,4] The ESBL enzymes are plasmid mediated and hence can be transferred to other species of bacteria. These enzymes are the result of mutations in ß-lactamase enzyme commonly found in the *Enterobacteriaceae* a family of bacteria. The widespread use of third generation cephalosporins is believed to be the major cause of the mutation in these enzymes.[4] This has severely restricted the therapeutic options for treatment of such infections, leading to a significant morbidity and mortality.[5] In the United State of America, ESBL *K. pneumoniae* resistant to third generation cephalosporins increased from 1.5% in 1989 to 3.6% in 1991, with much higher prevalence (14.4-21.8%) in the intensive care units (ICUs) and teaching hospitals.[6] The prior indiscriminate use of broad spectrum antibiotics and third generation cephalosporins in the hospitalized patients is the independent risk factor of hospital acquired infection with ESBL *K.pneumoniae*, leading to longer hospital stay and higher cost of management.[7,8] Invasive devices such as intravascular catheters and Foley's catheter along with the underlying comorbid conditions are the other described risk factors for ESBL *K.pneumoniae* hospital acquired infections.[9,10] Most of reports available on ESBL *K.pneumoniae* infections are related to outbreaks caused by this bacterium in limited hospital settings such as ICU, oncology centers and pediatric wards.[11,12] However, the information on epidemiological descriptions and characteristics of hospital acquired ESBL *K.pneumoniae* bacteremia in general wards of the hospital and its outcome is very limited.

The present study was conducted to identify the risk factors for hospital acquired bacteremia due to ESBL *K.pneumoniae* in general wards of the hospital and to determine the clinical outcome in patients having bacteremia with ESBL producing and non-ESBL producing *K.pneumoniae* strains. In order to avoid the difficulties in differentiation between colonization and infection, only patients' developing bacteremia were included in the study.

Methods. The study was conducted at the Infection Control Department, King Fahad Hospital and Tertiary Care Center, Al-Hofuf, Kingdom of Saudi Arabia (KSA). Retrospectively infection control and microbiology laboratory records of patients having hospital acquired *K.pneumoniae* bacteremia during July 2001 to July 2003 were reviewed. In case there were multiple blood cultures positive for *K.pneumoniae* from one patient, only the first episode was recorded. Data on age, gender, location of the patient in the hospital, duration of stay, comorbid conditions, invasive devices and clinical condition of the patients were recorded. The severity of illness following *K.pneumoniae* bacteremia was calculated by Acute Physiology, and Chronic Health Evaluation III (APACHE III) score.[13] Antibiotic therapy and any surgical procedure performed during the previous 2 weeks of onset of bacteremia was recorded. Blood culture samples were collected by peripheral venipuncture using aseptic technique and processed in BACTEC 9240 system (Becton Dickinson, USA). The isolated *K.pneumoniae* strains were identified by API20E system (BioMerieux SA, France). Antimicrobial susceptibility was determined by Kirby Bauer disk diffusion method on Mueller-Hinton agar (Saudi Prepared Media Laboratory, KSA). The interpretation of susceptibilities test was performed according to the guidelines of National Committee for Clinical Laboratory Standards.[14] *Klebsiella pneumoniae* strains resistant to third generation cephalosporin were screened for ESBL production by synergy between third generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime) and clavulanate. Synergy was detected by placing disk of Augmentin (amoxicillin 20µg plus clavulanic acid 10µg) and 30µg third generation cephalosporin disk, 30 mm apart on Mueller-Hinton agar. Clear cut extension of the edge of cephalosporin zone of inhibition towards the Augmentin disk was interpreted as production of ESBL.[15]

Bacteremia was defined as isolation of *K.pneumoniae* from one or more blood culture of patients having clinical signs and symptoms of bacteremia. Date of collection of the first positive blood culture was considered as date of onset of bacteremia. Bacteremia was considered as hospital acquired if the blood culture collected 72 hours after admission of the patient positive for *K.pneumoniae*. The body site was considered as source of bacteremia on the evidence of inflammation and isolation of *K.pneumoniae* from this site with a similar antibiotic sensitivity pattern. When the local site or sites cultures were negative, it was classified as unknown source of bacteremia. Antibiotic therapy was considered as appropriate if the isolated strain was sensitive to the antibiotic prescribed. Antibiotic therapy was considered as inappropriate if the isolated *K.pneumoniae* strain was resistant to the administrated antibiotic. Death of the patient was considered to be related to the *K.pneumoniae* bacteremia if there were no other condition documented as cause of death.

Statistical analysis. Statistical Package for Social Sciences (version 10.1) software was used for data analysis. The 2-tailed chi-square test and Fisher exact test were used for categorical variables and student t-test for continuous variables for the univariate comparison. A 2-tailed $p<0.05$ was considered as statistically significant.

Results. During the study, out of the 53036 admissions at this tertiary care center, hospital acquired *K.pneumoniae* bacteremia was documented in 26 (0.04%) patients with an annual rate of 0.02% per year. The mean age of the patients was 44.3 years (range 10-98 years), 15 of them were males and 11 females. Of these, 17 patients were admitted to medical specialties and 9 to surgical specialties. Extended-spectrum ß-lactamase *K.pneumoniae* was the responsible for bacteremia in 10 (38.4%) patients and non-ESBL in 16 (61.6%) patients. Mean age of the patients with ESBL *K.pneumoniae* bacteremia was significantly higher (54.1 versus 39.5 years, relative risk [RR] 1.836, 95% confidence interval [CI] 1.008-3.351, p=0.04) than the patients with non-ESBL *K.pneumoniae* bacteremia. Diabetes was the single most common (12/26, 46.1%) comorbid condition among patients with *K.pneumoniae* bacteremia. Other comorbid conditions were polytrauma (3), surgery (5), malignancy (2), peritonitis (1), polycystic kidney (1), obstructive uropathy (1) and pneumonia (1). Extended-spectrum ß-lactamase *K.pneumoniae* bacteremia patients had significantly higher mean (41 ± 18 versus 22 ± 14, p=0.007) APACHE III scores than the patients without ESBL *K.pneumoniae* bacteremia.

Elderly age was observed as one of the major risk factors of ESBL *K.pneumoniae* bacteremia, as significantly (RR 3.210, 95% CI 1.224-4.615, p=0.004) higher, 6 of the patients with ESBL *K.pneumoniae* bacteremia were of >65 years of age. Diabetes as comorbid condition was another significant risk factor as 8/12 (66.6%, RR 3.200, 95% CI 1.175-6.419, p=0.02) of the patients having diabetes developed ESBL *K.pneumoniae* bacteremia. Primary bacteremia (unknown source of bacteremia) was more common (13/16, 81.2%) in non-ESBL *K.pneumoniae*, whereas secondary bacteremia (known source of bacteremia) was common (7/10,70% RR 3.733,95% CI 1.633-5.215, p=0.0001) among patients with ESBL *K.pneumoniae* bacteremia. Invasive devices were more often observed (urinary and vascular catheter) among patients with ESBL *K.pneumoniae* bacteremia than non-ESBL *K.pneumoniae* bacteremia. Out of 10 patients with ESBL *K.pneumoniae* bacteremia, 9(90%, RR 7.200, 95% CI 3.128-9.625, p=0.001) had previously received third generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime), while one patient received amikacin. Patients with non-ESBL *K.pneumoniae* bacteremia received third generation cephalosporins (4), gentamicin (3), ampicillin (2), amikacin (2), piperacillin (3) and aztreonam (2). Patients with ESBL *K.pneumoniae* bacteremia had significantly longer (34.2 versus 24.1 days, RR 2.488 95% CI 1.303-4.770, p=0.005) stay in the hospital than the patients who developed bacteremia with non-ESBL *K.pneumoniae* (**Table 1**).

Overall mortality due to *K.pneumoniae* bacteremia was 7/26 (26.9%). The ESBL *K.pneumoniae* bacteremia attributed to significantly higher mortality (6/10, 60%, RR 4.071, 95%CI 0.458-4.942, *p*=0.0001) than (1/16 (6.2%) in non-ESBL *K.pneumoniae* bacteremia. Out of 9 elderly patients of >65 years of age with *K.pneumoniae* bacteremia, 5 died and 4 survived. Among 17 patients of <65 years of age, 2 died and 15 survived. Mortality was higher in secondary bacteremia than in primary bacteremia. Higher mortality was observed among diabetic patients than other comorbid conditions. Out of 11 patients who received prior third generation cephalosporins, 5 died. The antibiotic treatment was inappropriate in 4 patients, who died (3 were receiving ceftriaxone and one gentamicin whereas the isolated *K.pneumoniae* strains were resistant to both these antibiotics) and 8 patients who survived (ampicillin [2], amoxicillin/clavulanic acid [3], ceftriaxone [3]) (**Table 2**).

Out of 26 strains of *K.pneumoniae* isolated from blood, 10 were ESBL producing and 16 negative for ESBL production. The ESBL producing strains showed more resistance than the non-ESBL producing strains. All the isolated strains were resistant to ampicillin and sensitive to imipenem.

Table 1 - Comparison of risk factors in patients with extended-spectrum beta-lactamase (ESBL) and non-ESBL *Klebsiella pneumoniae* bacteremia.

Risk factors	**ESBL N=10** n (%)	**Non-ESBL N=16** n (%)	***p* value**
Age (years)			
>65	6 (60)	3 (18.7)	0.004
<65	4 (40)	13 (81.2)	NS
Diabetes	8 (80)	4 (25)	0.020
Urinary catheter	9 (90)	4 (25)	0.004
Vascular catheter	8 (80)	2 (12.5)	0.001
Third generation cephalosporin therapy	9 (90)	2 (12.5)	0.001
Hospital stay (days)	44.2	24.1	0.005
Bacteremia primary	3 (30)	13 (81.2)	NS
Bacteremia secondary	7 (70)	3 (18.7)	0.001
Urinary	2	1	
Wound	1	1	
Vascular catheters	4	-	
Sputum		1	
Mortality	6 (60)	1 (6.2)	0.001

NS - not significant

Table 2 - Clinical outcome and prognostic factors of hospital acquired *Klebsiella pneumoniae* bacteremia

Prognostic factors	Died N=7 n (%)	Survived N=19 n (%)	*p* value
Age (years)			
<65 years	2 (28.5)	15 (78.9)	
>65years	5 (71.4)	4 (21)	
Non-ESBL	1 (14.2)	15 (78.9)	0.02
ESBL	6 (85.7)	4 (21)	0.005
Primary bacteremia	1 (14.2)	15 (78.9)	
Secondary bacteremia	6 (85.7)	4 (21)	0.005
Non-diabetics	2 (28.5)	15 (78.9)	
Diabetics	5 (71.4)	4 (21)	0.02
Third generation cephalosporin therapy			
No	2 (28.5)	13 (68.4)	
Yes	5 (71.4)	6 (31.5)	0.05
Inappropriate Antibiotic therapy	4 (57.1)	8 (42.1)	
Appropriate Antibiotic therapy	3 (42.8)	11 (57.8)	NS

NS - not significant

Table 3 - Antimicrobial susceptibility of *Klebsiella pneumoniae* strains isolated from blood of patients having bacteremia.

Antibiotic	Total N=26 n (%)	ESBL N=10 n (%)	Non-ESBL N=16 n (%)
Ampicillin	0	0	0
Augmentin	0	0	0
Cephalothin	8 (30.7)	0	8 (50)
Co-trimoxazole	13 (50)	2 (20)	11 (68.7)
Cefoxitin	16 (61.5)	10 (100)	13 (81.2)
Chloramphenicol	16 (61.5)	2 (20)	14 (87.5)
Gentamicin	23 (88.4)	9 (90)	13 (81.2)
Amikacin	22 (84.6)	10 (100)	12 (75)
Cefotaxime	16 (61.5)	0	16 (100)
Ceftriaxone	16 (61.5)	0	16 (100)
Ceftazidime	16 (61.5)	0	16 (100)
Aztreonam	14 (53.8)	0	14 (87.5)
Piperacillin	0	0	0
Imipenem	26 (100)	10 (100)	16 (100)
Ciprofloxacin	22 (84.6)	6 (60)	16 (100)

ESBL - extended-spectrum beta-lactamase

Susceptibility to ciprofloxacin was observed in 60% and 100% of the ESBL producing and non-ESBL producing strains. Better susceptibility to amino glycosides was observed among non-ESBL producing than the ESBL producing strains (**Table 3**).

Discussion. The hospital acquired infections with ESBL *K.pneumoniae* resistant to third generation cephalosporins and other ß-lactam antibiotics has increased worldwide, since the initial description in 1983 from German.[12,16] The third generation cephalosporins are one of the most commonly used antibiotic in hospitals worldwide, hence exerting selective pressure leading to emergence of ESBL producing strains of *K.pneumoniae* and other gram negative bacteria. Restrictions in use of cephalosporins lead to reduction in resistance in *K.pneumoniae*.[17] The appearance and spread of ESBL *K.pneumoniae* strains are posing a serious problem in therapy of patients having bacteremia, leading to high morbidity and mortality.[10,18,19]

The appearance of ESBL in *K.pneumoniae* in this region of KSA is a matter of concern as 10/26 (38.4%) patients had bacteremia due to these strains. The mean age of patients who developed ESBL *K.pneumoniae* bacteremia was 54.1 versus 39.5 years in those who had non-ESBL *K.pneumoniae* bacteremia. The majority of patients in ESBL *K.pneumoniae* bacteremia group were of >65 years of age, suggesting that the advancing age is an important risk factor for ESBL *K.pneumoniae* hospital acquired bacteremia. Similar observations have been recorded in studies from Taiwan and Spain.[12,20] In these reports, the majority of the patients acquired ESBL *K.pneumoniae* bacteremia during their stay in ICU, while in the present study the majority of these elderly patients acquired bacteremia in medical specialties wards. Elderly population of this region requires frequent hospital admissions for the underlying diseases such as diabetes, hypertension, ischemic heart disease and renal diseases. These elderly patients with bedsores, intervenous lines, indwelling urinary catheters and comorbid conditions appear to be at 3-fold higher risk of hospital acquired *K.pneumoniae* bacteremia. Diabetes was the predominant comorbid condition among patients developing *K.pneumoniae* bacteremia and 8/10 patients with ESBL *K.pneumoniae* bacteremia were diabetics as compared to 4/16 with non-ESBL *K.pneumoniae* bacteremia, suggesting that diabetes is an important risk factor for hospital acquired ESBL *K.pneumoniae* bacteremia. Diabetes as comorbid condition has been reported as a risk factor for the community acquired *K.pneumoniae* bacteremia.21 *K.pneumoniae* were together responsible for 36.4%

cases of bacteremia among diabetics.[7] In the present study, secondary bacteremia (with known source of infection) was more common (7/10) among patients with ESBL *K.pneumoniae* bacteremia. The identifiable source of infection in these 7 patients was urinary tract infection (2), bedsore wound infection (2) and central venous catheter (3), as *K.pneumoniae* with the same antibiotic sensitivity pattern was isolated from the catheter tips and bedsore wounds of these patients. While the primary bacteremia (unknown source of infection) was more common in patients without ESBL *K.pneumoniae* bacteremia. Colonization of the invasive devices by *K.pneumoniae* is often a prerequisite of hospital acquired bacteremia, the ESBL *K.pneumoniae* strains have greater capacity to adhere to the intravascular devices as they possess special type of fimbrial antigen allowing better attachment to these devices.22 The majority of patients with ESBL *K.pneumoniae* bacteremia had invasive devices, (indwelling urinary catheter [9], central venous catheter [8]) as compared to non-ESBL *K.pneumoniae* bacteremia patients. Of these, 2 developed indwelling urinary catheters associated urinary tract infection and 4 had vascular catheter colonization of ESBL *K.pneumoniae* leading to bacteremia. In the present study, elderly patients who received prior third generation cephalosporin therapy were 7 times at higher risk of hospital acquired ESBL *K.pneumoniae* bacteremia, as third generation cephalosporins were given to 9/10 patients with ESBL *K.pneumoniae* bacteremia and 2/16 without ESBL *K.pneumoniae* bacteremia. Association of third generation cephalosporin use with ESBL *K.pneumoniae* bacteremia has been reported in 24% versus 1.5% in non-ESBL *K.pneumoniae* infections.[7] Previous treatment with third generation cephalosporins was associated with ESBL *K.pneumoniae* bacteremia leading to high mortality (reports from China and South Korea).23,24 In the present study, it was associated with significantly longer hospital stay as compared to non-ESBL *K.pneumoniae* bacteremia suggesting that not only the ESBL *K.pneumoniae* bacteremia leads to higher mortality but also it increases the cost of patient care because of longer hospitalization. Similar observations have been reported from USA and South Korea.[7, 24]

In the present study, mortality was higher among elderly patients, of >65 years of age having ESBL *K.pneumoniae* bacteremia than in patients of <65 years of age having non-ESBL *K.pneumoniae* bacteremia. Secondary bacteremia had higher mortality than the primary bacteremia. Diabetes as a single comorbid condition had higher mortality. Patients receiving prior treatment with third generation cephalosporins had higher mortality. The difference in mortality between the patients who received inappropriate antibiotics and those who received appropriate antibiotics did not reach the statistical significant level, however, the group receiving inappropriate antibiotics were at 33% higher risk of mortality due ESBL *K.pneumoniae* bacteremia (RR: 1.333, 95% CI: 0.956-1.846, p=0.06) . This could be because of associated co-morbid conditions or the appropriate antibiotic, was started late or the smaller sample size. The over all mortality due to *K.pneumoniae* bacteremia in the present study was 7/26,26.8%. The mortality rate of 20-60% has been reported in ESBL *K.pneumoniae* bacteremia.[20,21,23-25] Restriction of third generation cephalosporins use in the hospital not only improves the antibiotic susceptibility of bacteria but also reduces the mortality related to infections due to ESBL producing bacteria.[26-29] In the present study imipenem appears to be better choice for treatment of ESBL *K.pneumoniae* bacteremia, as 5/10 patients who received imipenem, 4 survived and one died. Better efficacy of imipenem over quinolones in treatment of ESBL *K.pneumoniae* bacteremia has recently been reported.[30] Elderly age, diabetes, prior third generation cephalosporin therapy and invasive devices were the main risk factors identified for the hospital acquired ESBL *K.pneumoniae* bacteremia, in the present study. The ESBL *K.pneumoniae* bacteremia appears to be a risk factor associated infection, requiring very aggressive and meticulous following of the infection control precautions to prevent the bacteremia in hospitalized patients, along with restraint in the use of third generation cephalosporins, to prevent mortality, reducing patient suffering and lowering the cost of hospitalization.

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